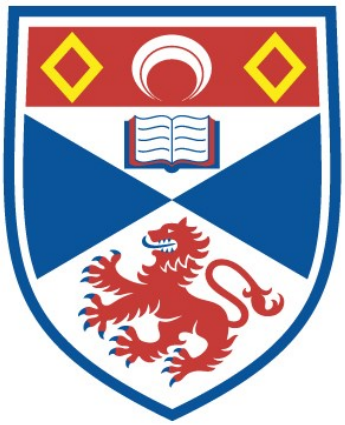
COST-EFFECTIVENESS CONSIDERATIONS IN FINDING APPROPRIATE CHEMOTHERAPY TREATMENTS FOR BACTERIAL DISEASES IN DEVELOPING COUNTRIES: THE CASE OF TUBERCULOSIS.

Lisa M. Bethel

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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LISA M. BETHEL

A Thesis Submitted for the Degree of Doctor of Philosophy at the University of St. Andrews

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For Mom and Dad

(JMJ)

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ABSTRACT

Infectious bacterial diseases in developing countries represent a major health threat. Living conditions and environment decrease health status such that those in developing countries are left vulnerable to many diseases that are seldom seen in industrialised countries. Many treatments for these diseases have proven very effective, making infectious bacterial disease one of the best targets for high yield, low cost health interventions. Antibiotics remain the primary approach in treating infectious bacterial disease, yet mismanagement in their use has led to unnecessary resistance making many major diseases difficult to treat. Additionally, poor antibiotic choices for treating diseases have further contributed to unnecessary resistance. The appropriate choice for treating diseases is not always made and many diseases continue to be treated with inappropriate drugs or combinations of drugs. Many treatments are chosen on the basis of their easy availability or their small cost, when in fact other treatments could be obtained that have a more substantial impact on decreasing the incidence of a given disease. This is especially true in the treatment of tuberculosis. Tuberculosis, once thought to have been almost eradicated, has been revived by the growth of HIV. TB still claims a substantial proportion of human lives and will be responsible for 30 million deaths in this decade alone. Of particular relevance is the rising incidence of drug resistant cases of TB, which is primarily due to inappropriate antibiotic use. Although some past research has acknowledged the influence of resistance on the cost of TB treatment in developing countries, few studies have thoroughly analysed this relationship. This thesis presents a comprehensive study of the impact of drug resistance on the cost of TB treatment within the context of a cost-effectiveness analysis comparing short-course chemotherapy and the standard drug regimen in Ethiopia. In addition, the impact of HIV on TB treatment is analysed together with other factors, such as case holding, in order to assess their respective influence on the cost of treatment. Criteria for better management of tuberculosis control efforts in order to eradicate this disease and control resistance are subsequently explored. Finally, a discussion of the broader applicability of the conclusions of these studies to many developing countries is presented.

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KEY TO ACRONYMS AND ABBREVIATIONS

ACH	Air changes per hour
AFRO	Africa Regional Office of the WHO
AFRO	African region
AIDS	Acquired Immune Deficiency Syndrome
ALERT	All Africa Leprosy and Rehabilitation Training Centre
APUA	Alliance for the Prudent Use of Antibiotics
AMRO	American Region
ARI	Annual Risk of Infection
BCG	Bacille Calmette-Guèrin
BEUC	Bureau Europeen des Unions des Consommateurs
BUKO	Bundeskongress Entwicklungspolitische Aktionsgruppe
CDC	Centre for Disease Control
CEYLL	Cohort Expected Years of Life Lost
CUA	Cost-Utility Analysis
DALY	Disability Adjusted Life Year
DANIDA	Danish International Development Agency
DAP	Drugs Action Programme
DPM	Drug Policies and Management
E	Ethambutol
EDP	Essential Drugs Programme
EPI	Expanded Programme for Immunisations
EEC	European Economic Community
EMRO	Eastern Mediterranean region
ENI	Ethiopian Nutrition Institute
EPHARMECOR	Ethiopian Pharmaceutical and Medical Supplies Corporation
EPI	Expanded Programme on Immunisation
ERRP	Emergency Recovery and Reconstruction Project
FC	Fixed Cost
FDA	U.S. Federal Drug Agency
GP	General Practitioner
H	Isoniazid
HAI	Health Action International
HEPA	High-efficiency particle filter
HIV	Human Immunodeficiency Virus
IDA	International Dispensary Associates
IFPMA	Internationl Pharmaceutical Manufacturer's Association
IUATLD	International Union Against Tuberculosis and Lung Disease
IUD	Intra-uterine device
JCHP	Joint Comittee on Health Policy
JHSI	Jimma Health Science Institute
MALAM	Medical Lobby for Appropriate Advertising
MC	Marginal Cost
MDR-TB	Multi-Drug Resistant Tuberculosis
MIMS	Montly Index of Medical Specialties
MOH	Ministry of Health
NDA	New Drug Application
NGO	Non-governmental Organisation
NRIH	National Research Institute of Health
NSAIDS	Non-Steroidal Antiinflammatories
NTP	National Tuberculosis Control Programme
ODA	Official Development Assistance
ORS	Oral Rehydration Solution
PDR	Physician's Desk Reference
PEYLL	Period Expected Years of Life Lost
PHC	Primary Health Care
PPD	Protein Purrified Derivative

PYLL	Potential Years of Life Lost
Q	Quantity
R & D	Research and Development
R	Rifampicin
S	Streptomycin
SCC	Short Course Chemotherapy
SDR	Standard Drug Regimen
SEARO	Southeast Asian region
SEYLL	Standard Expected Years of Life Lost
T	Thiacetazone
TC	Total Cost
TB	Tuberculosis
UNICEF	United Nation's Children's Fund
UNIPACK	UNICEF Packing and Assembly Centre
UV	Ultra-violet
VRE	Vancomycin resistant enterocci
VC	Variable Cost
WEMOS	Dutch International Group on Women and Pharmaceuticals
WFPMM	World Federation of Proprietary Medicine Manufacturers
WHA	World Health Assembly
WHO	World Health Organisation
WPRO	Western Pacific region
Z	Pyrazinamide

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CHAPTER ONE
INTRODUCTION

Developing countries were once the ultimate frontier: a place where imperialistic powers could expand their wealth and influence. As many were hot and tropical locales with virtually untouched native cultures, there was a certain romance associated with developing countries. However, in the twentieth century, colonies no longer proved to be viable and imperialists granted developing countries the ability to govern themselves, along with the responsibilities of caring for their inhabitants. These countries, with little industry, mainly depend on agriculture to feed their population. However, this has left many countries with little money for anything else, and many areas suffer such as sanitation, education and nutrition, all having an impact on health. Efforts to rectify this with feeble health care delivery systems were obviously ineffective with so many other variables decreasing health status.

A substantial amount of literature has been written on the problems of developing countries as well as frustration as to why, in the late twentieth century, people in developing countries are starving and dying of diseases long eradicated in developed countries. This is certainly a fascinating area: the final frontier in challenges to global development. Improving health is one of the most immediate areas for this development. However, this has proven a great challenge. Global organisations such as the WHO have defined health, delineated several possible areas for drug rationalisation, outlined areas for improvement in various disease areas, discussed ways to decrease expenditure, but such semantics have lacked the financial drive needed to make them manifest.

The path to greater levels of health care provision differs in every developing country according to its cultural needs and values, resources and economic and political situation. Changes in literacy rates are an important step in order for people to learn how to systematically improve their quality of life. Also necessary is a form of established social and political order that offers stability and the capacity for growth. Good transportation and communication infrastructure establishment are important for the transport of patients and personnel to health facilities as well as supplies. Clean

water and sanitation are necessary for better hygiene and the containment of infectious diseases. In addition, there is a need for equality between men and women as well as more education for women. Also, determining better health and welfare is a well balanced agricultural economy that allows for a good supply of food and better nutrition, but does not hamper industrial growth. Finally, sufficient secondary and primary health care are essential in providing treatment and care and vaccines for those needing them. It is these elements that finally allow for better levels of health to be achieved, however these require sound financial support.

Mortality and certain types of morbidity are negatively related to GNP per capita (Feldstein, 1993). In essence, the poorer a country is, the higher death and morbidity from infectious diseases that it experiences. Greater funding is the key to improving health status, however, this is not available. Instead, developing countries must improve health status on what little funds they have, and in some cases, when paired with such poor living conditions, this becomes an unrealisable task. As health service coverage is low, emphasis is placed on treating as many patients as possible with the meagre funds available. However, all too often, quality is compromised.

In an effort to treat large populations, case loads become unmanageable and supplies are poorly organised and often unavailable. The results of this can be significant whereby patients receive a kind of treatment, but no cure, and in some cases, are even harmed by treatment. Therefore, a balance must be achieved between the quality of treatment and the number treated. This must be correlated with the amount of available funding, and therefore, priorities must be set in order to treat the most pressing conditions. Logically, those diseases that wreak the greatest devastation in terms of morbidity and mortality, but are cheaply cured, rank at the top of this list. It is through finding a balance in health care interventions that the inadequate funding available to developing countries for health care delivery can be optimised.

The problem comes in setting these priorities and systematically defining health interventions according to their greatest utilitarian value. Such optimisation is well suited to health management and health economics, however, these are relatively new areas in developing countries. Compared to other disciplines, health economics is a relatively new area, still in its nascent stages. Notwithstanding this, it is not surprising that there is very little literature in health care economics specific to developing countries. Where there are at least a hundred books written in the area of health economics, there are less than five on health economics in developing countries. Many tools and applications for health care cost and welfare analysis have yet to be created. Systematic utility measures such as the disability adjusted life year (DALY) are still being developed. These efforts are hampered by poor data records in developing countries, so that analysis in some cases is impossible. Also, health economic analyses in developing countries are primarily governed and propelled by academic work because there is not

enough of a monetary incentive for health care delivery in this area to be analysed in an industrial environment. Many existing specialists in industrialised countries who could aid in the analysis of cost and health care interventions are wooed away by larger sums offered for work applied to health care delivery in a developed context. Likewise, in developing countries, there are few individuals who have any expertise in health economics. For example, where Glaxo might have 4 health economists, Ethiopia, a country with approximately 55 million, does not even have one. Nevertheless, it could be argued that in light of their economic situation, no area in the world actually *needs* health economic analysis more than developing countries: no countries need to optimise and rationalise their health care delivery system more than developing countries.

It is for this reason that more research is needed in the area of health economics and health management in developing countries. Developing countries offer a rich and unexplored area of research for health economists. Poor funding and living conditions present the ultimate challenge to the health economist who can not only provide useful information but work with a substantial impact on social welfare. A logical area for health care optimisation is drug treatment of infectious bacterial diseases, many of which are curable but wreak large-scale devastation on low income countries. Drugs are generally an effective but inexpensive health care intervention, especially for infectious diseases. A large number of individuals with infectious diseases can be readily and cheaply treated by drugs with outstanding results. The drug of choice for treating bacterial infectious diseases, of course, is an antibiotic, a non-invasive selective intervention that only kills microscopic bacteria rather than its host. The use of antibiotics for the treatment of infectious bacterial disease might seem relatively straightforward, but their utilisation is riddled with problems. Little research has specifically dealt with the cost of treating bacterial resistance in developing countries, especially that of TB. Resistance is often mentioned in studies of antibiotics, but little more consideration on its effect on treatment costs is presented.

This thesis explores the impact of resistance on the cost of drug treatments for infectious bacterial disease, primarily concentrating on tuberculosis. Infectious disease is one of the greatest targets for low cost, high yield health care interventions.

In order to answer the question of the impact of resistance on the cost of tuberculosis treatments in developing countries, other variables affecting this question must be addressed such as health, health care delivery, drug management and utilisation, antibiotic management and utilisation and the impact of tuberculosis. This thesis consists of two fundamental parts. The first part of the thesis addresses the current management and cost in health care, drugs and antibiotics with recommendations on the improvement of delivery in these areas. These sections focus on variables affecting the cost and therefore, cost-effectiveness of treating infectious disease, especially resistance. The second part of

this thesis gives a specific example of an opportunistic disease particular to developing countries, tuberculosis. It discusses cost effective-interventions of TB treatment, first looking at other variables affecting the cost-effectiveness of TB treatments and then assessing the impact of resistance on TB treatments.

Chapter 2 of this thesis defines health. It also shows how living conditions and environment have a detrimental effect on health status, and what effect health services have on health. Health care expenditure is analysed along with the influence of external aid on health policy formulation in low income countries. Having looked at these variables, the choices that developing countries face in the quality and quantity of health care is addressed along with the limited options available to countries' ministries of health. Inherent problems in health care delivery are analysed in detail in order to impart an understanding as to why these systems function sub-optimally. The challenge of infectious diseases to health care systems and the impact of these diseases are then discussed. At this point, a tool for the prioritising of health care interventions, the DALY, is critically analysed. The method of derivation for the DALY is shown alongside its attempt to measure both the disability and premature mortality from a given disease. The performance of this DALY in maximising the benefits of health care with available resources is then shown.

After this overview of health care, the influence of drug utilisation, regulation and production on effective health care delivery is examined in Chapter 3. The problems of ignorance in drug use are illustrated, showing how patients with poor education are likely to misuse drugs. In conjunction with this, the consequence of poor drug regulation and rationalisation are presented along with a description of past external efforts to improve it. Following this, drug procurement and the role of drug producers in drug utilisation are shown, concentrating on their influence on drug information and quality. Controversies within the drug industry in developing countries are addressed, clarifying the multitudinous literature and opinions in this area. Drug counterfeiting, generics scandals, drug testing, drug salesmen, and traditional medicine are also discussed in this section. Efforts to improve this problem are shown along with approaches in regulating drug producers and theories on the industry's responsibility to the consumer.

In Chapter 4, one of the most heavily relied on therapeutic groups in the world, antibiotics, is discussed. Antibiotic resistance is shown to have a substantial impact on these drugs' effectiveness and the cost of treatment. Mechanisms of resistance are described and an economic model of resistance is discussed. After this, the intricate problems of antibiotics and inappropriate use in developing countries are explored. Developing countries, with such a high demand for antibiotics, also suffer from the highest amount of associated negative externalities, antibiotic resistance.

In Chapter 5, tuberculosis and the related management of drugs, health care delivery, health care management and appropriate treatment for TB are discussed. Tuberculosis was chosen for analysis because it is the paradigm of an opportunistic disease that flourishes in the living conditions of developing countries: conditions that weaken immune systems. It is ideal for an analysis of the impact of resistance on the cost-effectiveness of drug treatments because of the fact that it is such a deadly disease and resistance to it proves very significant. Indeed, tuberculosis treatment is specifically designed to as multiple therapy in order to *avoid resistance*. Unlike some bacterial diseases, subsequent resistance to TB primarily arises from human factors that can be controlled.

A disease with devastating consequences, tuberculosis can be responsible for the premature mortality of as many as 10-50% of the population, depending on the quality of treatment. It is not generally a disease of the rich, but a disease of the very poor. Even in industrialised countries it is those in poor conditions, such as the homeless, that suffer from this disease. This is not considering the synergistic effect that tuberculosis has in conjunction with HIV. Tuberculosis has the most virulent effect in combination with HIV. Not only does it more quickly kill HIV patients, but increases an infectious tuberculosis pool that revolves in an endless cycle between HIV patients and other vulnerable individuals. Chapter 5 defines tuberculosis so that the reader can gain an understanding of approaches in managing and containing the disease. It is shown how tuberculosis and HIV are so closely linked to each other due to TB's progression to disease in those with weakened immune systems. After this the management of tuberculosis containment is shown, applied to drug supply, diagnosis, isolation, preventative therapy, case holding and their associated costs. The global impact of TB is then shown with its share of the global burden of disease expressed in costs. New cases of tuberculosis are on the rise because of the disease's effect in conjunction with HIV. Current expenditure is shown to be insufficient to diffuse the current and future threat of tuberculosis.

Chapter 6 shows the problems of tuberculosis in developing countries and how this disease has become problematic because of poor sanitation, malnourishment, ignorance, HIV and resistance. This is where the methodology of this thesis is presented. This chapter also shows prior studies on the cost and the cost-effectiveness of TB treatments. TB must be a priority for health care delivery, and developing countries need to form a standardised systematic national method for tuberculosis control. Although TB is a curable disease, its prevalence is inordinately high along with its mortality rate in developing countries. Effective management of this disease can reduce morbidity and mortality from the disease by as much as 45% where applied correctly. The challenge comes in formulating an approach to curing the disease and finding the right cures. Possible approaches in drug treatment are presented, focusing on types of short course chemotherapy and the older standard drug regimen. By using applied economics to health care, the appropriate choice for decision making in tuberculosis

treatment becomes more apparent. Hence, the methodology of health economics applied to infectious diseases is discussed. After this discussion, the existing literature applying health economics to tuberculosis treatment in developing countries is presented with various criticisms of each.

Chapter 7 and 8 presents a case study in Ethiopia. It is in Ethiopia where the question of the impact of resistance on TB treatment will be more thoroughly explored. Further analysis on the impact of resistance on the cost-effectiveness of the two main treatments is also addressed. Ethiopia was chosen for this study because it is one of the very poorest developing countries with high rates of morbidity, structural problems, heavy dependence on agriculture, and poor health service coverage. At the beginning of Chapter 7, demographic, environmental, organisational and political determinants of health are presented. This is followed by a detailed analysis of data from the Ethiopian Department of Pharmacy on drug supply and especially, the management of the tuberculosis drug supplies. After this, a discussion of current methods in controlling tuberculosis, including recent changes in the control system, are presented. Tuberculosis in Ethiopia is a severe problem and efforts to control it in the past have been all but effective. HIV's effect in Ethiopia is then presented at the end of Chapter 7, giving detailed data on all reported AIDS cases from the detection of the first case to its growth up to 1994.

In the beginning of Chapter 8, the effect of HIV and TB is shown by looking at data from the St. Peter's Sanatorium in Addis Ababa, where a sample of nearly 800 TB patients have actually been screened for HIV. Here the impact of resistance on the cost of treatment is explored in the context of critical TB patients. Following this, the approach to the diagnosis of TB through the screening of patients is analysed, showing how diagnosis is sub-optimal, incurring needless costs. Finally, the end of Chapter 8 presents a cost-effectiveness analysis of TB treatment between two regimens in the public sector of Addis Ababa. Results from nearly 500 patients are analysed in order to find their response to treatment. The associated costs of these two treatments are researched and the impact of several variables, including that of resistance, is illustrated. The impact of the Ethiopian National Tuberculosis Programme, when compared to two years ago, is shown. This is followed by a description of the problems and challenges of delivering effective TB treatment in order to stop resistance and the growth of the disease at each health centre. This discussion further emphasises the need for better control to contain the disease and avoid TB resistance.

CHAPTER TWO
AN OVERVIEW OF HEALTH CARE AND INFECTIOUS DISEASES IN DEVELOPING COUNTRIES

Introduction

In order to assess the impact of resistance on the cost of tuberculosis treatment in developing countries, it is important to first define influencing variables such as epidemiological patterns and health care resource capacity. The design of this chapter is to impart the reader with some background information into the health priorities of developing countries. This includes a description of the challenges in infectious diseases developing countries face and what health care delivery capacities these countries have in order to meet these challenges. This will later be analysed within the context of tuberculosis treatment.

In developing countries, one of the most interesting areas to observe changes in epidemiological patterns of morbidity is in the area of infectious bacterial disease. In developing countries, this is an area with a vast potential for change. Despite the fact that the prevalence of many infectious diseases remains high, the predominance of these diseases can be cured.

Section 2-1 of Chapter 2 defines health and attempts to show what variables have a significant impact on health, also illustrating the health problems in developing countries and why they persist. Section 2-2 endeavours to show the challenges of health care delivery, highlighting its constrained nature and significant problems that require a prioritisation of health demands. Section 2-3 focuses on infectious disease and its impact in developing countries. The epidemiological morbidity patterns are analysed and future changes are projected. Section 2-4 discusses disease priorities in health care and presents one methodology for measuring the utility from health care interventions with the disability adjusted life year (DALY). The technical basis of DALYs is critically assessed as well as examples of their use in prioritising health care interventions.

Section 2-1

DEFINING HEALTH AND HEALTH DETERMINING VARIABLES

This section discusses those variables that determine health in developing countries. Health is defined and influencing factors on health status such as environment and living conditions are presented. Total health care expenditure in developing countries as well as external aid is then explored. Those variables that influence health status will be later shown to also be specific determinants of the growth of tuberculosis, more so than many other infectious diseases.

2-1:1 The Impact of Living Conditions and Environment on Health Status

The standard of health of those in developing countries is certainly poor when compared to many other countries. It is complicated by poor living conditions, poverty, environmental and political disasters. Disasters seem to wreak wider devastation on developing countries than elsewhere in the world. From 1980-1990 in Africa, 6 613 deaths were attributed to floods, cyclones and earthquakes, 566 000 deaths occurred from famine, drought and food shortages while also rendering 9.3 million homeless refugees. Between 1961 and 1981, cyclones, earthquakes, drought and flood took 1.1 million lives in developing countries, 345 000 lives in middle income countries and 11 300 lives in high income countries, although the numbers of disasters were very close (Kloos and Zein, 1992).

In six countries where widespread famine occurred in Africa, famine was attributed to rebellion which in 4 cases was financed externally (Kloos and Zein, 1992). Indeed, disasters have a greater impact on the impoverished: more buildings fall on people in earthquakes in developing countries because, their construction is generally of a lower quality; diseases spread faster in cities in developing countries because of ignorance and the extremely close living quarters; drought strikes harder because more people depend on agriculture to feed them.

The poor are far more likely to get sick due to the fact that they depend on an income from physical labour and when they get sick, they are unable to make any more money. Therefore, illnesses leave the poor in a worsened financial situation. This is exacerbated by poor living conditions at home as well as malnourishement. Indeed, the poor are more crippled from disease and more of them die because of it. In the late 1980's in Porto Alegre, Brazil, adult deaths in impoverished areas were 75 percent higher than richer areas. In Kenya, for families where a mother was less educated, a child's probability of dying before reaching the age of two was 18.4% in areas where half the families were below the poverty line, but ten per cent for areas where one fifth of the families lived below the poverty line. (World Bank, 1993). The World Bank captures the plight of the poor:

> "The poor are exposed to greater risks from unhealthy and dangerous conditions, both at home and at work. Malnourishment and the legacy of past illness mean that they are more likely to fall ill and slower to recover, especially as they have little access to health care. When a family's breadwinner becomes ill, other members of the household may at first cope by working harder themselves and by reducing consumption, perhaps even of food. Both adjustments can harm the health of the whole family. If free health care is not available, the costs of treatment may drive a household deeper into debt." (World Bank, 1993: p. 21)

As compared to developed countries, developing countries suffer from lower living standards and higher levels of morbidity and mortality which force them to solicit outside assistance. Although necessary, such outside assistance only lends superficial help instead of rendering the support that the country needs to independently maintain a health care system. The country finds that it is in greater debt from this assistance whereby it is placed in a repeating pattern of increasing debt causing it to borrow more. World Bank data would suggest that total debt repayments are now greater in developing countries than the value of all new aid payments and loans per year and that these repayments equal 25 per cent of the monetary value of their exports (Mills and Lee, 1993): exports that are primarily commodities whose prices are falling. Developing countries, forced to depend on an economy primarily based on agriculture, find that they cannot support a health system that meets the standards of an industrialised country.

In 1975, a World Bank Policy paper determined that the primary causes of poor health in developing countries were malnutrition, poor sanitary living conditions and inadequate housing (World Bank, 1975). To fully understand the health problems of developing countries, one must explore the causes. Developing countries suffer from poverty which increases their debt and decreases their ability to manage themselves. Among other things, this in turn manifests itself most acutely in their respective health care systems which exhibit poor information infrastructures, poor quality, poor referral systems, poor choices in supplies and concentration and hence, poor utilisation by the individual. In effect, this results in health care systems without direction. With so many other things to compound health care delivery, problems in the effectiveness of drugs as important as antibiotics have the potential for dire consequences on overall health status.

2-1:2 Definitions of Health

The World Health Organisation has defined health as "...a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, is a fundamental human right..." (WHO, 1978). Undoubtedly, the "absence of disease or infirmity" is a common definition of health, but "complete physical, mental and social well-being" is rather vague, and at best, extremely difficult for individuals to obtain on a constant basis deriving from the fact that the definition includes the word "complete". Such global *complete* health for all is a goal that is inherently unrealistic. This does, however, suggest the idea of health as including something other than just the absence of disease and

remains a term that refers to the state of the body. Where the boundaries of this state should start and end is open to debate.

The WHO set the undeniably ambitious goal of health for all by the year 2000 at the Alma-Alta conference proclaiming "The attainment of all people of the world by the year 2000 of a level of health that will permit them to lead a social and economically productive life." (World Bank, 1993: p. 13). This is an impossible and idealistic goal because it suggests a curing of diseases that are far from curable. Indeed, this goal was set when the year 2000 seemed like it was a distant point in the future. In order to even begin to change overall health rates to approach this goal, each country would have to invests the predominance of its GNPs in its health as well as the health care of more disadvantaged countries.

There is a large disparity between the health of developing countries and established market economies. Developing countries still suffer from diseases that have long been cured in industrialised nations. Therefore, it is largely in developing countries where WHO must concentrate its efforts in trying to achieve this goal. Such efforts centre around improvements in the standard of health care, and also, improvements in general living conditions. One can consider health care as one of many inputs that contribute to the final output of health, and the relationship between these outputs can be termed a health production function (Feldstein, 1993).

2-1:3 The Effects of Health Care Versus Other Variables on Health Status

The question arises as to what effect health care has on the level of health as opposed to other improvements in living standards. The measurement of health is extremely difficult and cannot depend on a single variable. In addition, more often than not, health is measured according to the incidence of the absence of health such as the death rate and levels of morbidity and mortality. Such data are tautologically not a full measurement of health. Compounding this in developing countries, not much reliable data are available, making such an assessment difficult.

In 1960, in the United States, Auster, Leveson, and Sarachek (1961) set out to find the percentage change in mortality that would occur from a one percent change in the level of health services. Indeed, the authors concluded that environmental and individual variables have a greater impact on the level of mortality than does health care delivery. Their analysis also included the effect of other factors such as environmental variables and personal variables. Where health care only had an elasticity of -0.1 with respect to mortality rates, education had an elasticity of -0.2. At low income levels, increases in income would decrease mortality whereas at high levels of income, mortality increased reflecting a change in lifestyle.

This work was supported by the work of Benham and Benham (1975), whose findings in the United States suggested that between 1963 and 1970, the increase in the use of health services, primarily catalysed by the implementation of Medicare and Medicaid, did not produce an improvement in health status. It is difficult to say if these studies can be generalised to cover developing countres. Whereas in industrialised countries, a large proportion of infectious diseases have been eradicted with inexpensive drugs, lifting health status to a stable level so that it is dependent on changes in curing chronic and non-communicable diseases. This is not the case in developing countries. It is possible that health care, when health service coverage is high, can increase health status when treating cheap and curable infectious diseases. Health status in developing countries may not only be dependent on changes in living environment, but also it might be significantly affected by health care delivery and its function in educating individuals in elements such as nutrition and preventative care.

In developing countries, economic factors can also be shown to have a strong influence on health. In 1993, child mortality declined by 60 percent in those countries whose average incomes rose by over 1 percent per year (World Bank, 1993). At lower levels of income, greater income increases are often spent on better diets, better water supplies, sanitation and housing, all of which serve to improve health status. Supporting this point, the WHO has suggested at the Alma-Ata conference that "...the attainment of the highest possible level of health is a most important world-wide social goal whose realisation requires the action of many other social and economic sectors in addition to the health sector" (WHO, 1978). Certainly, the increases in health in industrialised countries in the early twentieth century could be attributed as much to health care as to increases in sanitation, nutrition and living conditions.

Hence, Policy makers are correct in assuming that along with the role of health care, increases in sanitation, diet and housing have an important effect on health. In addition, this might possibly explain the common pattern of donor pressure for very visible aid to physical infrastructures (Lee, Mills and Hoare, 1993). One could argue that the discrepancy in living environments between developed and developing countries could also have a strong correspondence to the discrepancies in their overall levels of health and patterns of morbidity. This is not to say that health care delivery must be completely discounted, but on the contrary, suggests that it works with other factors.

Health care represents the human effort to produce health. It characterises one of the many inputs forming health status. There is undoubtedly decreasing marginal returns to health inputs. When a programme is relatively small, each input produces relatively large outputs. Then as a programme grows, inputs expand, but the level of output starts to decrease until it becomes less

consequential despite additional inputs. This is partially why health care programmes in developing countries can have such a potential impact on health status.

Much of health care delivery is a public good (one person's use does not leave less for another), and some health care interventions even have the potential to provide a positive externality (or sometimes negative externality as shown in Chapter 4) to others. For instance, encouraging one to stop smoking renders a positive externality to society because it not only helps the individual, but also increases the utility of those around him or her by limiting passive smoke inhalation. Similarly, immunisation for yellow fever not only benefits the individual, but those around him or her by contributing to the containment of the disease. Private health markets leave excess demand for health care goods. This reason, combined with health service's ability to provide such strong positive externalities, suggests a strong case for government spending and regulation of health care.

2-1:4 Health Care Expenditure

Health care spending not only improves an individual's level of utility, but also benefits society economically by allowing for greater production on the part of the individual who might otherwise be impeded from work by illness. The effects of illness can have a substantial impact on a country's economy. The World Bank (1993) claims that a large decrease in the level of deformity of 645 000 lepers in India could have added an extra US $130 million to its 1985 GNP (how this figure is reached is not explained, but it is based on the assumption that each 'less deformed' leper would contribute $US 201 to India's GNP). Even the nature of work changes according to the level of health obtained. Farmers in Paraguay were found to choose to grow crops of lower worth just to avoid the malaria season (World Bank, 1993). Greater levels of health also benefit an individual's access to education as he or she is not debilitated. Likewise, money that would instead be used to treat illnesses, with greater health, can be spent on other efforts. The greatest potential for health care delivery is for the very poor who stand to benefit the very most, often for the least cost. For example, inexpensive interventions such as vaccinations that are already experienced by many in the middle classes have the potential to decrease a large proportion of diseases in the poor when properly administered.

Interestingly enough, the current level of expenditure shows that industrialised countries spend the most on health care per capita and developing countries spend the least. According to Chaulet and Zidouni (1993), 1990 global expenditure on health care amounted to US $1,700 billion of which 90 percent was accounted for by industrialised countries, and 41 percent of this was accounted for by the United States, approximately 12 percent of America's GNP. In contrast, developing countries spent 170 billion US dollars, 10 percent of total global expenditure, accounting for a full 4 per cent of America's GNP (See Table 2-1).

Table 2-1: Government Health Expenditure per Capita in Different Groups of Countries classified by GNP per Capita

Groups of countries	Population per million	GNP per capita $US 1989	Governmental health expenditure per capita in $US 1988
Low-income countries			
Total	2 948.4	330	2.0
China	1 113.9	350	3.0
India	832.5	340	1.0
Others	1 002.0	300	1.9
Middle-income countries			
Total	1 104.5	2 040	23.0
Lower part	681.8	1 360	8.5
Upper part	422.7	3 150	43.0
High-income countries	830.4	18,330	612.0

Source: Chaulet and Zidouni, 1993

2-1:5 External Aid and Its Impact on Policy Decisions

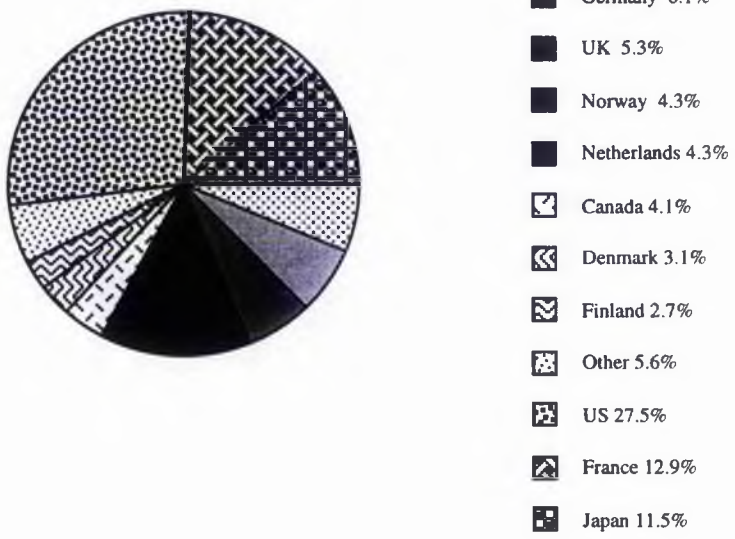
Much of the funding for health care in developing countries comes from internal sources, but external aid also funds many health care programmes. Because developing countries are so financially constrained they must sometimes rely on external assistance to help fund their health care programmes. This external assistance, comes from official development assistance (ODA), multilateral loans and nongovernmental flows. This assistance is given by bilateral agencies, which are organisations like USAID where each aid exchange originates from one country; multilateral agencies, which are organisations like the World Bank where aid originates from several countries; NGOs and foundations. Such aid can amount to a vast sum.

According to Michaud and Murray (1994), in 1991, total external aid amounted to approximately US $4800 million. However, this only amounts to 2.9% of the total expenditure for health in developing countries. Where Zaidi, (1994) claims that the influence of external aid is the most important determinant influencing health care planning, Michaud and Murray counter this with their results that suggest that the formulation of health policy should not depend on external aid.

Michaud and Murray make further observations from their study of external health funding. According to these authors, external health funding was low in the early 1980s but began to increase in 1986 from multilateral and bilateral assistance. From 1989-1990 external aid actually outgrew population growth. As shown in Figure 2-1, the largest donor countries are the US, Japan and France, but the Netherlands and the Scandinavian countries donate the largest proportion of their GDP to external aid for developing countries. Nearly one half of health aid funds go towards expenditure on developing the infrastructure of health for improving health service delivery and hospital care. The remainder is spent for specific health care programmes. Of these, leprosy, onchocerciasis, tropical

disease, STDs, HIV infection and blinding diseases take the lion's share. Behind these diseases are malaria and the Expanded Programme for Immunisations (EPI). Poor funding is observed for almost all non-communicable diseases, acute respiratory infections and injuries. According to Michaud and Murray, sub-Saharan Africa does not receive more aid than other regions when considering population, size and income. These authors maintain that the smaller and poorer a country is, the more aid it receives per capita. Total external aid for 1991 can be seen in Table 2-2.

Figure 2-1: Development Aid from OECD Countries to the Health Sector of Developing Countries, 1990



Source: Michaud and Murray, 1993

Summary of Section 2-1

The environment and living conditions in developing countries have a significant impact on morbidity and mortality, challenging health interventions to establish an appropriate level of health. Health, which is defined as an overall state of well being, devoid of disease, has proven to be an extremely difficult goal to accomplish. This cannot be entirely blamed on the quality of health care provided in developing countries. Health status has been shown to be significantly determined by other environmental factors besides health interventions. Still, it can be maintained that health care expenditure may have some impact on health status. Greater investment in health care is therefore necessary in order to decrease morbidity and mortality levels. External assistance is estimated to be a helpful factor in achieving this goal, nevertheless, total external aid is not large enough to determine health policy formulation.

Table 2-2: Total External Aid to Developing Countries in 1990 (in thousands)

Disease	Bilaterals	Multilaterals	NGOs	Foundations	Total
Communicable Diseases					
Tuberculosis	11 694	4 165			16 129
STD and HIV infection	64043	120 006	622	90	184 761
Diarrhoea	31 604	23 402			55 006
Vaccine-preventable childhood infection	39 654	160 109			199 763
Malaria	36 745	10 087			46 832
Worm infection					
Respiratory infection	7 986	4 525			12 511
Other	69 530	31 970			101 500
Hepatitis	990				990
Tropical Cluster	4 831	58 848		10 815	74 494
Trypanosomiasis	471				471
Chagas Disease					
Shistosomiasis	4 360			199	4 559
Leishmaniasis					
Lymphatic filariasis					
Onchocerciasis	4 835	22 720	4 518	3 041	35 114
Leprosy	2 770	3 108	71 000		76 878
Trachoma	453			3 150	3 603
Subtotal	**279 495**	**438 940**	**76 140**	**17 295**	**811 870**
Noncommunicable Diseases					
Malignant neoplasms	1 737		725		2 462
Blindness	2 080	22 720	30 661		55 461
Neuropsychiatric diseases	2 838	2 838			5 676
Cerebrovascular diseases					
Cardiovascular disease	961				961
Pulmonary obstruction					
Drug/alcohol dependence	6 950	2 785	7		9 742
Other	391				391
Subtotal	**14 957**	**28 343**	**31 393**		**74 693**
Injuries					
Unintentional		984			984
Intentional	8 024	546			8 570
Subtotal	**8 024**	**1530**			**9 554**
Other					
Nutrition	39 910	406 533			446 443
Maternal and child health	199 863	159 606	4 149	5 800	369 418
Population activities	558 000	332 000	22 000	24 000	936 000
Hospitals	178 905	44 546			223 451
Health services	396 034	547 904	938 378	13 959	1 896 275
Subtotal	**1 372 712**	**1 490 589**	**964 527**	**43 759**	**3 871 587**
TOTAL	**1 675 188**	**1 959 402**	**1 072 060**	**61 054**	**4 767704**

Source: Michaud and Murray, 1994

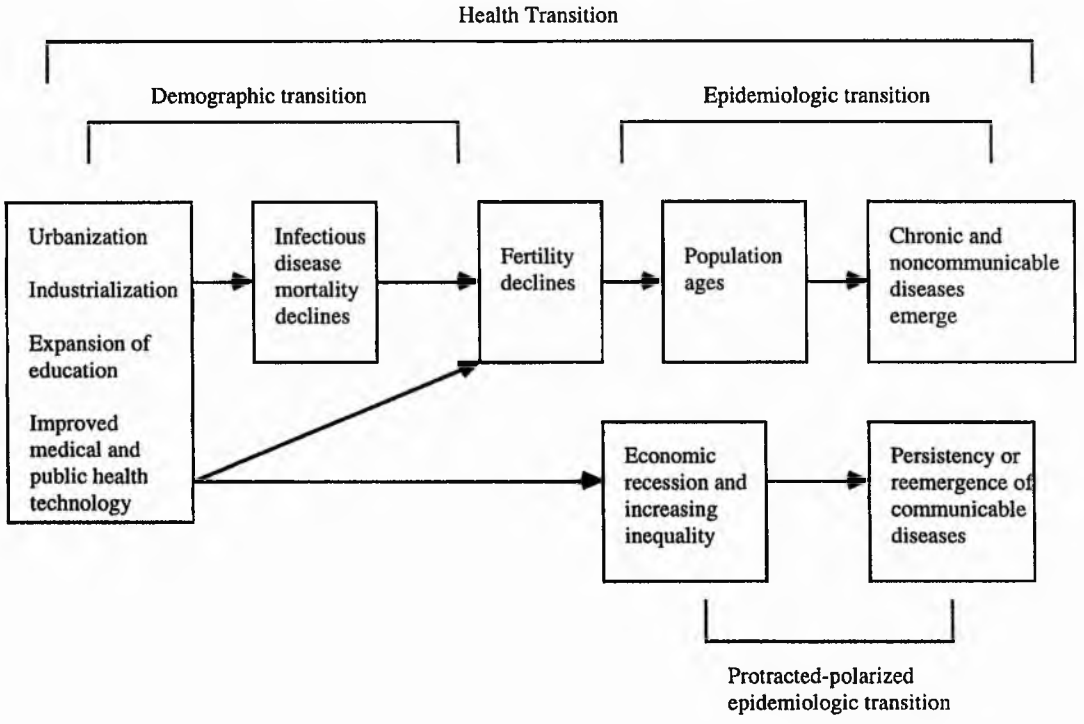
Section 2-2

CHALLENGES IN HEALTH CARE DELIVERY

This section analyses the problems of health care delivery in developing countries in order to show the context in which developing countries work in order to increase health status. It illustrates how difficult it is for developing countries to raise their health status. With this section, one will be able to later see how problems such as ineffective antibiotics (due to resistance) have the potential to cripple developing countries' health care systems in dealing with bacterial diseases.

Tautologically, the quality of health care delivery is determined by the ability of a health care programme to appropriately meet the health care demands of those in a developing country. This is influenced by the relative amount and concentration of expenditure allocated to a health budget. The relationship between health care quality and economic growth is somewhat circular: as an economy grows, often its health care system becomes more and more strongly funded and with ensuing healthier human capital, there is likely to be further growth in the surrounding economy. These improvements are likely to cause epidemiological and demographic transitions within the health of a population.

Figure 2-2: The Transition of Health as Influenced by Demographic and Epidemiological Factors



Source: Mosley, Bobadilla and Jamison, 1993

The transition of a health care system is portrayed in a diagram by Mosley, Bobadilla and Jamison (1993), shown in Figure 2-2. As can be observed, with urbanisation, industrialisation, greater incomes, rising levels of education and improved technology for health, there is a fall in infectious disease and mortality. Subsequently fertility falls, people live longer and chronic and non-communicable diseases become more common. In contrast, as a county becomes more and more urbanised, and inequality increases or economic recessions occur, communicable diseases are likely to reappear, especially in the economically disadvantaged segments of a population. This is compounded by the transmission of resistant forms of bacterial diseases. One of the best examples of this is tuberculosis in industrialised countries: once a disease that was thought to be almost eradicated, it is again a threat in large cities, especially among the homeless and immigrants. It is in these groups where there has also been observed a simultaneous rising incidence of multi-drug resistant TB.

2:2:1 The Trade-off Between Quality and Quantity

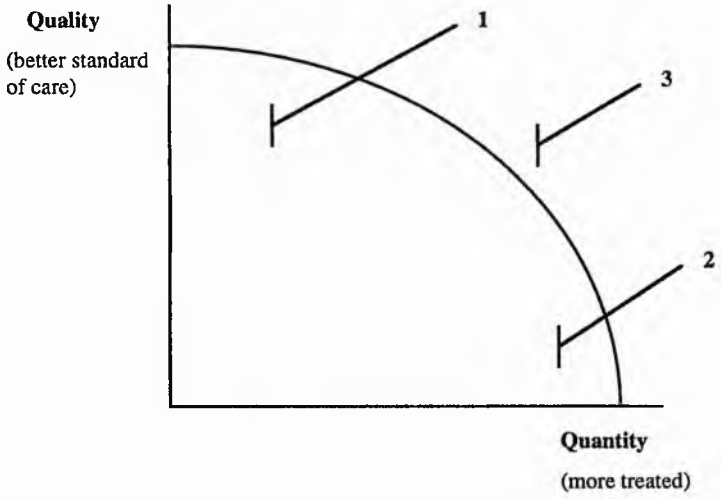
In seeking health care in developing countries, patients sometimes feel that it will be ineffective or too expensive to pay for, and too often they are right. Because of constrained resources, developing countries often have difficulties in supplying a quality-consistent level of health care or health care that covers a large enough percent of the population. As the proportion of those treated grows, components essential to proficient health care delivery such as drugs, sanitation equipment, medical tools and personnel are often random. It might be possible to use new disposable syringes for 100 patients at a small health facility, but as the number of patients grows, for instance to 200, these syringes will have to be reused. If the number grows to 300, this health facility might find that it is altogether depleted of syringes. Given limited resources, developing countries must decide what quality of health care that they aim to provide.

Developing as well as industrialised countries must trade quality for quantity in health care delivery. These countries must look at their production possibilities when planning any health care delivery system. Such an approach can be depicted in a production possibility curve, which defines all possible combinations of production (of health producing outputs) available between two outputs. This is illustrated in Figure 2-3 where a production possibility curve illustrates the trade-off between quality and quantity: two outputs that are not entirely substitutable (hence the concave shape). For example, technology-intensive health care on the secondary level would suggest a high quality-intensive health care approach that would reach very few people: a point high on the quantity-quality trade-off, such as point 1. In contrast, primary health care workers with limited education in medical care working in rural areas would suggest a concentration on quantity rather than quality. This approach might give access to a high percentage of people but simultaneously compromise quality: an

approach that would appear at point 2. Lastly, point 3 represents a combination of quality and quantity in health care delivery that is unobtainable from a developing country's resources.

One can see from this illustrated example that those countries concentrating on quality intensive resources encounter the problem whereby the population that has access to this health care is very small. Likewise, those countries who aim for the maximum coverage of health care to treat the largest quantity of population possible, often result in random and poor health care delivery. It is through finding a balance between quality and quantity that developing countries can optimise their level of health care delivery. Maximising the quantity of those treated is often the predominant goal rather than focusing on the quality of health care in developing countries. Nevertheless, emphasis on this must be controlled or health care can become pointless, random and even a cause of harm.

Figure 2-3: Trade-off Between Quality and Quantity in Health Care Delivery



2-2:2 Limited Choices and the Rationalisation of Health Care

There are indeed, strong differences between the health care possibilities available to developing countries and industrialised countries. Mosely, Bobadilla and Jamison (1993) capture the differences between strong and weak health care systems in responding to rationalising health demands, as shown in Table 2-3. This table is formulated from the burden of disease, cost-effectiveness and the relative strength of a health care system. The possibilities that lie within reach of a country with a strong, well funded health care system are much greater than those with a weak health care system. Those with strong systems might choose to restrict a low cost-effective intervention with little impact on the burden disease, whereas a country with a weak health care system would be forced to eliminate it.

Table 2-3: Responses of Strong and Weak Health Care Systems to Burden of Disease

Burden of Disease	Intervention Cost-Effectiveness	Strong Health Care Systems	Weak Health Care Systems
High	High	Aim for Full population coverage Improve quality of services provided	Reorient/train existing staff Develop technical /management systems Establish infrastructure
	Low	Research to improve interventions Do not expand services Institute cost recovery	Research to improve interventions Restrict or eliminate services
Low	High	Target high-risk groups	Provide services on demand
	Low	Restrict services or provide cost recovery	Eliminate services

Source: Mosely, Bobadilla and Jamison, 1993

2-2:3 Poor Allocation and Concentration of the Health Care Budget

There is often the underlying belief in developing countries that it is through obtaining a highly concentrated technology-intensive health care delivery system that these countries can begin to obtain the level of health care of industrialised countries. On the surface, large and costly machines provide impressive looking health facilities but tend to be used because they are there and perceived as 'superior' instead of necessary. Up to 70% of government expenditure in many developing countries is concentrated on costly technology-intensive secondary health care delivery for those in urban areas (Mills, 1990), when these resources could be more cheaply and efficiently utilised on the primary level of health care. Some developing countries have been known to use up to 20% of their budgets on a sole teaching hospital when lower level health care delivery proves less costly and more effective (Mills and Lee, 1993). Costly efforts to treat cancer are expended when little emphasis is placed on low cost, high result treatments for tuberculosis and sexually transmitted diseases. Likewise, large amounts of money is squandered on name-brand drugs instead of generic drugs, improper supervision of health workers and under utilisation of hospital beds (World Bank, 1993).

2-2:3a Urban Concentration of Health Care

Inconsistencies in the concentration of inputs for health care delivery between urban areas and rural areas are common in developing countries. These inconsistencies, for example, arise such that in urban areas, one can find the most expensive and often unnecessary diagnostic equipment, whereas in rural areas, (although high technology is not usually necessary in the presence of a good referral system) one might still be hard pressed to find a microscope or a boiler for reusable syringes. The effect is such that basic health needs are not fulfilled. Inconsistencies develop in these countries which

exhibit the use of the most modern drugs and health care facilities in some areas and a complete lack of drugs and facilities in other areas, both from a demographic and morbidity perspective. Of course, it cannot be denied that in urban areas there is a greater concentration of people using health care facilities because of those living in the area and those that travel from rural areas to urban areas. This makes treatment, in some cases, initially more cost-effective due to economies of scale with more people treated by the same health facilities and equipment. Nevertheless, rethinking the use of such expensive technological equipment when a less expensive, properly used method might suffice, should be seriously considered. Compounding this, such high levels of technology in hospitals encourage the greater utilisation by patients who perceive these facilities as 'better'. This can result in an overflow of caseload that compromises the overall level of care. This results in treatment of a random and inconstant standard. Hence, it is through careful consideration for the choice of technology that developing countries can create better health care delivery as well as influence utilisation.

Indeed, health care delivery should be relevant to both the resources and the requirements of developing countries: it should be technically suitable to the nature of the country's morbidity while being economically accessible for the country to maintain over a long period of time. As this is something that even developed countries have difficulty doing, it is no wonder that developing countries have difficulty with their more confining conditions and resources.

Such over-concentration on hospital care undermines the possibilities of treatment in a primary health care (PHC) environment. PHC interventions are under-utilised in many cases such as in the treatment of child malnutrition, child mortality, tuberculosis, prenatal care, delivery and AIDS education. This also highlights the cost-effectiveness of preventive care rather than treatment. The World Bank estimates that the majority of cost-effective interventions can be performed in primary health care settings rather than hospitals (World Bank, 1993). This is not to say that the use of primary health care is always more cost-effective than secondary care. When used prudently, hospitals have the potential to treat serious cases of disease more cost-effectively than health centres and clinics. Certainly, most clinics do not have the facility for treating life-threatening infections or open-heart surgery. The problem arises when hospitals are utilised for everything from serious AIDS complications to child delivery and the smallest cut. Used properly, primary health care should be contacted first in non-life-threatening situations and then, with the proper implementation of a referral system, those situations that clinics cannot adequately handle, should be referred to a hospital.

2-2:4 Referral

Ideally a health system in a developing country should have a hierarchy that effectively cares for its patients on its least expensive level. Primary health care (PHC) in the community can be a

manifestation of the least expensive form of health care delivery, and therefore, patients should be given the incentives to utilise this level of health care first before going to hospitals. Nevertheless, this relies on an effective referral system which often fails in its efforts to effectively deliver a patient to a higher level of health care. Due to more pressing matters, health care workers may not have the time to help patients travel to referral facilities or check to see if the patient arrived. Compounding this matter is the over-utilisation of secondary health care. Due to overcrowding, hospitals might send critical patients down to primary health care centres that often do not have the beds or facilities to care for them. On the primary level, patients might be referred to hospitals and spend the money to travel there only to be turned away from the hospital and told to come back on another day. Patient compliance to referrals also decreases as travel to a referral facility becomes more difficult.

2-2:5 Information

Developing countries suffer from an acute lack of information about the nature of their morbidity which stems from the fact that they fail to have the funds to support the necessary information network needed. Hence, disease control priorities become skewed or unknown ensuing in poor decisions. Appropriate infrastructures for the exchange of information are difficult to maintain in rural areas where transport and communication are difficult. Methods of recording information are hard to enforce and often result in incorrectly taken or incomplete information making the time and effort in taking it a waste. Likewise, such information that does become available can also be inappropriate to the decision needs of a health facility. Health care providers require appropriate information on morbidity and mortality to supply the right amount of medical tools, drugs and training to health care workers. This information comes from the correct accounts of previous amounts of supplies and expenditures as well as a continuous recording of disease patterns of patients and effectiveness of efforts in curing these diseases.

2-2:6 Utilisation

The utilisation of health care services is also an important component to the overall levels of health. Health care utilisation is a function of supply and demand: dependent on the perception of the effectiveness of a health service and the costs of the service such as the length of time for treatment, work forgone as well as the distance travelled to the service. In Peru, over sixty percent of the poor must travel over an hour to get primary health care (World Bank; 1993). Health services tend to be concentrated in urban areas allowing very little access for those living in rural areas because of the distance needed to get there. Those in rural areas seeking help must often travel through remote areas without roads and stay with friends relatives or in the street in order to get treatment. In light of this it

is not surprising that rural patients only seek medical care in cities when it is perceived as absolutely necessary and are far more likely to rely on closer pharmacies and more culturally accessible traditional healers. Similarly, education has an important impact on the perception of a health care facility and the overall demand and utilisation of it. For example, in many countries the education of females is discouraged. This has an adverse effect on health because many females ultimately become the major decision makers in families, determining family health status. It is often the women who decide diet, health care, fertility and lifestyle. Likewise, women are responsible for caring for their family's children and elderly and taking family members to health care facilities.

2-2:6 Summary of Section 2-2

With limited funds and therefore, limited health care facilities, developing countries usually choose to concentrate on treating the largest amount of individuals for its budget rather that concentrating on the quality of health care. Finding an appropriate balance between quality of care and quantity of those treated is an important element to raising health status under limited funding. Developing countries have limited choices available to them and must concentrate on those utilitarian interventions that have the most benefits for individuals, limiting concentration on those interventions which have low cost-effectiveness and a low contribution to the overall burden of disease. Unfortunately in practice, those interventions and levels of technology that developing countries choose to concentrate on do not compliment this approach. Among other things, health care systems in developing countries are crippled by poor referral systems, poor information infrastructures, poor health service coverage and therefore poor utilisation. Health status is unlikely to increase from health care services unless some efforts are made to improve these problems.

Section 2-3

MEASURING THE EFFECTS OF INFECTIOUS DISEASE ON HEALTH STATUS

This section will show the already crippling impact of infectious diseases on health status in developing countries. It shows that prominent among these diseases are bacterial diseases. These diseases are already difficult to treat for developing countries without problems of resistance to antibiotics.

In developing countries, seven million adults die per year of diseases that can be either prevented or cured (Chaulet and Zidouni, 1993). Child Mortality rates in developing countries are ten times higher than in industrialised countries, and indeed, if these rates were reduced to industrialised child mortality levels, there would be 11 million fewer deaths of children per year. Maternal mortality is thirty times higher than those of established market economies, 2 million of these deaths come from tuberculosis (Chaulet and Zidouni, 1993).

Table 2-4: Main Cause of Disease Burden in Children and Adults in Demographically Developing Countries in 1990

Disease and Injuries	Number Affected (million)	Main Intervention
Children		
Respiratory Infections	98	Integrated Management of the Sick Child (MSC)
Perinatal Morbidity and Mortality	96	Prenatal Delivery Care and Family Planning
Diarrhoeal Disease	92	ORS (Oral Rehydration Solution)
Childhood Cluster (diseases preventable through immunisation)	65	Expanded Programme on Immunisation (EPI)
Congenital Malformation	35	Surgical Operations
Malaria	31	Drug Treatment/Possible Vaccines
Intestinal Helminths	17	School Health Programme
Protein-energy Malnutrition	12	Expanded Education and Nutrition Aids
Vitamin-A Deficiency	12	EPI Plus
Iodine Deficiency	9	Iodine Supplementation
TOTAL	467	
Adults		
Sexually Transmitted Diseases	49.2	Condom Subsidy plus IEC
Tuberculosis	36.6	Short-Course Chemotherapy
Cerebrovascular disease	31.7	Case Management
Maternal Morbidity and Mortality	28.1	Prenatal and Delivery Care
Ischaemic Heart Disease	24.9	Tobacco Control Programme
Chronic Obstructive Pulmonary Disease	23.4	Tobacco Control Programme
Motor Vehicle Accidents	18.4	Alcohol control Programme
Depressive Disorders	15.7	Case Management
Per- Endo- and Myocarditis and Cardiomyopathy	12.4	Case Management
Homicide and Violence	12.2	Alcohol Control Programme
TOTAL	252.6	

Adapted from: Bobadilla *et al.*, 1994

It is projected that AIDS in developing countries will be responsible for 1.8 million deaths per year by the year 2000. Deaths due to malaria and resistant malaria is expected to double to account for 2 million per year in the next decade. The concentration of morbidity patterns is primarily determined by infectious disease and malnutrition. This is shown in Table 2-4 by Bobadilla *et al.,* (1994).

2-3:1 Comparing Epidemiological Disease Patterns between Industrialised and Developing Countries

Mortality rates in developing countries are alarming. A large percentage of these represent avoidable deaths from infectious diseases which can be cured. One only has to look at global causes of death to observe the large polarisation between industrialised and developing countries. Industrialised countries' death rates are dominated by non-communicable diseases and chronic diseases, whereas developing countries' death rates are primarily determined by communicable diseases. Lopez (1993) charts the causes of death according to disease categories which can be seen in Table 2-5. In all cases, the incidence of death from communicable diseases greatly outweighs that experienced in industrialised countries. Prominent differences in death rates are especially articulated in the total 504 000 deaths from parasitic diseases in industrialised countries compared to 17 000 000 deaths from parasitic diseases in developing countries.

Table 2-5: A Comparison of Causes of Death Between Developing Countries and Industrialised Countries, 1985 (in thousands)

Cause of Death	Total Industrialised Market Economies	Total Industrialised Non-Market Economies	Latin America and the Caribbean	Sub-Saharan Africa	Middle East & North Africa	Asia	Total Developing Countries
Infectious and Parasitic Diseases	308	198	900	4500	2 400	9 200	17 000
Acute Respiratory Infections	241	126	-	-	-	-	-
Tuberculosis	13	27	-	-	-	-	-
Neoplasms	1 607	687	300	250	200	1 750	2 500
Circulatory and Certain Degenerative diseases	3 455	2 475	900	650	550	4 400	6 500
Ischaemic Heart Disease	1 325	1 067	-	-	-	-	-
Cerebrovascular Disease	801	703	-	-	-	-	-
Diabetes	121	33	-	-	-	-	-
Complications of Pregnancy	1	3	35	125	80	260	500
Perinatal Conditions	42	58	300	680	420	1 800	3 200
Chronic Obstructive Lung Diseases	254	131	90	60	50	2 100	2 300
Injury and Poisoning	431	341	-	-	-	-	-
Ill-defined/External Causes	182	65	250	350	200	1 600	24 00
All Other Causes	535	272	425	585	400	2 090	3 500
Total	6 815	4 230	3 200	7 200	4 300	23 200	37 900

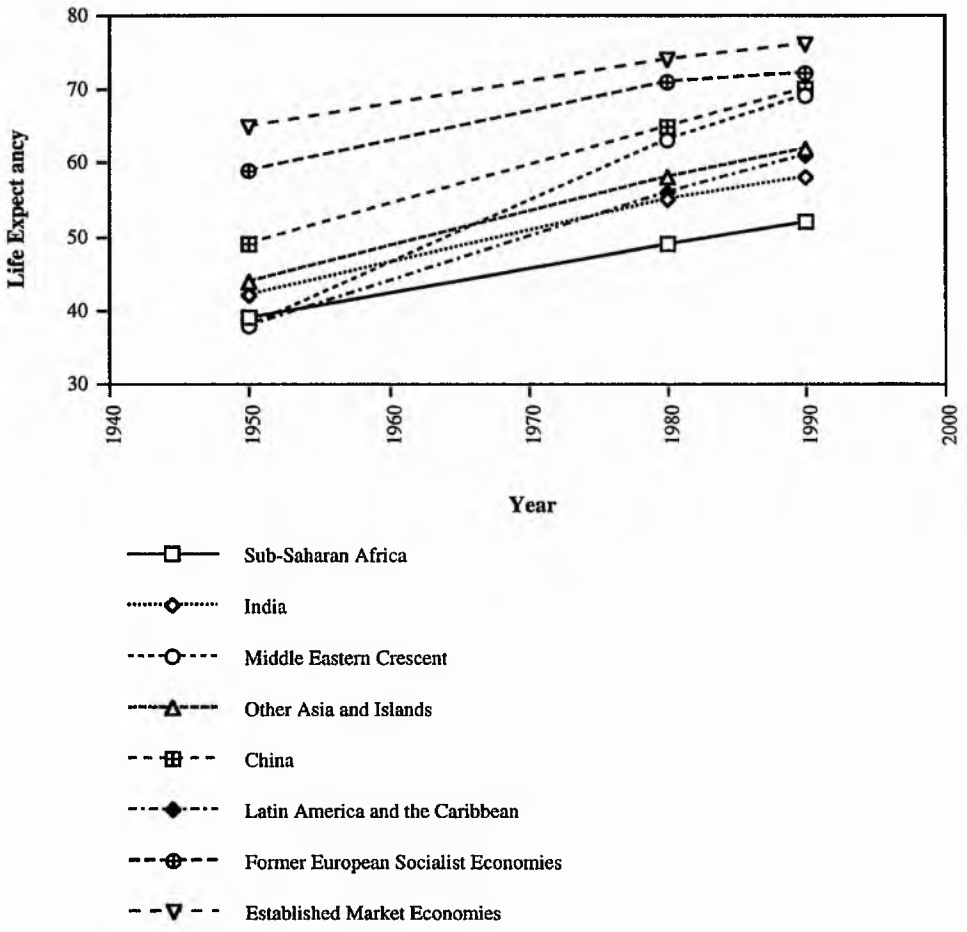
Adapted From: Lopez, 1993

Additionally striking, is the 100 000 industrial death rate from perionatal illnesses compared to 32 000 000 for developing countries; and the 4 000 industrial death rate from pregnancy complications compared to 500 000 in developing countries. Lopez concludes that unlike industrialised countries, in

developing countries, child and infant deaths account for 50-60% of total death rates. He observes that malaria, in some areas, can be responsible for the highest cause of death in children.

Although infectious diseases are the primary determinants of death rates in developing countries, it should be noted that non-communicable diseases and chronic disease are on the rise due to changes in lifestyle of sections of populations.

Figure 2-4: Life Expectancy Growth from 1950-1990 in Various Regions



Source: World Bank Data, 1993

Lopez observes that in some developing countries, chronic diseases are accountable for a higher and higher proportion of death rates. He remarks that the proportion of cancer deaths in developing countries is equal to those in industrialised countries and that other chronic diseases account for nine million other deaths. This is partially attributed to behavioural changes in developing countries such as greater numbers of the population engaging in smoking. It is estimated that the death toll from smoking-related illnesses will rise to 6-8 million in the next thirty years. A large proportion of these

deaths will occur in China, where smoking of manufactured cigarettes is becoming more and more popular.

Death rates and morbidity are all higher in developing countries due to poor living conditions, environment, poverty and to some extent, poor health care. World Bank data, as illustrated in Figure 2-4, show the rise in life expectancy rates according to area. All countries have experienced rises in their life expectancies from 1950. However, sub-Saharan Africa and India have the lowest average life expectancy of around 50-55 years. In contrast, established market economies and former socialist economies of Europe have the highest life expectancies, ranging at around 70-78 years.

2-3:2 Summary of Section 2-3

Infectious disease has devastating effects on the health status of those in developing countries. Environmental conditions such as poor sanitation, poor disease control and ignorance allow infectious disease to quickly spread. Undoubtedly, infectious disease is the prime determinant of epidemiological morbidity patterns in developing countries. A comparison between infections in industrialised countries and developing countries suggest a vast polarisation between incidence which is likely to be the result of different environments and intensity of health care interventions. Communicable diseases are undoubtedly a strong determinant of disease patterns in developing countries, but this will soon be compounded by rising incidences of non-communicable and chronic diseases.

Section 2-4

SETTING PRIORITIES IN HEALTH CARE

This section analyses the process of defining priorities in health care. It critically assesses one approach to this supported by the World Bank (the DALY). From this section, it is shown how tuberculosis and other bacterial diseases are perceived as strong targets for health care interventions.

Recent efforts in immunisation have saved 3 million lives a year and the Expanded Programme on Immunisation (EPI) protects 80% of children in developing countries against six major diseases for only 1.4 billion each year (World Bank, 1993). These were goals which were accomplished by placing them on the top of health care priorities. For instance, goals for the end of this century, according to the World Bank, suggest the following "Implementation of the public health and essential clinical care packages, pursuit of economic growth strategies that reduce poverty, and increased investment in schooling for girls would have the largest payoffs in averting deaths and reducing disability." and "Scaling back public spending for tertiary care facilities, specialist training, and clinical care with lower cost-effectiveness would help to increase the effectiveness of health spending." (World Bank, 1993: p.13). Prioritising health needs is undoubtedly difficult and there is always a question of whether these priorities are correct. Because of inadequate funding for health care in developing countries, it is important to purchase the health interventions that will result in the highest levels of health for the meagre funds available. It might even be argued that failure to minimise opportunity costs of health care expenditure in developing countries has a much stronger impact in terms of lives lost, than this failure would have in industrialised countries.

2-4:1 DALYs

There are several tools that evaluate health interventions. These can assess, for instance, the number of deaths averted, years of potential life lost, risk trade-offs, quantity-of-life trade-offs, cost and quality per life year gained from an intervention and costs per cures. One of the more recent applications of this, specifically targeted at developing countries, is the disability adjusted life year or the DALY, developed by Christopher Murray for the World Bank. This is a measure that was specifically developed to measure years of life lost from death and disability contributing to the global burden of disease (*World Development Report,* 1993). This measure avoids the difficulties associated with assigning a dollar amount to human life, only to undergo the problems of valuing it with a less tangible unit.

The DALY, similar to the QALY (quality adjusted life year) is defined by Jamison as "the number of years between the age at which a death would have occurred and the individual's expected

age at death, given survival to the given age, with years gained in future years discounted back to the present at a discount rate of 3 percent per annum..." (Jamison, 1993: p. 8). What this essentially means is that a DALY attempts to capture the impact of total years lived with a disease from its onset and the total years lost if a disease causes premature death. Years lived with a disability are calculated by assigning a weight to measure the level of disability experienced each year, and this is subtracted from either premature death or the time when the illness subsides. The level of disability from a disease is adjusted for DALYs according to a weighing process. So, for instance, a health intervention to treat malaria might render weights reflecting greater levels of disability than an intervention which treats arthritis. Premature death is calculated by subtracting the age of premature death from the natural potential life expectancy without the disease. Premature years of life lost are added to the number of disability life years from living with a disease and the sum of these are the DALYs per individual. In some cases there will only be disability adjusted life years and not premature death, but this still contributes to the overall burden of disease. These DALYs are then discounted at a rate of 3 percent so that their value can be assessed in the present time.

2-4:2 The Technical Basis for DALYs

The technical basis behind DALYs was developed by Murray (1994a). His final formula for DALY calculation includes several variables of years of life lost, an age weight function, disability weighting and time preference. Years of life lost were calculated by using the standard expected years of life lost method (elaborated in Chapter 7), which is calculated from the formula

$$\sum_{x=0}^{x=l} d_x e_x^*$$

Where

d_x = death at age x

In this case, e_x is calculated from the model life table West Level 26 (See Chapter 7) which sets life expectancy for women at 82.5 years and life expectancy for men at 80 years. Life expectancy is set at the highest average observed age in industrialised countries. Murray chooses to use this calculation of the years of life lost due to premature death because it reflects a more egalitarian measure over countries and will still measure years of life lost at ages above the average life expectancy. Murray argues that this was necessary because it standardises the years of life lost over all countries in order to measure the overall burden of disease in like terms from country to country.

2-4:2a Age-Weighting

In order to portray the value of years lost at different ages, Murray uses an age-weighting function, a variation of the human capital approach, in an attempt to represent the social contribution that changes at different stages of an individual's life. Like the human capital approach in valuing an individual's labour and earnings as his or her economic contribution to society, unequal age weights try to capture different social contributions of individuals at different stages in their life. Economic productivity for each year of life was not used to calculate DALYs because of inherent inequities of this approach. Instead, Murray used social contribution, which is different for individuals at different ages. Although each individual may not have the same level of productivity in their life, he or she can hope to be a part of every age group subsequently engaging in those social contributions associated with each group.

To capture these age-weights, Murray used a modified Delphi method which derives estimates from a panel of 'public health experts'. The Delphi technique can be inconsistent because it relies on estimation with a great likelihood of error. This is interesting because the potential for error, even for a panel of health experts in calculating weights is likely to be high. Because a panel of individuals agree on a particular weight or probability, does not mean that weight or probability is a predictor of what really occurs. These problems in the age-weight make the DALY a more arbitrary measure.

The DALY's age-weighing is captured in a continuous age-weight function in the formula.

$$Weight(x) = Cxe^{-\beta x}$$

Where

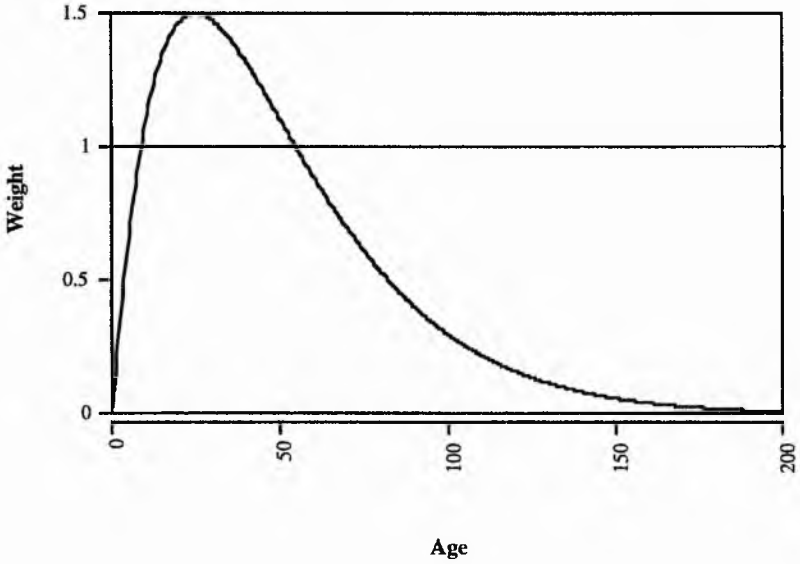
C = a constant equal to 0.16243

β = a constant for age patterns using the value 0.04

x = age

The age-weight function is shown in Figure 2-5. In this figure, it can be observed that ß is used in order to dictate the age pattern so that 1/ß is the maximum weight. This means that if ß is equal to 0.04, 1/0.04 will make the maximum weight in this function at 25 years. C is used in order to make sure that the overall estimated sum of global burden of disease is not changed from what it would be using uniform age weights. From looking at Figure 2-5, this means that the area underneath the curve using these age weights is adjusted by C so that it is equal to the area underneath the uniform weight curve (the straight line where weight=1).

Figure 2-5: The Age-Weight Function



2-4:2b Disability Weighting

In order to measure disability, six classes of disability were formulated between perfect health and death. Classes were formed to reflect greater and greater degrees of welfare loss. A disability in the same class might be experienced in different ways and impede different functions, but their total effect on the individuals is estimated to be the same. Disabilities in each class have the same impact on individuals regardless of economic standing.

Table 2-6: Definitions for Disability Weighting

Class	Description	Weight
Class 1	Limited Ability to perform at least one activity in one of the following areas: recreation, education, procreation or occupation	0.096
Class 2	Limited ability to perform most activities in one of the following areas: recreation, education, procreation or occupation	0.220
Class 3	Limited ability to perform activities in two or more of the following areas: recreation, education, procreation or occupation	0.400
Class 4	Limited ability to perform most activities in all of the following areas: recreation, education, procreation or occupation	0.600
Class 5	Needs assistance with instrumental activities of daily living such as meal preparation, shopping or housework	0.810
Class 6	Needs assistance with activities of daily living such as eating, personal hygiene or toilet use	0.920

These disability weights can be observed in Table 2-6. Limited ability was defined by Murray as 50% or greater in decreased ability. The severity of a disability for each class is exogenous to the time it was anticipated to last. In essence, disability experienced by individuals who perceived their condition

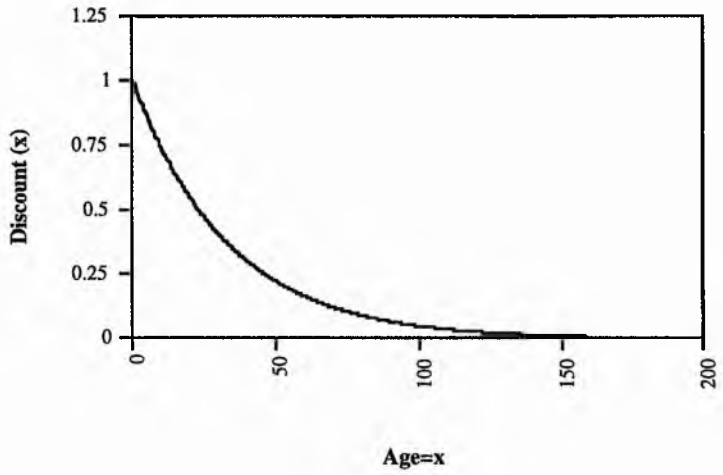
to be temporary were equal to that experienced by individuals who perceived their condition to be permanent. Hence, disability duration and severity are independent. Preferences for different disabilities were chosen by a panel of experts using a Delphi method. This is usually a method chosen because of the fact that there is not available evidence from literature, clinical or naturalistic trials.
To find these preferences, Murray had a choice of rating scales, magnitude estimation, time trade-off, person trade-off or standard gamble. Magnitude estimation was chosen (whereby individuals are asked direct questions about the comparative value of time endured in one state over another). Weights were chosen on the basis of word definitions and a set of disabling sequalae (fixed examples of what it might be like to experience various forms of a disability in a class) for each class. For every class, a number between 0 (death) and 1 (perfect health) was chosen. These numbers were averaged and appear in Table 2-6. The time of those who lived in these classes with a disability is multiplied by the class's associated weight in order to make it comparable to years lost due to premature death.

As stated earlier, DALYs attempt to measure the level of utility gained from health interventions. Derivation of utility weights is still a very controversial area. In looking at the sensitivity of his disability weights, Murray admits that the data are quite sensitive to changes within some of the weight classes. It would make little impact for classes 1 and 2 if weights changed 0.1, but in classes 3 to 6, a change as little as 0.05 has a significant impact on the final DALY calculation. Indeed, the varying of time and those questioned, depending on whether they have only observed a condition or actually experienced it, influences their answer. The external validity of these estimates are difficult to maintain and answers might change if the sample were made of different individuals. These answers might also be affected if the same individuals were asked the same questions again at a different time. This technique can be inconsistent because it relies on estimation with a great likelihood of error. This in turn will effect the derivation of DALYs making their use as a tool less accurate.

2-4:2c Time Preference

The amount of life lost due to premature mortality was discounted in order to reflect time preferences. Time preference essentially refers to the fact that individuals would rather experience a benefit in the current time period and a cost in a later time period (this is elaborated in greater detail in Chapter 7). This formula uses a continuous discounting function of $Discount(x,r)=e^{-r(x-a)}$ rather than a discrete discounting function, but this choice is likely to make little difference in the final value. The discounting function is shown in Figure 2-6 for a disability that starts at birth. Here it can be seen that if the individual lives, for example, to 50 with a disability, total disability years are multiplied by 0.2231. In effect, this means that because these years are experienced in the future, the years are only worth 11.15 years in the present (11.15 =(50)(0.2231)).

Figure 2-6: Discount Function for DALYs



The decision of having a discount rate automatically integrated into this measure limits the user. The choice of discount rate can no longer be made and is fixed at 3%. In addition, the actual measure itself becomes misleading because observers may not be aware of the fact that the measure has already been discounted. It is possible that evidence will arise which will not only justify the use of a different discount rate, but require it, making this measure invalid. Many use a discount rate of 10%, 6% or 5% and this can vary even more in some cases (Parsonage and Neuburger, 1992; Coyle and Tolley, 1992; Cairns, 1994). Murray does not adequately justify why he chose to use 3%, or why he chose to make it an endogenous part of the DALY.

Discounting is generally an accepted method of expressing the preference for benefits in the current time period. One problem of discounting DALYs is that it gives interventions affecting current generations preference over those affecting future generations. So, for instance, future generations might benefit from more education on smoking whereby there will be fewer low birth rates for future babies, but since the benefits of such actions are so far in the future they would be secondary to such programmes where benefits were immediate (Parsonage and Neuburger, 1992). This is very important because one of the interesting things that Murray is trying to illustrate is the effect of DALYs on the incidence of infectious disease, which indeed, has long term future effects on both the current and future generations. (Lower discount rates will highlight the effect of the programmes where benefits are experienced in the future) Another problem is with the choice of a discount rate. With lower discount rates there is an accompanied reduction in the cost per DALY rating. This is not an attack on discounting: it is a necessary element of most economic analyses where benefits are experienced in the

future. Nevertheless, the possible influences of discounting on results must nevertheless be considered, and with a discount rate automatically placed in the DALY calculation, there leaves little choice for these.

Parsonage and Neuburger (1992) maintain that non-monetary benefits such as the QALY (and DALY) should not be discounted. This is because, assuming that the welfare associated with them are autonomous to income, arguments relating to income (such as the argument that as society becomes more affluent, there is diminishing marginal utility to each pound) do not apply to non-monetary benefits such as the QALY or DALY (See Chapter 6 for a description of arguments for discounting). In fact the relationship between the value of non-monetary benefits does not appear to change with changes in income in different time periods. Parsonage and Neuburger go on to suggest that although more research is necessary, private discount rates referring to the 'pure' time preference, independent of income, is zero or negative. By automatically placing discounting in the formulation of DALYs, Murray has rendered them inflexible, especially when there is the argument that this kind of non-monetary benefit should not be discounted.

2-4:2d The DALY Formula

Time preference, age weighting, years of life lost due to premature mortality and disability weights are all placed into a formula to reflect the years lost from premature death and years lost from living with a disability. This is shown in the formula below

$$DALYs\ Lost(x) = \int_{x=a}^{x=a+L} DCxe^{-\beta x}e^{-r(x-a)}dx$$

Where

a = onset of the disability

L= duration of disability or time lost due to premature mortality

r = the discount rate (0.03)

C = age weighting correction constant (equal to 0.16243)

β = parameter from the age-weighting function (using the value 0.04)

D = disability weight (1 for premature mortality)

The solution for this integral is

$$DALYs\ Lost = -\left[\frac{DCe^{-\beta a}}{(\beta+r)^2}\left[e^{-(\beta+r)(L)}\left(1+(\beta+r)(L+a)\right)-\left(1+(\beta+r)a\right)\right]\right]$$

This function is graphed in Figure 2-7. Figure 2-7 shows that the most DALYs that an individual can lose from premature death from a disease occurs at age 10 and is equal to 36.86 DALYs for females and 36.71 DALYs for males. After age 10, DALYs lost due to premature death logically decrease as the age of death increases.

Figure 2-7: Total Female and Male DALYs Lost Due to Premature Death at Each Age

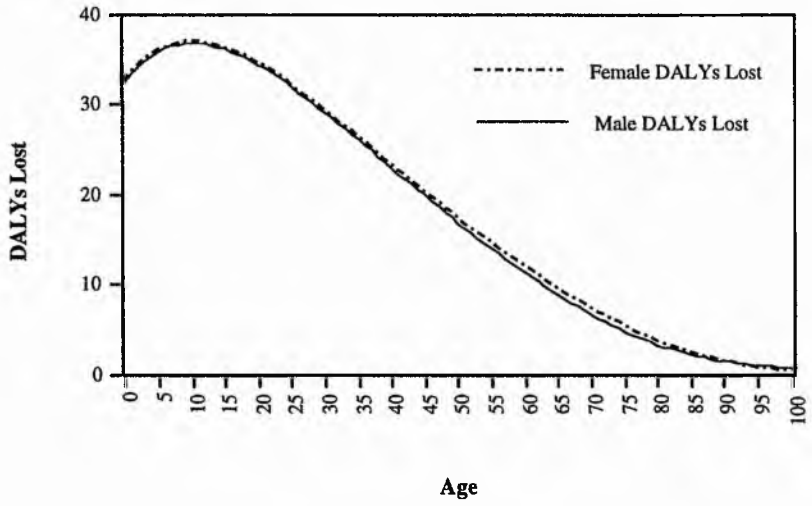
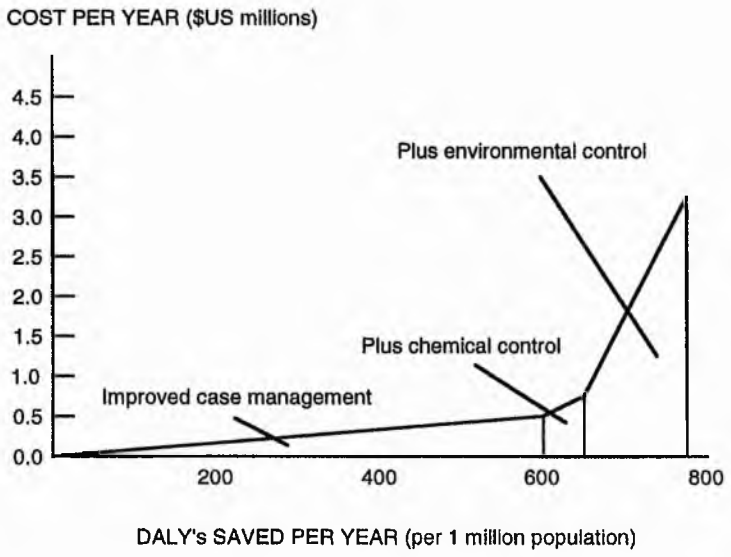


Figure 2-8: Estimated Cost per DALY for More Complete Dengue Control*



Source: Shepard and Halstead, 1993
*It should be noted that these figures are estimates which depend on the case mortality as well as other variables in the rate of infection and disease virulence.

DALYs like QALYs do not measure the full benefit of health care: they do not take into account the value of health care to patient's relatives, the value of the information provided by doctors, and the elimination of the burden of decision-making in the choice of health intervention (Gerard and Mooney, 1993). This is one reason why those observations based on DALYs should not be used without other information in making a decision.

The World Bank has accepted DALYs as a tool for making health resource allocation decisions. It must be remembered that DALYs are based on a vast number of assumptions and depend on data in developing countries, which are unreliable. DALY conclusions have been used to justify some of the previous contentions in primary health care. There is a tendency to take DALY conclusions at face value (possibly by those who do not understand the measure). The goal of making a definitive standardised measure has, in effect, compromised the DALY. The DALY was designed as such a general measure for so many different situations, diseases and countries, that its conclusions have lessened validity than if it were designed for one situation.

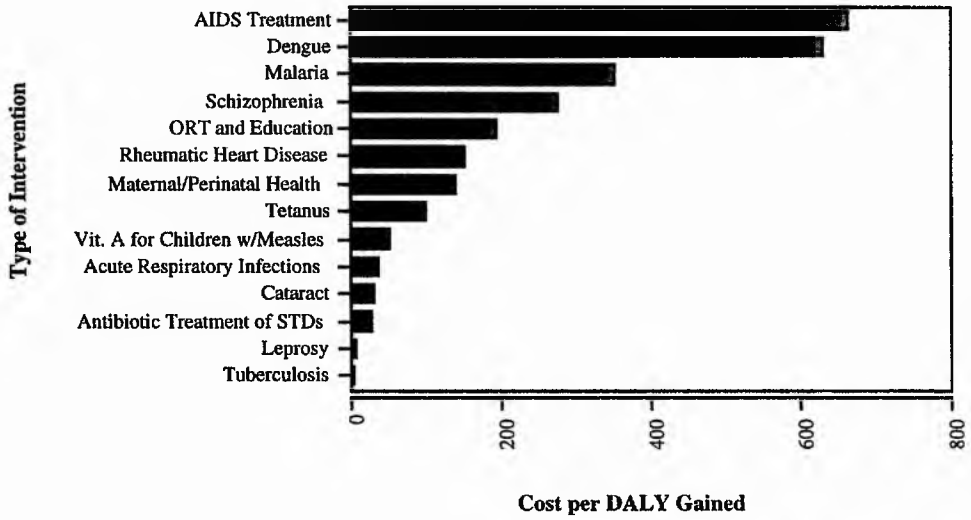
2-4:3 The Application of DALYs for the Optimisation of Health Funding

Health interventions can be evaluated according to the number of DALYs they save as well as their dollar cost per DALY gained. DALYs have been used to measure global disease burdens for

over 100 diseases in eight regions for five age groups of males and females. Through this measure, there have been attempts to show the impact and cost-effectiveness of efforts to more comprehensively contain diseases. For instance, according to Shepard and Halstead, (1993) the containment of dengue, a fever type of illness spread by mosquitoes, has a comparatively low cost per year when looking at case management, but this increases with the use of chemical vector control and then rapidly increases with the implementation of environmental control as is illustrated in Figure 2-8.

It should be noted that some communicable diseases have the potential to be less expensive per DALY saved than non-communicable disease interventions. This is simply because often the treatment of communicable diseases proves to be much cheaper with more significant results. This is especially true when quick and effective treatment such as antibiotics and antimicrobials can be applied (of course it should be noted that this is not always the case, as for instance, given the example of AIDS). Comparing costs per DALY saved across various medical conditions, one can see which interventions for conditions are highly effective per DALY and which are not, as seen in Figure 2-9. This cannot be construed as a complete priority list for disease control but may lend perspective in estimating which diseases require more concentration for control. For example, in looking at Figure 2-9, if tuberculosis chemotherapy is inexpensive to cure by chemotherapy but more efforts are targeted to AIDS treatment, perhaps more attention should be given to the former.

Figure 2-9: Cost Effectiveness of Clinical Interventions for Various Diseases in Developing Countries*



Adapted From: Jamison, 1993
*Figures are averages and are dependent on Case Fatality and Risk of Infection

Indeed, the analysis of DALYs point to the fact that less consideration should be given to those treatments that are not cost-effective. This also applies to concentration on those treatments that are effective but expensive. Also, the ultimate effect of a treatment should be considered. Given two health care interventions and a limited budget, one intervention might be slightly more cost-effective than the other, but the less cost-effective measure might serve to save far more lives for that fixed budget, making it the better choice even though it is more costly in DALY terms. It is possible when dealing with fixed budgets that more individuals can be treated for a less costly but less cost-effective treatment than treatment with a more costly, but more cost-effective treatment. This goes back to the previously mentioned quality versus quantity trade-off.

2-4:4 Creating National Health Care Packages to Reduce the Burden of Disease

Each country must decide what priority it will place on health. Diseases can have a strong burden on the productivity of a state and therefore, increasing health is a great priority for all countries. Following this goal, the approach to increasing health output can obviously vary in effectiveness. For example, Murray, Kreuser and Whang (1994) observe that a model that integrates the expansion of a health care infrastructure will save 40% more DALYs than a health care system that ignores the expansion of its infrastructure. The intensity of expenditure on different programmes to achieve goals must also be carefully considered to optimise existing funds. Developing countries spend very little on health care, but comprehensive packages for decreasing the incidence of disease are within their means. Bobadilla *et al.*, (1994) observe that the primary causes of disease burden could be cost-effectively treated for US $12 per person in low income countries and US $22 per person in middle income countries. The authors estimate that these interventions, when applied according to these packages, could reduce the global disease burden by 21-38% in children under 15 and 10-18% in adults. Interventions, their relative cost per DALY and their cost per capita are depicted in Table 2-7. According to Bobadilla *et al.*, the $12 per capita expenditure would require one district hospital bed per 1000 population, 0.1 physicians per 1000 population and 2-4 nurses per physician.

These estimates of US $12 per person for low income countries and US $22 per person for middle income countries, although highly attractive on paper, are unlikely to be instigated by developing countries in the near future. It is likely that middle income countries will adopt the US $12 package and the low income countries will continue to struggle with what they have. Low income countries, who often struggle to spend even US $1 dollar per capita with health service coverage as low as 60%, are unlikely to be able to apply such a US $12 package for many years to come. Nevertheless, Bobadilla *et al.* provide an interesting goal to work towards that countries might be able to achieve if health were one of their highest priorities.

Table 2-7: Cost-Effectiveness of the Health Interventions (and clusters of intervention) Included in the Minimum package of Health Services in Low- and Middle-income Countries

Intervention	Cost per Beneficiary	Cost per Capita	DALYs Potentially Gained (per 1000 population)[a]	Effectiveness[b]	Cost per DALY ($US)
Low Income Countries					
I. Public Health					
Expanded Programme of Immunisation Plus[c]	14.6	0.5	45	0.77	12-17
School Health Programme	3.6	0.3	4	0.58	20-25
Tobacco and Alcohol Control Programme	0.3	0.3	12	0.14	35-55
AIDS Prevention Programme[d]	112.2	1.7	35	0.58	3-5
Other Public Health Interventions	2.4	1.4	-	-	-
Subtotal	-	4.2	-	-	14
II. Clinical Services					
Chemotherapy Against Tuberculosis	500.0	0.6	34	0.51	3-5
Integrated Management of the Sick Child	9.0	1.6	184	0.25	30-50
Family Planning	12.0	0.9	7	0.70	20-30
STD Treatment	11.0	0.2	26	0.42	1-3
Prenatal and Delivery Care	90.0	3.8	57	0.42	30-50
Limited Care[f]	6.0	0.7	-	0.03	200-300
Subtotal	-	7.8	-	-	-
Total		12.0			
Middle Income Countries					
I. Public Health					
Expanded Programme of Immunisation Plus[c]	28.6	0.8	4	0.77	25-30
School Health Programme	6.5	0.6	5	0.58	38-43
Tobacco and Alcohol control Programme	0.3	0.3	9	0.14	45-55
AIDS Prevention Programme[d]	132.3	2.0	15	0.58	13-18
Other Public Health Interventions	5.2	3.1	-	-	-
Subtotal	-	6.9	-	-	-
II. Clinical Services					
Chemotherapy Against Tuberculosis	275.0	0.2	6	0.51	5-7
Integrated Management of the Sick Child	8.0	1.1	21	0.25	50-100
Family Planning	20.0	2.2	6	0.70	100-150
STD Treatment	18.0	0.3	3.7	0.42	10-15
Prenatal and Delivery Care	255.0	8.8	25	0.42	60-110
Limited Care[f]	13.0	2.1	-	0.03	400-600
Subtotal	-	14.7	-	-	133
Total		21.5			

Source: Bobadilla *et al.*, 1994

[a] Sum of Losses to Premature Mortality and to Disability, including losses to others because of secondary transmission of disease

[b] calculated by multiplying efficacy, diagnostic accuracy (when applicable) and compliance

[c] Plus refers to the vaccine against hepatitis B and Vitamin A supplementation

[d] DALYs lost from AIDS include dynamic effects (probability of transmission to others) only in the first year, which understates the value of prevention cases and thus the cost-effectiveness of preventive interventions

[e] Includes information, communication, and education on selected risk factors and health behaviours, plus vector control and disease surveillance

[f] Includes treatment of infection and minor trauma; for more complicated conditions, includes diagnosis, advice and pain relief, and treatment as resources permit. (Bobadilla *et al.*, 1994: p. 657)

2-4:5 Summary of Section 2-4

The concentration of health care interventions in order to procure the largest rises in health status per unit expenditure is a challenge for all countries. Up until recently, there was no large measure of utility from a health care intervention specific to developing countries. DALYs, developed by Murray

in conjunction with the WHO and the World Bank, is one standardised method for the measurement of disability and premature mortality saved per dollar for a given intervention. It is through this method that attempts are made to compare different interventions on the same scale. This measure has generated considerable literature on the appropriate concentrations of health interventions and possible health care packages per capita expenditure on health. Nevertheless, conclusions from DALYs must be carefully considered because of inherent errors in the measure and external factors to which DALYs fail to take into account.

Section 2-5

CONCLUSION TO CHAPTER TWO

Infectious disease in developing countries drives mortality and morbidity to appalling rates, considering a large majority of infectious diseases are curable. Health status in developing countries is continually threatened by unsanitary living conditions, malnutrition, political problems, environmental problems, poor education and meagre funding. Developing a health care system on a limited budget that will care for the health-damaging results of these living conditions is one of the greatest challenges in health care delivery today. Current health programmes in developing countries have flawed infrastructures and a concentration on inappropriate interventions. Because of high associated opportunity costs for inappropriate health interventions, developing countries need to prioritise their health demands in order to meet those that are more pressing. Prioritising tools, such as the DALY, are part of a greater strategy in optimising the concentration on health care interventions. With the development of systematic economic methodologies for health care intervention prioritisation, it is possible that developing countries will be more able to facilitate the formulation of effective health policies. One target for greater economic analysis and a potential for better management is the area of pharmaceuticals, as is shown in the following chapter.

CHAPTER THREE
THE UTILISATION AND CONTROL OF DRUGS IN DEVELOPING COUNTRIES

To find the impact of resistance on the cost of tuberculosis treatment in developing countries, it is important to show the context in which drugs, including antibiotics, are utilised, managed, marketed and regulated. This chapter analyses the role that pharmaceuticals play in developing countries, tracing their use and abuse and concentrating on those elements that may impede their potential as a comparatively inexpensive and effective health care intervention. Drug management and control will later be discussed within the context of tuberculosis treatment and tuberculosis drug resistance.

In developing countries, drug usage in the past could be described as chaotic at its best. These countries' lack of control of drugs and their marketing has sadly resulted in a great and unnecessary loss of life. Nevertheless, changes in behaviour and attitudes are allowing for an improvement in this much needed remedy, although there is still a significant area left for improvement. There are many drugs available to cure infectious diseases which are predominant in developing countries, but this relies on these drugs' controlled accessibility, rationalisation of their use as well as a genuine interest in the social welfare of those individuals affected. Section 3-1 describes the impediments to correct drug usage in developing countries. Section 3-2 assesses attempts to better regulate drugs with the Essential Drugs Programme and the Bamako initiative. Section 3-3 looks at the influence of the actions of pharmaceutical producers and how they have affected drug utilisation in developing countries.

Introduction

In November 1935, a little girl named Hildegard unexpectedly pricked herself with an embroidery needle in the soft web of muscle between her thumb and first finger. Shortly after this, the wound became badly infected with streptococcus which spread up her arm in red flares. Her glands

under her armpit became swollen and she was admitted to the hospital for urgent treatment. Current treatment at that time was solely surgical and this girl was given fourteen lancing operations, all having no effect. Some days later, her glands became filled with pus, she developed a temperature of 39°C and her infection became blood-borne. The surgeon in charge wanted to amputate her arm in an attempt to save her life, nevertheless, another doctor suggested an alternative. He treated Hildegard with a new drug, Prontosil, and in only two days, her temperature had became normal. After repeated doses, she recovered completely *without amputation.* (Ryan, 1992).

The above story illustrates the dramatic effect that drugs can have in the treatment of disease. Many other health interventions pale in comparison, often leaving a patient drastically changed in appearance and well-being. In contrast, drugs have the potential to quickly treat a disease, restoring a patient back to health, with few unpleasant side effects. Modern drugs have revolutionised health care delivery. Compared to other procedures, modern drug therapy is relatively new, but is widely depended on for the treatment of most major diseases. In comparing drugs to surgery, drugs are also much safer. Although surgery is now considered a last resort, in many cases before drug treatment, it was considered the first and only resort. When considering treatment for a critical condition, given the choice between equally effective surgical and drug treatments, a drug treatment will almost always be chosen by doctors as it is assumed to be safer when compared to surgery, which is viewed as quite risky. Deaths in Britain from surgery are an estimated 10 times higher than deaths from drugs (Smith and Quelch, 1991). Also, surgery often requires a highly paid specialist to perform it, invasive procedures, sedatives, anaesthetics, close monitoring of the patient during and after surgery and even long hospital recovery time. What surgery requires is more frequently absent from drug therapy, making drug therapy both a more effective and less costly alternative in a monetary sense and in terms of a patient's time and productivity. With drug treatment, the patient can often spend more time as a productive member of society rather than spending that time recuperating from his or her condition. Additional savings come from the fact that large amounts of manpower are not needed for the administration of most drugs unlike the majority of other health care interventions. Pharmaceuticals are less labour intensive and hence, are of greater value where labour is an expensive component of health care delivery. Indeed, in many countries, drugs encompasses only 10-15% of all health care costs (Smith and Quelch, 1991). A concise example comes from examining antibiotics, which in many cases, are undoubtedly the most efficient method of treating bacterial infections. The majority of them are inexpensive, easily administered, very effective and involve fewer complications than surgery. Where drugs cannot be used to cure major diseases, intervention is comparatively clumsy and costly in terms of the funds spent by the provider, the labour and equipment, and patient's time and discomfort. In 1989, for instance, in comparing the cost of drug treatment to the cost of surgery for ulcers, the cost

of ranitidine treatment for one month was approximately US $59.11 whereas the cost of surgery itself was US $7 777.00 in the United States. This is one hundred and thirty-one times the cost of ranitidine, excluding physician services and hospitalisation (Sonnenberg, 1989). Drugs offer an ease of treatment for the doctor and health worker that few, if any, other health interventions provide. Without available drugs for treatment, health care would be very labour intensive and very expensive. Hence, pharmaceuticals play an essential role in cost-effective health care.

Despite the fact that pharmaceuticals are one of the less expensive and more effective health interventions available to health care providers they are not available in a large enough supply to meet the needs of those in developing countries. In 1988, it was estimated that 25% of the world's population consumed 80% of manufactured drugs and 75% of the population only had access to 20% of all drugs. Seven years ago, the WHO estimated that between 1.3 and 2.5 billion people around the world had little or no access to drugs (WHO, 1988).

Section 3-1

PROBLEMS OF DRUG UTILISATION IN DEVELOPING COUNTRIES

This section addresses problems in the drug utilisation in developing countries, including problems that arise from unregulated drug availability and poor education in appropriate drug uses. To assess the influence of resistance on the cost of antibiotics, the environment in which they are used in developing countries is presented. It is from this analysis of drug utilisation that it will be later shown why antibiotic resistant diseases, and namely tuberculosis drug resistance, arise in developing countries.

The nature of morbidity patterns in developing countries can be broken into four categories of diseases. Category one consists of diseases such as heart disease, cancer, AIDS, and arthritis which are experienced by both developing and industrialised countries. In contrast, category two contains those diseases specifically found in impoverished nations such as tuberculosis, tetanus, meningitis and measles. Category three is defined by diseases that have long been eliminated in developed countries such as cholera, parasites and leprosy. Lastly, category four consists of tropical diseases that do not occur in developed countries but are commonly found in developing countries, examples of these disease are malaria and schistosomiasis. In developed countries, many of these diseases have long been cured by cheap vaccines and drugs and hence, there lies the potential for these diseases to be cured quite cheaply with startling effectiveness in developing countries. Nevertheless, like many elements in developing countries, drug utilisation is complicated. Due to a lack of funds and convoluted political ideologies, health care delivery involving pharmaceuticals has been tainted in every area. At the core of this problem is the lack of government influence, control and regulation of pharmaceuticals. From this stems the inability to obtain drugs, control information about them, produce them, and finally get the correct drugs in the correct amounts to each patient.

3-1:1 Drug Availability

Governments in developing countries lack the funds to control the utilisation of drugs and resulting control efforts are often inconsistent. Many developing countries have made elaborate plans and efforts to control drugs, but have lacked the impetus to *enforce* these controls and existing regulations, allowing access to drugs to almost anyone. Notwithstanding, such a system invokes some degree of rationale. In order to work in an environment where access to doctors to write prescriptions is often costly and difficult to obtain, given the doctor to patient ratio in developing countries, access to drugs has been relaxed. If access to drugs were as difficult as in industrialised nations, only limited to doctor's prescriptions, most individuals in developing nations would never see a drug and hence, never

benefit from it. Nevertheless, this is no justification for such poor regulation: drugs available outside of the context of health care facilities have led to many problems.

The control of drugs in developing countries proves to be either ineffective or non-existent. Anyone can walk into a pharmacy and buy any drug available there or can obtain black market drugs right on the street from vendors. Drugs have a substantial market value and it is not unknown for patients who are administered drugs in public hospitals for instance, to pretend to swallow a drug and then keep it to sell it later. Those finally purchasing such drugs often know nothing about them and are victims of the influence of cultural myths, poor education, and conjectures about these drugs.

3-1:1a The Black Market

Black market drugs are available on most street corners, and they are frequented by a wide variety of people from children, to mothers and the elderly. To illustrate the profile of those buying drugs off the street, Fassin (1988) studied 10 sellers in Dakar, Senegal. In this study, 144 buyers, aged from 5-60 years with a sex ratio of 1 male to every 2 females, were observed buying drugs off the street for reasons of convenience and low cost. 77% of pharmaceuticals were bought for pain and fatigue and aspirin accounted for 58% of all drugs sold. A further 12% were tetracycline antidiarrhoeals and 7% were antimalarials (4-aminoquinolines). The authors also found that total expenditure at the 102 illegal sellers in markets was 11 times that spent by the public sector in drugs at this location. It was also observed that the closer the location of the seller to the buyer, the more regular visits the buyer would make.

3-1:1b Pharmacies

Another similar problem is found in developing countries with the sale in pharmacies of those drugs which are only available with a prescription in most industrialised countries. In contrast, in developing countries, a majority of these drugs are bought without a prescription on the recommendation of the pharmacist or are self-prescribed. Krishnaswamy, Kumar and Radhaiah's (1985) study of 10% of the 330 retail pharmaceutical stores of Hyderabad and Secunderabad showed that 51.3% of all drugs, including a large proportion of ethical drugs purchased from these stores were from a doctor's prescription, classifying 48.7% as either self-medication or from the pharmacist's recommendation. The distribution of the types of these medicines bought without a doctor's prescription was highly concentrated in analgesics and anti-inflammatories however, other medicines were also purchased. A proportion of them were undeniably prescription drugs, including antibiotics as well as those for respiratory problems and neurological disorders. Table 3-1, depicts this distribution which exhibits one example of the nature of self-medication in developing countries.

Indeed, the other more common point of purchase for drugs, the pharmacy, does not just function as a place to buy drugs, but often as the primary point of health care: the pharmacist, acting as a doctor in providing drug information. Added to this, the pharmacy has an advantage over the health care facility in that the transaction costs of receiving care are often not as costly as a health care facility and the value of the care received is perceived to be equally good. It is likely that the farther away the pharmacy is from an urban area and the more difficult access is to a health care facility, the more likely a pharmacy will take on this role.

Table 3-1 Therapeutic Classes of Drugs Purchased in Pharmacies in Hyderabad and Secunderabad

Therapeutic Class	% Self Medication	% Prescribed by Doctor
Nutritional Products	19	26.5
Sulfa and Antibiotics	9.3	15.5
Analgesics/Antipyretics Anti-inflammatories	23.8	13.0
Gastro-intestinal Disorders	11.9	9.0
Respiratory Disorders	10.8	8.3
Neurological Disorders	4.6	6.2
Cardiovascular Disorders	4.7	4.1
Hormonal Preparations	3.3	3.9
Anti-Infectives	2.7	4.2
Other	2.8	3.3
Topical Preparations	6.1	5.3
Ayurvedic Preparations	1.0	1.1

Source: Krishnaswamy, Kumar and Radhaiah 1985: p. 365

This is because the cost of travel is often prohibitive for those seeking health care, and pharmacies by virtue of their number, are often closer to the individual than a health care facility. In Thailand, for example, the ratio of physicians to population in the late eighties was 1:4 790 whereas the ratio of pharmacies to the population was 1:2 817 (Kunin, 1987). With nearly twice as many pharmacies as doctors, such ratios indicate that there is greater access to pharmacies. Another perceived advantage of using a pharmacy is that the pharmacist does not charge a consultation fee where a doctor might. Also, from a cultural perspective, pharmacists are more likely to cater to consumer needs, combining cultural beliefs with his or her recommendations of drugs. This was observed in a study performed by Bledsoe *et al.* (1988) in the Mende of Sierra Leone. They found that pharmacists dispensed pills according to colour because of the buyers' strong belief in the link between colour and effectiveness. Likewise, Kunin (1987) observed in Thailand that patients felt more at ease telling a pharmacist about embarrassing conditions such as venereal diseases. In India, Kapil (1988) observed that those commonly buying drugs range from the very poor to tradesmen and government employees. She also observed that patients more frequently use self-medication utilising a pharmacy or traditional healer before seeking medical attention from a doctor. This is supported by Logan (1988) whose study,

although based on a rather small sample size, found in 1988 that out of 48 patients living in urban areas in Mexico, 50-90% of patients used self-medication for treating illnesses. However, if an illness persisted, approximately two thirds of patients sought medical care from a physician and approximately 10% continued to use self medication.

Unfortunately, a pharmacist or pharmacy clerk is not often trained as a health care advisor the way a doctor or health personnel are, and therefore, the information he or she imparts may be more inappropriate for the patient. This polarisation between doctor and pharmacy can be even more accentuated if the person at the pharmacy dispensing pills is not a pharmacist. Although most developing countries stipulate that there be a licensed pharmacist at every pharmacy, this regulation is not adequately enforced and the pharmacist is not required to be there during business hours (Kunin, 1987). Hence, it is possible for a patient to receive drugs and advice from a clerk not even as qualified as a pharmacist, which leaves a large margin for error. A drug vendor may lack medical and pharmaceutical knowledge combined with an enthusiastic need to sell drugs. Compounding this, many who request drugs can only afford to purchase a few of them so that drugs are often separated from their original containers making their later identification difficult. Thus, the free availability of drugs serves to dilute attempts to obtain better levels of health both in the micro sense considering the patient and in macro sense considering policy planning designed for improved health.

3-1:2 Education

Lack of education is a universal problem in developing countries penetrating all areas including health care. Ignorance in health care affects patients seeking treatment, those providing it such as doctors, nurses and medical technicians, and those disseminating information such as pharmacists and drug salesmen. As is illustrated by Table 3-2, patients receive little formal education compared to those in developed countries and also have little access to informal educational media such as televisions, newspapers, magazines, and radio. Even those that can afford these do not always benefit due to its inconsistent quality in developing countries. The case is little better for health technicians, nurses and doctors, because although the majority of this group receives formal education, there is still little opportunity to update education in health due to the cost of medical periodicals. For instance, medical journals from industrialised countries are often so very expensive that a hospital library, even in an urban area, can only maintain them through exterior charitable contributions. In some countries a subscription to these journals can amount to one month of a local doctor's salary. It is because of this that the quality of education media sources are poor. Braithwaite (1984) found that Cuba's national medical library only contained literature from before the revolution. Added to this, doctors, nurses and technicians are often so much in demand due their small numbers, that there is seldom time for them to

peruse medical journals. This is especially true for those who are working in public sector hospitals and health centres. Also, drug compendia are difficult to obtain and can be of a dubious nature (see Silverman, 1982). The situation is worse for pharmacists, who lacking easy access to the large institutional libraries such as those in hospitals have even fewer opportunities to benefit from health media.

Table 3-2: Percentage of Each Age Group Enrolled in Education in Selected States*

Country	Primary Education	Secondary Education	Tertiary
Tanzania	69	5	0
Ghana	77	38	2
Pakistan	46	21	3
Madagascar	92	19	3
Bangladesh	77	19	4
Ireland	103	101	34
Canada	107	104	99
Japan	102	97	31
New Zealand	104	84	45
United States	104	90	76

Source: World Bank, 1993: p. 216-217
*Data for developed countries goes over 100% because it includes those receiving education who are not in the conventional age group for each category

Compounding this, both health personnel and pharmacists often rely on pharmaceutical salesmen (detailers) for an update in their education in drugs for health. Unfortunately, these detailers are frequently poorly trained but are still given monetary incentives to sell drugs over their regular salary (Krishnaswami, Dinesh and Radhaiah, 1985; Taylor, 1986; Kunin *et al.*, 1987; Lexchin, 1992). This can result in their often making wide-spread, biased claims about a drug that they know little about. This works together with ignorance to further taint the education of health personnel with misinformation. The results of insufficient medical education can result in an incorrect diagnosis, an incorrect treatment and commonly, an incorrect drug prescription. The ramifications of this ignorance can be serious, suggesting just how integral education is to health, as is poignantly experienced in developing countries.

3-1:3 Summary of Section 3-1

Developing countries suffer from a combination of problems in pharmaceutical utilisation which work concurrently to render drugs of dubious quality and availability. Education on drugs is poor and the availability of dangerous, useless or poor quality drugs is high. Efforts to regulate these drugs have been impotent due to a lack of available funds, higher placed priorities and in some cases, political upheaval. Less concentration should be laid on irrational drugs, which must be replaced by

appropriate drugs. Certainly, appropriate drugs need to be available at the right location, at the right time and in the correct amount. In order to rationalise their utilisation, doctors, health workers and pharmacists need to be educated on appropriate drug use. This is a process that will not occur quickly and will depend on the support of outside aid agencies, economic growth, and a greater placed emphasis on drugs in health care delivery.

Section 3-2

ATTEMPTS TO REGULATE DRUG USE, PURCHASE AND MANUFACTURE

After looking at drug utilisation, the following section illustrates more problems necessitating regulation, and then shows regulatory efforts from within developing countries and external agencies. It looks at the design of the Essential Drugs Programme and the Bamako Initiative and also shows some of the progress of these. This section is designed to show what general regulatory factors have attempted to influence appropriate drug usage, including antibiotics (the control of which is also meant to stop unnecessary antibiotic drug resistance in diseases).

Table 3-3: Drug Failures in the Past: 1930-1991

Year	Place	Problem	UK Fatality Reports 1964-1980	Result
1930s	Germany	Live tubercle bacilli given instead of BCG vaccine		72 deaths
1939	USA	Sulphanilamide elixir produced in ethylene glycol solvent		107 deaths
1950s	France	Stalinon boils remedy contained more of tin compound than used in clinical trials		102 deaths
1955	USA	Cutter polio vaccine unsafe even though passed by Laboratory Biologics Control		58 cases 5 deaths
1961	USA	Monase, a psychic energiser leads to blood disorders		7 deaths
1962	**World-wide (not USA)**	**Thalidomide hypnotic is a teratogen**	**4 000-5 000 deformed**	**10 000 deformed**
1949-1967	World-wide	Aplastic anaemia from chloramphenicol	42	
	World-wide	Aplastic anaemia from gold compounds used for arthritis	37	
1961 (warning 1967)	Britain	Formulation of isoprenaline as an aerosol led to overdose	64	4 000 deaths
1970-1976	World-wide	Beta-blocker practolol turned out to cause eye damage and sclerosing peritonitis	23	1 200-1 400 damaged
1959-	World-wide	Phenylbutazone and oxyphenbutazone caused blood dyscrasias (441 deaths) and gastric bleeding (71 deaths)	512	
1958 (warning 1969)	World-wide	Thromboembolism from oral contraceptives (pulmonary embolism 268, myocardial infarction 136)	404	
	World-wide	Gastric bleeding from non-steroid anti-inflammatories (aspirin 96; indomethacin 83; phenylbutazone see above; other 76)	285	
	World-wide	Osmosin (controlled release form of indomethacin) lodged in fold of intestine and perforated it		51 deaths
1967-80	World-wide	Nephropathy from analgesics (aspirin 44; phenacetin 105)	149	
	World-wide	Some antibiotics cause pseudo-membranous colitis (lincomycin 15; clindamycin 36; tetracyclines 2)	53	
	World-wide	Anaphylactic shock from penicillin allergy	23	
1969-1983	World-wide	Lactic acidosis from phenformin for diabetes	47	
	World-wide	Hepatic necrosis from halothane	150	
1934-1980	Japan	Myelooptivc neuropathy from clioquinol antidiarrrhoeal over sustained period	0	1 100 victims 700 deaths
1980-1982	World-wide	Benoxaprofien anti-arthritic inadequately metabolised by the elderly	76	26 in US
1990	USA	L-trytophan formulation causes eosinphiliamyalgia		1 478 ill 21 deaths

Source: Burstall and Reuben, 1990

3-2:1 Problems Necessitating Regulation

In 1958, the drug thalidomide, developed by Chemie Grunenthal and used as a hypnotic was licensed world-wide except in the United States and could be bought over the counter in Germany. In some cases it was also used to treat illness in the early stages of pregnancy. Unfortunately, alarming evidence emerged that thalidomide was a teratogen (a substance that causes birth defects) and tragically became responsible for 10 000 deformed children world-wide. As illustrated in Table 3-3, although there had been side effects to drugs previously to this, there had never been one that caused such visible and wide-scale damage. Such damage brought intense scrutiny on the drug industry and proved to be a turning point in drug regulation. Drug companies began to realise the amount of liability that they could potentially face on the introduction of a drug and governments started to realise the importance of regulating these new drugs.

In developing countries such large-scale availability of drugs has necessitated greater consideration for their regulation and control, but these efforts have largely centred around decreasing the brands and types of drugs.

3-2:2 Regulation in Developing Countries

Unfortunately, it took a while for the importance of such regulation to reach developing countries. As the thalidomide disaster occurred in 1962 and regulation in industrialised countries was being strengthened in these areas, regulation in developing countries was not really highlighted until the 1970s and did not really take much effect until the late 1980s. Many developing countries, both emerging from unstable political situations and experiencing intense need due to unforeseen natural disasters, required outside assistance to help them with regulation. Efforts on the part of developing countries to improve drug utilisation through regulation were burdened with the poor education of its inhabitants as well as the unmonitored availability of drugs. Indeed, the influence of external bodies such as the WHO played an integral part in these countries forming better methods of drug regulation.

Internally, the effects of the lack of education and poor regulation of drugs within developing countries fomented large changes in drug utilisation. To make treatment with pharmaceuticals simpler, the ministries of health in various developing countries instigated several measures. Such measures included reforms to make drug prescribing simpler and an action requiring less thought. These reforms have either been formal programmes such as the Essential Drugs campaign, or less formal reforms such as more careful transport of drugs, storage of drugs and controlled access to drugs.

Drug usage and demand for pharmaceuticals began after colonisation of developing countries, and focused on keeping the colonising population from contracting infectious disease as well as keeping native work forces healthy. Concentration of health care and pharmaceuticals was limited to

urban areas, giving little or no concern for those in rural areas (Basch, 1990). Ultimately, with independence, there came an increasing growth in developing countries' effective demand for drugs and in the 1970's large proportions of the health budgets of developing countries went towards them. In 1976, Thailand spent 30.4% of its budget on drugs and Bangladesh spent 63.7% on drugs (Mamdani, 1992). This is far greater than the budget proportion that is normally spent on drugs in industrialised countries . Nevertheless, the bias towards the wealthy in urban areas continued with those living in urban slums and remote rural areas with little access to drugs to treat infectious diseases. Of Tanzania's 1977 drug expenditure, 79% of drugs went to hospitals, 14% to dispensaries yet only 7% to health centres (Yudkin, 1980). Large remote areas of land made transport and travel difficult. Population in these areas was less dense and it was easier to concentrate drugs where the population was highly concentrated, minimising costs. Resource allocation for drugs remained distorted and still suffers from an urban bias. In contrast, in urban areas there could be found a surplus of inappropriate drugs. In the 1970s Argentina had approximately 17 000 brand names, and Brazil had approximately 24 000 brand names on the market (Mamdani, 1992). Still, in the 1980s, Brazil had 30 000 different drug products for sale, and Mexico had 80 000 branded products available as compared to 11 000 and 12 300 in 1993, respectively (Ferguson, 1988; Hartog, 1988, SCRIP, 1995). This is a luxury that established market economies could afford, but it only served to confuse drug utilisation in developing countries. The result was a situation in the 1970's and the 1980's that exhibited great waste and inefficiency of funds allocated for pharmaceuticals which were irrational, dangerous and ineffective. In some cases, items that a poor individual could not rationalise purchasing, such as acne medicine and eye drops, were available when necessary antibiotics were not. This was further complicated by misleading and inappropriate marketing actions of transnational pharmaceutical companies.

Many in developing countries could not get access to drugs at all, but those that did have access, did not necessarily find the right drugs for their needs: drugs were often either inappropriate or past their expiration date. A schism developed whereby there simply were not enough of the right drugs to treat infectious diseases but there was a proliferation of drugs of a dangerous or dubious nature. This suggested that drug deprivation was not solely due to a lack of funds. This situation necessitated reforms to control the amount and kinds of drugs available in the public sector. In the 1970s, it caught the attention of many outside of developing countries such as those in aid agencies, critics of the pharmaceutical industry, and in the United Nations. These individuals who found this situation undesirable were partially responsible for causing the WHO to attempt to try to develop guidelines on the regulation of drugs.

3-2:3 The Essential Drugs List

A movement towards the regulation of pharmaceuticals was reflected in 1975 when the Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce was adopted by the 28th World Health Assembly (WHA). This stipulated that all products exported were to have a certificate available from health authorities proving that the product was authorised in the exporting country and that the location of manufacture followed Good Manufacturing Practice (Chetley, 1990). Initially less than 33% of WHO member states adopted this.

At this same time Speight (1975), in a study in Tanzania, compared older effective drugs to newer brand-named drugs still on patent. The results of this concluded that newer drugs could be as much as 10-150 times the cost of older effective alternatives. Newer drugs were thought to be consuming a disproportionate amount of drug budgets in developing countries. Such realisations as this and previously mentioned actions in certifying drugs for export, reflected a climate whereby better drug policy formulation was favoured.

In 1975, the call for a policy on the part of the WHO first appeared in the director-general's report to the 1975 WHA. In this report, he highlighted the high expenditure on drugs and illegal and unethical practices associated with them in developing countries (Walt and Harnmeijer, 1992). Subsequently, in 1977, the WHO, formulated guidelines for countries on 220 compounds that were designed to meet 90% of pharmaceutical health needs (Chetley, 1990). These guidelines became known as the Essential Drugs Lists. The WHO's actions in establishing these guidelines were in partial response to pressure from other parts of the UN to regulate pharmaceuticals, but they were also a product of WHO's growing emphasis on primary health care (Hartog, 1993). A greater focus on these guidelines was designed to ensure a more regular supply of basic drugs, an important element of PHC.

Essential drugs were to be "those considered to be of utmost importance and hence basic, indispensable, and necessary for the health needs of the population. They should be available at all times, in the proper dosage forms, to all segments of society." (WHO, 1975). These drugs were known to be effective and the majority of them were available in a generic form (a form of drug that is beyond it's patent protection, and therefore, has the advantage of being less costly and of a more competitive price). The concept of a restricted list of drugs was not new, but was strengthened by the WHO. Accompanying the essential drugs guidelines, a campaign was designed to foster concentration on a smaller number of drugs specified in developing countries in order to articulate less management, less expenditure and less confusion in drug therapy. It was hoped that this would make the most essential drugs for treating diseases available, increasing drugs supplies or replacing those that were less useful.

In 1977, the WHO's Drug Policies and Management team (DPM) brought together an expert committee for creating a model essential drugs list. It also gathered information from developing

countries in order to better assess the needs in formulating essential drugs policy. In 1978, the DPM proposed to create the *action programme on essential drugs* in order to empower developing countries to better utilise, obtain, produce and control the quality of essential drugs in the long term and ensure that necessary drugs and vaccines would be available to more of the population in the short term. This proposal was endorsed by the WHA in 1978, but it was three years before it was implemented (Walt and Harnmeijer, 1992). The DPM was then abolished and became the Action Programme for Essential Drugs known as the Drugs Action Programme (DAP). The DAP focused on making slight changes to the essential drugs list and helping developing countries research their potentials for domestic drug production and obtaining greater drug supplies. However, the director-general was much more in favour of a strong policy that would increase supplies through less expenditure and purchasing agreements. Funding for the DAP was less than needed and progress was slow.

In 1982, the DAP was one of the agencies affected by the consensus of some that the WHO was moving outside of its political mandate (Walt and Harmeijer, 1992). It was unclear as to whether the WHO would be able to provide technical support for procurement, pricing, quality control and distribution of essential drugs (Walt and Harnmeijer, 1992). The DAP's plan for implementation had become ambiguous. Change came when the medical advisor of the Danish International Development Agency (DANIDA), became the programme manager of the DAP and was to start implementing DAP in developing countries. Hence, the most important function of DAP became country support (Walt and Harnmeijer, 1992).

Before the Essential drug programme, only a few countries were using restricted drugs lists. In 1959, Sri Lanka had a restricted drug list followed by Cuba in 1963, Peru in 1971, and Mozambique in 1977 (Walt and Harnmeijer, 1992). With the help of the DAP and other parts of the WHO, many countries started to develop their own list of essential drugs, with the purpose of restricting drugs to only those that met basic needs. Kenya had a pilot project whereby essential drugs for 3 000 patients were made available using centrally packed kits of these drugs to lessen breakage, theft and spoliation. This pilot project provided the model that catalysed more widespread instigation of essential drugs schemes. In 1982, Tanzania soon adopted the programme as well as Bangladesh. However, there were some uncertainties and resistance to this programme.

3-2:3a Uncertainties in the Essential Drugs Programme

Policy for essential drugs supported all aspects of the originally conceived essential drugs programme by 1988 and after 1983, the DAP was central to these results. In formulating policy the WHO found itself in a position between radical consumer groups demanding action in favour of a more comprehensive policy and conservative members of industry demanding that the policy be

limited. The general director gave the DAP more visibility and protection in 1983, by moving it into his own office but this changed in 1988 when a new general-director moved them back out implying to some that the DAP might be given less support.

With the implementation of essential drugs programmes (EDP) in developing countries, EDP policy framework became dilute (Kanji, 1992). The Essential Drugs Programme was advocated by many who wanted to extend the concept to industrialised countries, and rationalise their overall respective prescribing behaviour. Some, such as Jayasuriya (1991), claimed that the design of the concept was only to give preference and greater availability to a group of drugs for rationalisation. In contrast, many others wanted to extend the policy to one not just designed to supply drugs, but that focused on these drugs' utilisation. Likewise, there was the heated problem of defining whether this policy would be limited to the public sector, or would alternatively be made compulsory in the private sector. The enforcement of essential drugs lists in the private sector would give the government greater control over drugs imported into the country as well as concentrating services in the private sector more on essential procedures. This, of course, would be very unpopular in the private sector as it would cause this sector to lose prescribing control. Private sector health facilities resented this enforcement because they thought that since their patients were paying for special treatment and not "essential treatment", it would be compromised by a mandatory essential drugs list. Regarding this, Taylor (1986) argued that keeping the richer, private sector from using certain drugs, would not necessarily make more drugs and funds available for the poor in the public sector.

There was the question of whether essential drugs lists should be made mandatory and enforced by the law or be optional to health care providers. Although it makes some sense to make the lists mandatory to maximise the rationalisation of drugs, there also is the argument to suggest that such compulsory lists controlling prescribing would limit a doctor's ability to prescribe drugs for patients with unusual conditions. This highlights the fact that restricted lists by definition only carry the most needed drugs rather than some rarer and less used drugs for patients with special illnesses. Some of this need could be satisfied by using a supplementary list of drugs outside of the essential drugs list for special cases. Bangladesh has only 150 essential drugs but has added a supplementary list of 100 drugs for special cases (Srinivasan, 1986).

Undoubtedly, the utilitarian nature of an essential drugs policy causes a small minority to suffer, especially if the policy limits imports. This was difficult to accept as it took the decision-making for drugs out of the hands of the doctors and into the hands of the government and funding bodies. Doctors with more expertise in hospitals in urban areas might be more equipped to decide for themselves what appropriate drugs his or her patient might need. Such arguments suggested that the

essential drugs policy is more suited to rural areas where there is inclined to be less expertise in prescribing, fewer doctors and more health care workers prescribing drugs.

Another argument was whether the essential drug *policy* should actually be limited to only an essential drugs *programme* (EDP) within developing countries. Although it might seem an exercise in semantics, Kanji (1992) suggest that limiting the idea to a programme would mean that each country involved would have the freedom to allow some drugs not appearing on their essential drugs list to be allowed in urban areas, whereas they could limit drugs in rural areas to only those that were "essential". In spite of the fact that this would allow for more freedom in prescribing for doctors, it still would allow for the possibility that irrational drugs would be prescribed in areas outside of the programme thereby thwarting the essential drug list's purpose of limiting costs. Arguments such as these continue with little agreement. These ambiguities capture the empirical problems in maintaining EDP policy framework within each country that attempts to adopt an essential drugs list.

3-2:3b Resistance from the Transnational Pharmaceutical Industry

The transnational pharmaceutical industry found the idea of essential drugs unpalatable by definition because it would determine the kinds and amounts of drugs that they could sell and the programme condoned the use of cheaper drugs that were no longer protected by patents. This was a threat to the pharmaceutical industry as it endangered potential profits and because of this threat, the transnational pharmaceutical industry took action to thwart the implementation of restricted drugs lists in developing countries, in hopes that these would never manifest. The International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) with member associations in 47 different countries, lobbied the WHO regarding the Essential Drugs issue. Such pressure from an industry with an annual turnover of US $100 000 million, could not be ignored and was especially felt in developing countries where transnational pharmaceutical companies dominated a large proportion of the market (Walt and Harnmeijer, 1992). In these countries, many pharmaceutical companies were observed taking several actions that made it very difficult or impossible for these developing countries to implement an essential drugs programme.

In 1982, the Bangladeshi government identified 150 essential drugs and 100 supplementary drugs that would meet most health care needs. Of those left over, 1 500 drugs were withdrawn and out of this, 237 were regarded as dangerous and therefore banned (Rolt, 1985). This left a disgruntled pharmaceutical industry that tried to compromise the programme through a misinformation campaign and pressure on the governments in developing countries. This was significant because eight multinationals had 75% of this market. In order to alter the nature of this programme and possibly discredit it, a misinformation campaign started using a pharmaceutical industry funded journal, *The*

Pulse. 10 000 copies of *The Pulse* were printed each week and distributed freely to doctors by industry detailers and this periodical served as a medium of information for the drug industry. These journals ran editorials with messages such as "Drug policy now a total failure", "Most drugs banned not harmful", "Shortage of right medicines spread cholera and other diseases", and other misrepresentations and frightening anecdotes. All of these were unfounded and served as parts of a harmful marketing campaign against the Bangladeshi EDP for which its government could do little to fight (Rolt, 1985). Indeed, the effects of this campaign were damaging because many doctors and drug vendors were manipulated into believing the worst about the government's essential drugs programme despite the fact that the country's EDP was a logical plan. Such an effective spread of misinformation in the absence of any effective government media to counter these claims was a powerful weapon, indeed. This misinformation campaign was further supported by industry salesmen who claimed that in response to the policy, the pharmaceutical industry had withdrawn some popular goods when in fact these goods were ineffective, suggesting their withdrawal for other reasons.

Political and economic pressure was the second manifestation of pharmaceutical industry pressure on the government of Bangladesh. Multinational pharmaceutical companies lobbied their own governments to act against the EDP. This kind of pressure had been successful in the past in 1974, when the US indicated that they would cut off food aid if centralised drug purchasing was instigated. In this later case, it was suggested by the US State Department that the continuation of such a policy would deter future foreign investment and lead to legal action. Likewise, this programme was very strongly ridiculed by the US, German and British ambassadors. Protecting the interests of transnational pharmaceutical companies was a powerful motivation, indeed. In one instance, a demand for the withdrawal of a product of the US-based company Pfizer, was not responded to by this company but rather President Reagan's office, resulting in the withdrawal of the demand on the part of the Bangladeshi government (Rolt, 1985). Similar pressure occurred in the Philippines when President Aquino received a letter from Senators Cranston and Lugar in reference to the Philippino ministry of health's essential drugs effort that suggested that she should look at her efforts carefully as it might limit future investment by US firms (Tan, 1988).

These examples of political pressure on the part of the governments of industrialised nations as well as the pharmaceutical companies themselves is not new or uncommon. Developing countries which are infinitely entangled with and dependent on industrialised countries to meet their needs, cannot afford to proverbially 'bite the hand that feeds it'. Such strong tactics illustrate one example of how powerfully entrenched is the pharmaceutical industry in developing countries and how difficult it is for a country to establish a policy when the industry finds it invidious. The pharmaceutical industry will no doubt continue to resist restricted drug lists because these lists limit each company's market.

Such resistance is illustrated by Hartog and Schulte-Sasse (1988) whose study of German and Swiss drug suppliers to developing countries showed that of those drugs sent to developing countries in 1988, only an average of 12.5% of drugs were essential and only 44.2% appropriate. The remaining 55.8% were inappropriate drugs defined as those that were: (1) combination drugs, (2) drugs without good data on effectiveness, (3) drugs with uncertain efficacy, (4) drugs with amounts of active ingredients that are too high or too low, (5) drugs within an ineffective dosage form, (6) drugs considered poor choices when cheaper or safer alternative to them are readily available and obtainable (Hartog and Schulte-Sasse, 1988: p. 27). Lee (1991) also found in Panama in 1991 that of 3800 products on the market, 50% were vitamins, tonics and combination drugs with an added large proportion of drugs with dubious safety and efficacy. These examples of the lack of imported essential drugs reflect the fact that the Essential Drugs Programme is still new. With pressure from the WHO and changes in demand for essential drugs, the proportion of those imported by developing countries is likely to increase.

3-2:3c Aid from Transnational Pharmaceutical Companies

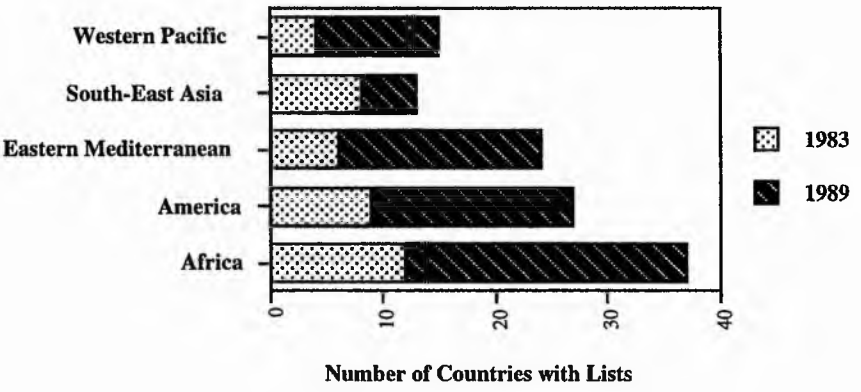
Once the Essential Drugs Concept was well established, many multinational companies, with concern for their image, attempted to take part of the establishment of EDPs, but such conflicting interests between profit and policy ultimately resulted in their influencing the nature of these programmes. Three Swiss drug companies, Roche, Sandoz and Ciba-Geigy, under the name Interpharma, offered to help the WHO in establishing an EDP in Burundi. Shortly after, the WHO withdrew from its collaboration with Interpharma and this company then found funds from the Swiss Development Agency that offered US $300 000 which Interpharma matched. Unfortunately, the result of this project was that no clear policy for drugs was identified and several non-essential drugs and drugs under patent were contained on the essential drugs list. The attempt lacked direction and most funds were spent on drug storage and transport facilities (Kanji, 1992). Following this, other industry-driven programmes have resulted in a greater market share for multinational companies rather than national producers. The EDP in Colombia had multinational investment contingent on incentives such as tax breaks, low customs charges on imports and subsidies from the Colombian government for the building of plants. Kanji (1992) maintains that this had a strong influence on national production. Whereas national production was at 55% in 1955, it has reduced to approximately 15% in 1992. Needless to say, these figures do not take into account demand and the quality of those nationally produced drugs, nor if there was a greater benefit from national production or multinational imports, however, this example is still illustrative of the pitfalls involved when a party with a specific interest attempts to start EDP's in countries.

3-2:4 The Progress of the Essential Drugs Programme

The Essential Drugs Programme is one approach to rationalising drug utilisation. Many countries have embraced the concept and established their own essential drugs list making these drugs' availability greater for primary health care (PHC). The WHO's work in essential drugs has highlighted the need to better organise drug utilisation in developing countries and has made the issue more visible. The effects of this programme can be shown by the amount of developing countries that have developed their own essential drugs list as observed in Figure 3-1.

The Essential Drugs concept was successfully marketed through WHO members and various periodicals, looking to change the nature of national drug policies. In a decade, it became a successful project with the help of consumer groups, non-governmental organisations (NGOs) and flexible donors. Additionally, the project was assisted by the Drugs Action Plan (DAP) which organised essential drugs supplies with the United Nations Children's Fund's (UNICEF) supply division, organised donors to promise funding, and convinced governments of developing countries to support the idea.

Figure 3-1: The Number of Countries that Adopted Essential Drugs Lists: 1983-1989



Adopted from: LSHTM/KIT, 1989

3-2:5 UNICEF

UNICEF has served as a basic supplier of drugs and vaccines to developing countries and the WHO, but became involved with the Essential Drugs Campaign in 1981 when the organisation instigated more direct liaisons with the WHO. In 1981 the WHO and UNICEF were linked with the Joint Committee on Health Policy (JCHP) whose major focus was on securing drugs and making visits to countries to evaluate their deficiencies and obstacles to the effective delivery of pharmaceuticals. At the request of thirty-three African countries, the JCHP scheme was developed to aid drug procurement

with bulk purchasing. Aggregate purchasing had been largely unsuccessful up until this point, having never gone beyond a concept in South America, Africa and Asia due to its overwhelmingly intricate nature. The process itself is complex alone without the required legal and commercial agreements, funding needs and organisation. To make this more viable, UNICEF increased the volume of drugs bought by the UNICEF Packing and Assembly Centre (UNIPAC) in Copenhagen from US $17 million in 1982 to US $35 million in 1985 and to US $60 million in 1986 (Walt and Harnmeijer, 1992). This bulk buying along with careful attention to competitive prices resulted in decreases in these bulk bought essential drugs of between 50% and 60%. After this success, UNICEF started to focus on its Bamako Initiative.

3-2:5a The Bamako Initiative

The Bamako Initiative was a resolution with the intention of improving PHC in Africa. It resolved to supply essential drugs for maternal and child health centres as long there would be a charge for these drugs. The initiative was designed so that the resulting funds that came out of these charges would be used to pay primary health care workers and to improve the quality of PHC. This appeared to be a well designed plan, but it was heavily criticised possibly in part because it was developed without consulting the WHO. Charging the very ill for essential drugs seemed to conflict with the essential drugs policy of getting essential drugs to those who most needed them, regardless of the patient's ability to pay. Also, there was the problem of the amount that should be charged for the drugs, as initially no one seemed sure whether the charges should encompass an amount that covered most of the cost of the drugs or just a nominal part. In addition, developing countries received many drugs free from donors and charging those receiving them to meet the costs of funding health care in rural areas was a somewhat controversial issue for those funding these drugs. Nevertheless, with some struggle, this initiative was executed with co-operation from the Africa Regional Office (AFRO) of the WHO.

Summary of Section 3-2

Efforts to regulate drugs have been made efficacious by outside agencies such as the WHO and UNICEF. This has primarily focused on limiting the availability of inappropriate drugs through restricting imports rather than regulating overall drug availability at the point of purchase. The adoption of the Essential Drugs concept for drug rationalisation in developing countries has been relatively successful proven by many countries' recent development of their own restricted drug lists. Although there were problems in the Essential Drugs concept and some resistance was encountered by the pharmaceutical industry, many have come to accept restricted drugs lists and work with them.

UNICEF has been quite instrumental in the instigation of essential drugs lists through their endeavours to supply drugs at minimum costs, making them more accessible for purchase. They have also made attempts to improve PHC through their Bamako Initiative. Although these regulation initiatives have been effective, they do not represent a cure to poor drug regulation. Essential drugs lists are a utilitarian concept and therefore, ignore some specialised needs. Tremendous effort and dedication on the part of developing countries is still needed to rationalise drugs, and restricted drugs lists only represent a very small part of drug regulation.

Section 3-3

DRUG PRODUCERS

In this section, the influence of the actions of pharmaceutical companies on drug utilisation will be discussed. The industry structure, drug procurement, generic drugs, domestic production in developing countries, and the marketing of drugs by domestic and transnational pharmaceutical firms will be presented. It is in this environment that one will be able so see how drugs, and namely, antibiotic utilisation, is influenced by the actions of pharmaceutical firms.

3-3:1 Industry Structure

Those companies that produce pharmaceuticals are also referred to as ethical, generic and OTC companies depending on the type of drugs that they manufacture. In this context, 'ethical' is referring to those drugs that are only available under prescription in developed countries and are not advertised to the general public, OTC are over-the-counter drugs and generic drugs are those ethical drugs that are no longer protected by intellectual property rights (see section 3-3:3).

The global drug industry is primarily formed from two parts, multinational pharmaceutical producers and domestic pharmaceutical producers. Most multinational companies work inside of several countries and quite often world-wide. The transnational pharmaceutical industry is very profitable, producing products that face a relatively inelastic demand in industrialised nations, both due to doctors acting as intermediary purchasing agents and because the perceived demand for these goods in saving lives. Similarly, in developing nations, where competition from domestic companies is small, demand can also be quite inelastic. In the past recessions between the 1970s and the 1980s, the small number of industries that made a profit included the pharmaceutical industry and ironically, the arms industry.

The transnational market for innovative pharmaceuticals includes many companies, but is dominated by a small number of multinational companies and is globally classified as an oligopoly. This is an industry where few new drug companies rise next to long-established industry world leaders. The nature of this industry has recently been affected by small biotechnology companies being acquired by large companies. For the innovative pharmaceutical market, barriers to entry are heavy with high entry costs, intellectual property barriers, and high research and development costs (R and D) with only one in 10 000 developed compounds ever making it to a market (Ciba-Geigi Pharmaceuticals, 1991). This case is not true in the generic drug industry. Many barriers to entry are removed when these companies no longer have to contend with R and D costs and intellectual property rights. In fact, given that many of these companies are seeking to make an identical product (with

identical bioavailability to the original as their goal), this industry in contrast can start to approach perfect competition: with large innovative companies in this industry only having an advantage of having invented a generic drug and having previously monopolised marketing of this drug during the period that the drug was covered by patent.

Unlike the market for brand-name products from multinational producers, depending on the competition, the market for generics within developing countries can range from a monopoly government producer, to a market that offers more competition in pricing. This is especially true in those developing countries where there are few barriers to entry including the absence of patent property rights and more attainable start-up costs. India is a good example of one of these countries because drug production is widespread and there is a firmly entrenched market for generic products whose producers face far more competition than that experienced between multinational brand-named drug producers. Instead of a few, very large companies dominating a large proportion of the market, multinational producers of generics and domestic firms compete among each other for market power. Multinational firms might have the advantage of size, but domestic firms have the advantage of government subvention and support combined with the knowledge of a familiar market. In addition, the more lax is the enforcement of intellectual property rights, the more freedom domestic producers are given. India does not acknowledge property rights even on new drug products so that there is more competition between firms because the products they market can be produced to look nearly the same. Following this, the consumer's perception of the quality of these generic products can dramatically affect this market.

3-3:2 Drug Procurement

Drug procurement in developing countries can be classified according to three types of countries: those that have no facilities for drug production, those that have limited facilities for drug production and those that have strong facilities for drug production. Those countries that have no facilities to produce drugs must depend on multinational pharmaceutical companies to meet their drug need. These countries primarily rely on drug salesmen to spread information on drugs. Drugs are purchased from international buyers by a local company representative of a transnational pharmaceutical company. Foreign currency is necessary for this and is supplied by the developing country's government. Countries in this group are, for instance, Burundi, Mozambique and Ethiopia. In contrast, where countries have greater local production facilities, domestic producers are in competition with transnational companies for supplying drugs to buyers. Fierce competition occurs in these countries where many generic drugs, are produced both locally and by transnational companies. Countries with these facilities, for example, are Kenya and Zimbabwe. Unlike these first two groups,

the last group contains those countries that are able to produce the majority of their drugs locally, with relatively sophisticated manufacturing facilities. An example of those countries with these facilities include India, the Philippines, Argentina, Mexico, Cuba, South Korea and Egypt. In this category of countries, competition is the most severe between local and international producers and incentives for both are often in conflict. It is not uncommon for governments to give transnational companies investment incentives while they will purchase their drugs from local suppliers (Kanji, 1992). In this way a government can encourage foreign investment and take advantage of the positive externalities that come from this, but they can simultaneously encourage domestic production in order to gain some independence from multinational drug producers as well as a better bargaining position.

3-3:3 Generic Drugs

Most domestic production in developing countries focuses on generic drugs which are often long established drugs whose technology for production is in many cases, more readily available. Hence, these drugs are less expensive and often easier to obtain. Most or all of the drugs appearing on each developing country's essential drugs lists are generic drugs. For this reason, there has been strong pressure on the part of developing countries' governments as well as external funding bodies to establish local companies who could produce generic drugs.

Drugs are identified by three names, a chemical name, a brand name and a non-proprietary name (Gupta, 1986). Hence, for instance, a popular ulcer medicine's brand name is Tagamet, its non-proprietary name is cimetidine and its chemical name is *N*"-cyano-N -methyl-*N* " [2-[[(5-methyl-1 H -imidazol-4-yl) methyl] thio] -ethyl]-guanidine (*Physician's Desk Reference*, 1992). Strictly speaking, generic names refer to groups of drugs with similar characteristics such as analgesics and non-steroidal anti-inflammatories (NSAIDS). Nevertheless, the non-proprietary name is also generally accepted to be a drug's generic name by the majority of people using them and so will also be assumed in this work for all references to 'generic drugs'. Generic names are designed to give some information about a drug in contrast to a brand name. Whereas brand names are meant to be easy to write and easy to remember by a doctor, a generic or non-proprietary name is meant to reveal information about the class of pharmaceuticals that a drug comes from. As stated before, generic drugs are those drugs distinguished by the fact that they are no longer protected by their patent and therefore can be produced by any company. This freedom of production allows for greater competition in the market for generic drugs if the drug is a simple entity without requiring overly complicated technological means to produce it. Without such a large differentiation between products, there is a greater emphasis on price competition, and because of this, invariably the prices of generic drugs are lower than brand named equivalents. It is predominantly the perception of the quality of these drugs that largely

influences their prices. This is especially true in developing countries, where the governing focus of production for domestic pharmaceutical firms is on generic drugs because much of the technology to make these is readily available.

3-3:3a Controversies Involving Generic Drugs

Pertaining to quality, there is a fierce controversy over whether generic drugs are chemically equivalent or bioequivalent to brand-named drugs. In order for the human body to absorb the active ingredient in a drug, certain catalysts are often necessary and these are provided in each tablet along with its active ingredient. There is evidence that when the catalysts for this absorption differ in nature or amount, so will be the amount of active ingredient absorbed. This amount of active ingredient that a drug allows the body to absorb is referred to as a drug's bioavailability. Such bioavailability is important as it can determine whether a drug is effective or even potentially lethal. A brand-named drug might have a different bioavailability of active ingredient than a generic and so generics must also be thoroughly checked by a drug regulatory body to make sure that their bioavailability is consistent both from pill to pill and with the brand-named drug. Hence, one argument against generics is that they do not offer the same degree of bioavailability of the original brand-named counterpart and therefore, do not give the same effectiveness and safety. In industrialised countries, this may be true in some cases, but a former FDA investigations showed in 1989 that of 30 top-selling generics tested including 36 000 tests on 2 500 samples, only 1.1% did not meet FDA product quality standards. Also, these findings showed that of 500 sample studies on bioequivalence completed at that date, only one was a fraud (Ingersoll, 1989). Despite this evidence of generic drugs' effectiveness, suspicion is still common and many doctors still stick to prescribing those drugs with which they are familiar and have been prescribing long before there were generic versions. This can be accentuated in many developing countries where the level of quality for these drugs is not particularly good or consistent. In addition, the brand named versions are easier to write down and remember by the doctor, cutting down on the transaction costs of prescribing to patients. This market is unique because the prescriber only acts as a purchasing agent for the patient and therefore, does not consider the cost incurred by a brand-named drug as opposed to a generic drug. Following this, such practices also apply in developing countries where brand-named drugs have grown familiar through marketing and prove easier to recall by doctors, consumers and pharmacists.

Generic drugs are either sold by multinational pharmaceutical companies, multinational generic companies or produced locally. There is considerable pressure on governments and their health facilities to prescribe generic drugs and this therefore, represents a market with a large potential for profit. Even multinational companies have increased their interests in generic drugs often making their

own version of a generic drug which is simply the same as their brand-named drug but without the name. Similarly, the generic drug market has grown remarkably in the last ten years and many multinationals have acquired generic companies. In 1994, Bristol-Myers Squibb bought 25% of a German generics company, Bayer had a US $310 million stake in the generics company Schein and Hoechst had a US $546 million stake in the generics company Copley. Such generic ventures have been profitable. Marion Merril Dow Inc. had a 9% increase in earnings from US $2.8 billion to $3.1 billion partially due to acquisitions in the US generic drugs market (SCRIP Reports, 1995).

3-3:3b Generics Scandal

With greater profits and large-scale growth, there inevitably came scandal in the generic drug industry in the late 1980s. Some drugs sold by local companies and multinational generic companies had dubious amounts of active ingredient and dubious bioavailability. Such inconsistency in these drugs caused many health care workers to be suspicious of them. Many doctors in Senegal, for instance are not comfortable with using generic drugs (Lee, Lydecker and Silverman, 1992). Such poor quality for drugs in developing countries has had a large impact on health when these countries have rationalisation policies limiting the drugs used in the public sector to generic drugs. Indonesia's law stipulates that only small domestic producers, rather than multinationals, can sell generics. Nevertheless, production limited to only small domestic companies leaves the potential for a compromise in quality in a country where quality checks for drugs are difficult, expensive and often ignored. Limiting drugs to cheaper generic versions can be beneficial in controlling drug costs, however, when the quality of these generics is faulty, these drugs become a hazard to drug rationalisation.

Generic scandals have had an impact on both industrialised and developing countries. A large generic drug scandal developed in 1988, in the United States, when the generic form of Ciba-Geigy's Tegretol was recalled by its supplier, Pharmaceutical Basics. This generic was recalled after controlled trials by the Federal Drug Agency (FDA) which concluded that the pills did not dissolve well enough to enter the bloodstream, a complication that had resulted in seizures in some cases. This was compounded by evidence that those in the generic division of the FDA were being bribed to impede approval of generic versions of drugs (Stricharchuk, 1989). This was later proven to be true with the conviction of Charles Chang a chemist high in the FDA's generics division and other chemists overseeing drug approval. Another part of the scandal was that, in an attempt to get their version of brand named drugs approved by the FDA, these companies were submitting the actual drug that they were trying to copy rather than their own version for testing. It was inevitable that the FDA concluded that these drugs were identical in equivalency to the brand named drug because these *were* the brand

named drug. Independent analysis of the Bolar's generic version of Sandoz's Mellaril for psychoses revealed during testing, as the pills became chipped, the actual logo of Sandoz could be seen underneath illustrating that the drug to be tested was not actually the generic that Bolar claimed it was. Such scandal, when there was already doubts about the bioavailability of these drugs, generated considerable questioning of the effectiveness of generics. The result of this was that many of these drugs could not be sold in industrialised countries. Hence, these were exported to developing countries where controls were more lax.

3-3:3c Ramifications for Developing Countries

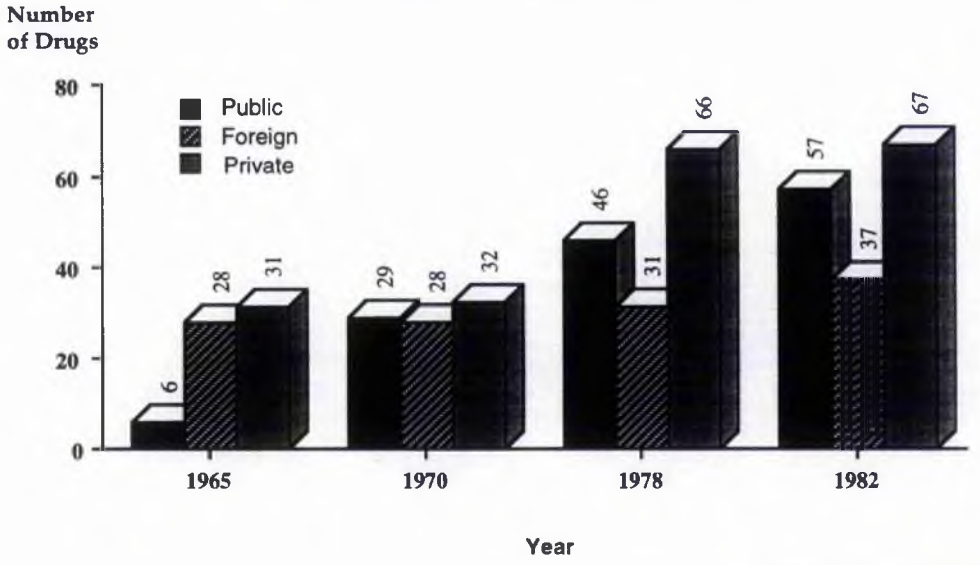
From the repercussions of this scandal, some generic companies exported (dumped-see section 3-3: 9c) large quantities of their substandard drugs in developing countries in order to recoup losses. Most developing countries lacked sophisticated testing equipment and were not able to decipher the quality of those imported generic drugs. This is not surprising when the FDA was challenged in testing these drug's quality. In 1989, the executive vice-president of Par Pharmaceuticals stated that the company had exported millions of inferior drugs to developing countries (Silverman, Lee and Lydecker, 1992). Likewise, the United States Senate Dingell committee for assessing the generic drug approval process, discovered that starting in 1986, generic products sold in Thailand had between 20% and 200% of active ingredient. Dingell discovered that many of these drugs were accepted by doctors and pharmacists in Thailand because of bribes. The situation was exasperated by Thailand's attempt to rationalise drugs by limiting their availability in the public sector to generics on the advice of the Government Pharmaceutical Organisation, which was a primary producer of these drugs and therefore had a personal interest in this action (*PMA Newsletter*, 1991). In essence, rationalisation, dependent on the quality of generic drugs, had gone wrong.

3-3:4 Domestic Production

A country that has the technology and expertise to produce drugs locally has the potential to maintain a consistent supply of essential drugs. Most developing countries cannot produce modern synthetic products, but can often produce some drugs by utilising native plants and animal products. Also, with careful attention to quality, generic drugs, whose production is not overly complex, can be readily produced in many developing countries. The availability of technology to developing countries is continually increasing, making domestic drug production a better option. Mehrotra (1989) shows the growth of technology availability in India where the production of new drugs has more than doubled, depicted in Figure 3-2. Indeed, by locally producing drugs, a country gains more independence and introduces more competition with transnational companies. Some drugs can be

made more cheaply than they can be bought and this is especially significant for those drugs that are supplied free of charge in the public sector. Some estimate that as much as 60% of drug costs can be saved through the use of domestic production (Patel, 1983). In addition, the increased competition from domestic drug firms in the market serves to decrease drug prices overall.

Figure 3-2: Technology Availability Trends for Domestic and Foreign Firms in India



Source: Mehrotra, 1989: p. 1059

The World Bank estimates that competition between suppliers in developing countries has reduced costs by 40-60% (World Bank, 1993). Likewise, these drugs will be available when there is a price increase or shortage in external sources. By producing its own drugs, a developing country can also experience externalities such as a stimulation of commerce. Nevertheless, this is a controversial area complicted by potential problems. Quality control is expensive, and drugs produced domestically may not be of the same quality as those that are produced internationally. In 1977, the WHO estimated that ninety developing countries had no facilities for quality control (WHO, 1977). Those who are earnestly trying to make drugs may not adequately check their quality, resulting in radically inconsistent amounts of active ingredient in each pill or injection making the drug either ineffective or deadly. This is compounded by those seeking profit by making counterfeit drugs that simply look like the real thing. Pills needed to save lives are sadly often replaced by those with inactive or ineffective ingredients.

3-3:4a Domestic Production is Problematic

Strong intentions on the part of the developing country to make drugs locally is often disastrous, resulting in the production of useless products that threaten lives. The extreme importance and means

to establish both an external government body and internal form of effective quality control that will check drugs before and after they leave production must be considered first in domestic production before anything else. Quality control might seem beyond the means of developing countries, but without it, domestic production is a futile venture and should not be considered. Nevertheless, empirically, quality is sadly ignored. Although the implementation of the Essential Drugs Programme has stimulated domestic production, the quality of these products has not been consistently good. Bangladesh's domestic production of 45 drugs for PHC increased from 30.3% in 1981 to 64.7% in 1984 (Srinivasin, 1986). Unfortunately, although domestic production increased, quality was ignored in many cases as proven by a 1984 WHO-sponsored survey of Bangladesh which studied the quality of the products of drug producers (Jayasuria, 1985). Interestingly, the results of this survey showed that: eight large multinationals and twenty-five medium sized domestic firms were rated as having *good* quality control, fifteen medium-sized firms were rated as having *fairly satisfactory* quality-control mechanisms, five to ten medium-sized firms and twenty-six small firms had *poor* quality control, and 104 small firms were rated as essentially having *no quality control* (Jayasuria, 1985). Hence, quality control proves to be a particularly challenging area for domestic producers in developing countries, and there is some evidence that it directly correlates with size: small firms prove to have more difficulty in maintaining drug quality.

Table 3-4: Imported versus Locally Produced Drugs in Selected Latin American Countries

Country	% Imported Drugs	% Local Production	Total Sales $US
Brazil	70.6	29.4	3 708.5 million
Mexico	70.0	30.0	3 618.5 million
Argentina	45.0	55.0	2 582.0 million
Colombia	64.0	36.0	850.0 million
Venezuela	72.0	28.0	553.5 million
Peru	61.6	38.4	386.5 million
Guatemala	76.0	24.0	112.9 million
Uruguay	35.0	65.0	-

Source: SCRIP, 1993

Despite this, it is not outside of the potential for smaller local companies to make good quality drugs, there have been some success stories in domestic production where quality control of essential drugs was high and consistent as is reported by Chetley (1990) of the Gonoshasthaya Pharmaceutical company in 1985. This article traces the development of this company citing the strong social welfare motive involved. This was, for instance, illustrated by their policy of employing mostly women and giving these worker's children meals and a school to attend. This company proved that local firms

have the potential to become established with local expertise and successfully make essential drugs of a consistently high quality, even if transnational firms were to withdraw (Chetley, 1990).

3-3:4b Current Levels of Domestic Production

The current situation in Africa is such that an average of 59% of pharmaceuticals for sale are imported, leaving 41% domestically produced. This is an average obtained from, for example, a low figure of 17% in Egypt to a high figure of 93% in Tanzania (SCRIP, 1995). Local production has been somewhat affected by the Essential Drugs Programme which has influenced those drugs produced. In Nigeria, local production has declined because local producers were forced to withdraw products not appearing on the country's list (SCRIP, 1995). Similarly to Africa, local production in Latin America averages at approximately 39% which is depicted in Table 3-4.

3-3:4c Patents

Until rather recently, domestic producers in developing countries enjoyed a good reputation in various consumer groups who viewed them as a better option for supplying drugs as compared to those supplied by transnational pharmaceutical companies. Transnational pharmaceutical companies, perceived as both profit-hungry and guilty of overt ethical transgressions, had a reputation that paled in comparison to new domestic firms who were perceived to have no interest in profits whatsoever. To many, these domestic firms were perceived to be healing the poor who could not obtain or afford drugs from transnational companies. Hence, intellectual property rights became a very heated issue as domestic firms such as those in India violated the drug patents of multinationals. These actions were justified under the pretence of stealing technology from the rich and letting the poor benefit from it, suggesting that these local companies were 'pharmaceutical Robin Hoods', as coined by Silverman, Lydecker and Lee (1992). Nevertheless, these infringements infuriated the multinational pharmaceutical companies that owned the patents. Many developing countries refuse to give pharmaceutical products infringement protection or approval for new products. For instance, Venezuela will not approve of a new patented drug from a national pharmaceutical company for import until a domestic company can make the drug and quickly get it on the market. According to one representative interviewed by Silverman, Lydecker and Lee, patent infringement in Taiwan cost Bristol-Myers 70% of its sales of one drug and 40% of sales of another drug. In 1969, Brazil reworked its policy on intellectual property to include other products but not pharmaceuticals. After much pressure from the drug industry in America, President Reagan stated that Brazil's actions were a violation of the Trade Act of 1974 and that he would impose sanctions against many Brazilian imports. A 100% tariff was imposed on Brazilian exports of paper products, electronics, and drugs to the US

(Silverman, Lee and Lydecker, 1992). Such pressure on Brazil and other countries caused South Korea, Indonesia, and Taiwan to change their policy on intellectual property. Nevertheless, India, Pakistan, Thailand and Mexico have decided not to consider patent protection for foreign drugs until 1997 or later.

3-3:5 Drug Counterfeiters

Drug counterfeiting can be a very profitable business, and in a developing country where jobs and money are hard to come by, it is very tempting. Drug counterfeiters make pills and capsules to mimic drugs in size, shape, colour and even packaging. These are pills that rarely contain the active ingredient stated, but consist of useless ingredients such as flour compounds. This is not an area where one will find transnational pharmaceutical companies as the perpetrator, but rather, most production is done either locally or smuggled in from another developing country. Profiles of counterfeit drug producers range from local firms and illegal companies to any individual such as a grocer or an architect. The elusive nature of these counterfeiters can make them very difficult to catch. In Bangladesh, for instance, perpetrators are hard to trace because production is of a spurious nature and the location of these counterfeiters is constantly changing. Counterfeiting on a massive scale was found in Indonesia where over 30 kinds of drugs were discovered to be fakes, including anaesthetics, tranquillisers, analgesics and antibiotics. This number represented 30% of all drugs for sale in Indonesia (*Tempo*, 1988). Counterfeit drug production and sale is a lucrative business. Indonesian counterfeiters, if successful, can earn one hundred thousand dollars per venture. Penalties for counterfeiters are not strong enough to dissuade profits like these. Like Indonesia, Brazil suffers from an acute problem of fraudulent drugs whereby an estimated 20% of items sold in non-hospital pharmacies are estimated to be counterfeit (Silverman, Lydecker and Lee, 1992). Silverman, Lydecker and Lee have been very instrumental in uncovering this problem and an example of drugs that they discovered included,

> "•A drug labelled as Lilly's anticancer vincristin intended for intravenous administration was found to contain less than 20 percent of the amount stated on the label.
>
> •Capsules of the antiepileptic phenytoin contained barely 25 percent of the labelled amount, far too little to control convulsions.
>
> •Psychoactive drugs such as Valium and Librium were deliberately spiked, not by the manufacturer but by enterprising pharmacists, with a substance such as atropine in the mistaken belief that this, by causing dry mouth, would prevent drug abuse - and possibly help evade the laws covering treatment of drug addicts. 'Unfortunately,' says Luiz Gonçalves Paulo of the Federal University of Rio de Janeiro, 'too many of the patients came too close to dying from atropine poisoning.'
>
> •A supposedly remarkable new antibiotic was so highly praised that it was purchased by the welfare system. It was found to contain only an inert substance, fubá flour. It was promptly renamed Fubacicline and then thrown out." (Silverman, Lydecker and Lee, 1992: p. 154)

Control of drugs such as these is difficult or impossible in Brazil. Corrupt government officials such as state drug inspectors are often guilty of taking bribes, exacerbating the situation. Some state inspectors are even guilty of pushing the drugs on various pharmacies by threatening to close them down if they do not purchase these drugs.

In addition to this, the testing of these drugs as well as the control of their marketing is hampered by complex legislative subtleties. In one incidence, a company claimed to have produced an eye-ointment containing interferon. Interferon is a rather expensive compound with many treatment applications, including cancer and viruses, and so this claim was thought to be dubious, so the ointment was tested. Brazil did not have the facility to test this ointment and so referred the ointment to the Pan American Health Organisation who also did not have the facilities for testing. This organisation therefore forwarded the testing to the National Institute of Health in Bethesda, Maryland. This testing institute finally concluded that there was no interferon in the ointment. Because of this, the license to market the drug was withdrawn. The producers of the ointment then went to court and won their case based on a claim that the test had no validity since it had not been performed in Brazil (Silverman, Lydecker and Lee, 1990). These are all examples illustrating the complex situation involved in controlling counterfeit drugs. Indeed, the producers are difficult to catch, the drugs are difficult to identify, and those who police them may be corrupt.

3-3:6 Traditional Medicine

Unlike industrialised countries, traditional medicine plays a strong role in health care in developing countries. In virtually every developing country there is some form of traditional curer, witch doctor or shop that specialises in herbals cures. Where western education has failed to permeate, strong cultural beliefs and values have remained along with associated beliefs in cultural medicines and cures for ailments. Some of these beliefs have merit. Aspirin or salicylic acid, for instance, comes from a bark that was used by the ancient Egyptians. Such discoveries in the past have encouraged pharmaceutical companies to research many traditionally cures in ayurvedic medicine to examine their worth. Supporting this, the WHO has encouraged research into traditional plant cures to find new medicines and is currently working with the World Federation of Proprietary Medicine Manufacturers (WFPMM) (*Essential Drugs Monitor*, 1991a). Unfortunately, many forms of traditional medicine are worthless or harmful to the patient. The treatment with drugs containing inactive ingredients only delay the patient in seeking effective medical care for his or her condition. Likewise, some forms of traditional medicine can be quite dangerous with ill effects. Silverman, Lydecker and Lee (1992) identified nine "sex tonics" from Indonesia, Malasia, Singapore, the Philippines, Mexico and Central America. These "sex tonics" claimed to increase stamina, work capacity, decrease premature senility

and increase sexual pleasure. Those buying these tonics would be buying products with ingredients such as testosterone to arginine aspartate to ginseng and vitamins which would either has the potential to cause increased virulisation or do virtually nothing. Hence, for these reasons, this is an area that requires careful consideration and regulation.

3-3:7 Unscrupulous Marketing Practices of Domestic Producers of Drugs

The favourable reputation of many domestic firms did not last for long as unethical marketing practices of some served to change it. Unless a domestic pharmaceutical company was run by a developing country's government, and in some cases not even then, the absence of unscrupulous marketing practices could not be assured. Indeed, in an update of their studies of the marketing practises of domestic firms in developing countries, Silverman, Lee and Lydecker (1992) found that much of the unscrupulous marketing behaviour that was previously exhibited by the transnational industry, is now much more commonly seen in domestic firms. Their follow-up study mainly looked at labelling and promotion of both domestically and internationally produced drugs, and published data centred primarily on the disclosure of warnings for the use of these drugs. Numerous examples illustrate domestic firms omitting warnings for drugs. In the case of Dypyrone, an analgesic, no warning was given on the danger of serious or fatal agranulocytosis in 19 cases: 4 of these were multinational firms, the other 15 were domestic firms. Similarly, the authors note that often when a transnational pharmaceutical company withdrew a dangerous or inappropriate product from the market of a developing country, it would leave a void where a domestic firm would move in and sell the same product under a different name. Indeed, these authors observe that many of these firms have had surprising political influence and are firmly entrenched in the country. They suggest that it is not uncommon for those who run domestic drug companies to be related to those at the ministry of health or to the president of the company.

3-3:8 Incentives of the Transnational Pharmaceutical Industry

Before the actions of the pharmaceutical industry can be broached, its incentives must be discussed. All too often, critics of the actions of this transnational industry forget that the motives of the pharmaceutical industry will and should not necessarily coincide with those of developing countries. It is certainly the job of developing countries to regulate the actions of this industry in order to make these actions more compatible with the objectives of a developing country.

Like all commercial organisations, the final objective of the pharmaceutical industry is undeniably to make larger and larger profits and it has been rather successful at this. In 1983, globally, the pharmaceutical industry had invariably been either the first or the second most profitable industry

since 1955 (Patel, 1983). The transnational pharmaceutical industry has been able to continually maintain a leading profitable position due to four main factors. This is an industry which continually produces innovative breakthrough drugs and product differentiation is high. In addition, there are high barriers to entry because of the large capital needed for research and development. Also, there is very little pressure from purchasers, unlike other markets (McGahan, 1994).

Table 3-5: The Most Commonly Advertised Drug Groups Among the Top 50 Selling Drugs

Drug Group	No. of ads.
H2-receptor antagonists	428
NSAIDs	409
Benzodiazepines	262
Calcium-channel blockers	241
Oral antimicrobials	184
ACE inhibitors	150
Nitrates	149
Beta-blockers	111
Beta-adrenergic bronchodilators	93
Diuretics	84
Antihistamines	80
Total	2 191

Source: Herxheimer, Stålsby Lundborg, and Westerholm, 1993: p. 165

It could be argued that all efforts of these firms go towards profit: research and development, drug production, drug marketing, drug packaging, and drug delivery. Pharmaceutical companies focus on producing an effective drug, for which they can charge a very high price that a very wealthy body will be willing to pay for, and for which they can completely monopolise intellectual property rights for a limited period. The majority of advertising for drugs is centred around these high profit drugs either by virtue of the fact that each dose is expensive, such as H_2-receptor antagonists, or a very large amount of these can be sold, as for example, antibiotics. Table 3-5 shows a study by Herxheimer, Stålsby Lundborg and Westerholm (1993) of the top fifty drugs of 6 710 advertisements appearing in 23 journals in 18 developed and developing countries over 12 months. It appears from Table 3-5 that the most frequently advertised drugs are not necessarily the most essential drugs or the most demanded by developing countries. Developing countries, frequently lacking the purchasing power to buy high volume or high profit-per-unit drugs, do not have their needs focused on by the advertising of transnational pharmaceutical companies.

Indeed, as compared to industrialised countries, developing countries lack large enough individuals or bodies that have the available resources to pay for expensive drugs and therefore, are unable to obtain them without outside assistance. Compounding this, many of the drugs that these countries do need are those drugs whose patents have expired, and are therefore, cheaper. Therefore,

the driving force behind pharmaceutical R and D is determined by the morbidity patterns of industrialised countries: focusing on diseases such AIDS, cancer and heart disease which although also affect developing countries, are responsible for the lion's share of morbidity in industrialised countries. Indeed, in these countries is the most highly concentrated effective demand to pay for the expensive drugs that are the product of such research. From a free enterprise perspective, there is no reason why the transnational pharmaceutical industry should have to consider the specific needs of developing countries if it is given no incentive.

3-3:9 History: Poor Reputation and Reform in the Transnational Pharmaceutical Industry

It must be considered in looking at criticism of the transnational pharmaceutical industry that too much literature only considers their bad actions. The normal activities of the pharmaceutical industry marketing appropriate products is not captivating enough to report on whereas the idea of a rich industry that is harming its consumers for profit is very interesting. This factor causes the tendency to sensationalised and generalise from available instances. It cannot be denied that marketing is a problem in developing countries but the incentives of writers and critics to paint a picture of corruption from anecdotal evidence is high whereas the incentive to report on the industry's everyday activities is much lower. It must therefore, be remembered when considering the following evidence from writers on unethical practices, that there might be another side of the argument that remains unhighlighted.

Up until the mid-1970s the pharmaceutical industry enjoyed a favourable reputation because most of what they did was viewed as saving lives while engaging in R and D at the forefront of technology in order to improve the quality of life enjoyed by most individuals. However, in the late 1970s and especially the early 1980s, information emerged about transnational pharmaceutical industry activity in developing countries that strongly affected its image. Transnational pharmaceutical companies who were previously held in high esteem, were accused of inappropriately marketing drugs, bribing officials and doctors and testing dangerous drugs on unknowing individuals in developing countries. Several authors were instrumental in drawing close attention to these activities, notably, Silverman (1976), Heller (1977), Medawar (1979), Melrose (1982), Braithwaite (1984) and Chetley (1990). These authors claimed that the pharmaceutical industry was responsible for the inappropriate use of drugs resulting in a large scale loss of lives of those in developing countries. Threatened by a poor public image that might hurt sales, transnational pharmaceutical companies started paying closer attention to their activities in developing countries to make sure that the actions instigating such criticism would not occur again.

3-3:9a Silverman

Perhaps the most influential writing on the activities of pharmaceutical companies in developing countries is Milton Silverman. In 1976, Silverman, at the University of California School of Medicine at San Francisco, published *The Drugging of the Americas* which would later be viewed as the catalyst leading to an avalanche of reports of inappropriate pharmaceutical marketing. This book revealed a study that suggested that physician's desk references for pharmaceuticals in Latin America were not consistent with the US *Physician's Desk Reference* and that these inconsistencies were to the advantage of pharmaceutical companies who were trying to increase their share in this market. This publication showed that these references omitted counter-indications and adverse side-effects as well as expanded indications for pharmaceuticals. Added to this, the predominance of information in these publications was from the companies themselves, not an external regulatory body. Most major transnational pharmaceutical companies were implicated in these observed inconsistencies including Squibb, Schering, Boehringer, Searle, Eli Lilly, Wyeth, Merck, Upjohn, Smith Kline and French, and Johnson and Johnson. Counter-indications for drugs such as those that cause teratogenic effects on unborn foetuses were omitted as well as adverse side effects. One of the most pointed examples is that of chloramphenicol which is considered a somewhat dangerous drug due to its side effect of asplastic anaemia and blood dyscrasias. Chloramphenicol is primarily used for the treatment of typhoid fever and sometimes for cases of meningitis where the patient is allergic to other antibiotics, but in these Latin American publications, chloramphenicol was recommended for minor infections such as tonsillitis, pharyngitis, bronchitis, urinary tract infections, streptococcus infections and gonorrhea when these conditions could be effectively treated with much safer antibiotics (Silverman, 1976). Another example was with Ciba-Geigy, their NSAIDs Butazolidin (phenylbutazone; Tanderil (oxyphenbutazone); the anticonvulsant for epilepsy and neuralgia, Tegretol (carbamazebine); and the antidepressant Tofranil (imipramine) all were given wide claims not appearing in the *Physician's Desk Reference* and an absence of warnings and contraindications. In the case of Tegretol, only the *Physician's Desk Reference* discouraged the drug's use for minor aches and pains due to possible death from to aplastic anaemia. Such misinformation and lack of information undoubtedly has served to confuse many doctors who might otherwise have chosen drugs that they thought were safer. In another instance, oral contraceptives were recommended not just for contraception, but also) for pre-menstrual tension and menopause with little acknowledgement for thromboembolic dangers leading to dangerous blood clots. Likewise, Sandoz's drug Mellaril (mentioned earlier for treating psychoses) was indicated for such minor ailments as insomnia, bed-wetting and nail biting while none of its side effects were included in any Latin American countries studied except Mexico (Silverman, 1976).

In support of Silverman's work, Yudkin (1978) compared the African *MIMS (Monthly Index of Medical Specialities)* with the version of *MIMS* in Britain and found evidence supporting Silverman that these publications were not consistent in terms of disclosed side effects and indications. *MIMS* Africa, for instance, omitted many adverse side effects and expanded drug indications where *MIMS* in Britain did not. Later work by Lasagna and Alloza (1983) compared four national drug compendia from Spain (Vademecum Internacional de Especialidades Farmacéuticas y Biológicas), Brazil (Dicionário de Especialidades Farmacéuticas), Mexico (Diccionario de Especialidades Farmacéuticas) and the United States (*PDR*). These authors discovered that the compendia from Brazil, Spain and Mexico together contained only 70.5% of the words in the *PDR*. As well, of the 15 reference products studied, the *PDR* contained far more contraindications and adverse effects and drug interactions compared to the other three. This suggests that those doctors in the US who have access to the *PDR* are given a far more comprehensive education on drugs, compared to those in these developing countries using other compendia.

3-3:9b Heller, Medawar and Melrose

Heller, Medawar and Melrose are three other authors that were instrumental in portraying the transnational pharmaceutical industry as unethical. Heller's book *Poor Health, Rich Profits*, published in 1977, questions drug companies' role in the social welfare of developing countries as well as the applicability of some of their products to the countries' needs. Following this, Medawar (1979) explored the inconsistent nature of recommended dosages of drugs, further exposing the iniquitous actions of the transnational pharmaceutical industry. In his publication, he showed how the maximum recommended dosage allowances for many drugs are often expanded in developing countries with the suspected intent on selling more of the product. He cites that Burroughs-Wellcome's drug Migril's company recommended dose is twice as high or more in Africa and Asia as in the US and the UK Ironically, this drug used for treating migraine, is observed to give a drug-induced migraine-like headache at such large doses. In addition, Melrose (1982) unearthed evidence about the promotion of anabolic steroids for appetite stimulation in children in developing countries. One of the side effects of these drugs is oedema which can worsen a situation where a children is already experiencing oedema from kwashiorkor and marasmus, both childhood forms of malnutrition caused either by a deficiency of protein in the case of kwashiorkor or a severe deficiency of both protein and calories in the case of marasmus. It should also be added that these drugs are seldom, if at all, prescribed to children in industrialised countries. Supporting this work, Muller (1982) in his *Health of Nations*, also pointed out that diuretics were being marketed for the treatment of bloating or oedema caused by these two conditions. The use of these diuretics is a waste of money for the child as these drugs do not treat the

problem, but only one of the symptoms. The results of this can be quite deadly because the child is not as likely to receive the correct cure of better nutrition, and therefore, his or her life will be at risk.

Medawar is also know for his publication with Freese, *Drug Diplomacy*, (1982) which describes Social Audit's fight against the improper use and marketing of G.D. Searle's drug, Lomatil for the treatment of diarrhoea. Lomatil is a drug used for the treatment of diarrhoea which presents a danger, especially in children, since its toxic dosage is very close to its therapeutic dosage, allowing for only a small margin of error. Patient response to Lomotil is unpredictable and at doses, only slightly higher than therapeutic levels, a child may experience respiratory depression, coma, atropism and death (Medawar and Freese, 1982). This is compounded because Lomotil functions by slowing down the motion of food through the intestines, treating the symptoms of diarrhoea instead of the diarrhoea itself. The WHO recommends that most diarrhoea can be effectively and ideally treated by an oral rehydradion solution (ORS) containing potassium, sodium salts and glucose. This allows for an inexpensive method of rehydrating the body that is accessible to those in developing countries. Drugs such as Lomotil and antibiotic-antidiarrhoeals can be dangerous because they do not rehydrate the body and they can hide the symptoms of fluid loss. They are furthermore, a waste of resources. In industrialised countries and more specifically by the FDA, Lomotil is contraindicated for children under two years old due to its toxicity. Nevertheless, in developing countries, it is recommended for the treatment of diarrhoea in infants. This is significant as diarrhoea is one of the leading causes of death in children in developing countries. Accentuating this, Lomatil's recommended dosage varied from developing country to developing country with its dosage in Thailand twice as high as in India. It should be noted that all of Searle's company was to blame for this inappropriate marketing. Searle India took the initiative for marketing the drug for infants, but US Searle recommended it in its *International Product Disclosure* for its use in infants weighing over 3 kilograms (Medawar and Freese, 1982: p. 46). This evidence about Lomotil is only one example of the large amount of inappropriate antidiarrhoeals available on the markets of developing countries. Many of these formulations have antibiotics or antibiotic combinations in them. Antibiotics are not recommended for the treatment of the majority of diarrhoea because there is little evidence that they are effective against it and most cases of diarrhoea will clear up without them. Indeed, they can prolong cases of diarrhoea and they also allow for the development of antibiotic-resistant infections, both in diarrhoea and other diseases. Despite this, companies still market them as diarrhoea cures. In India, Boehringer Knoll quoted UNICEF's "Diarrhoea is the largest killer of infants" to market the combinations of the dangerous antibiotics streptomycin and chloramphenicol for diarrhoea (Srinivasan, 1986). Large quantities of antibiotic-containing or Lomotil-like treatments for diarrhoea are useless and inappropriate, but are still available on the market in abundance, overshadowing the role of ORT in

diarrhoea treatment. Medawar and Freese cited that between 74% and 85% of antidiarrhoeals listed in prescribing guides in developing countries were 'undesirable', meaning they contained ingredients such as antibiotics or Lomotil-like substances (Medawar and Freese, 1982).

3-3:9c Braithwaite: Drug Dumping

Braithwaite (1984) was another author instrumental in revealing faults in the activities of the transnational pharmaceutical industry. In his book *Corporate Crime in the Pharmaceutical Industry*, he reveals how individuals and companies in the pharmaceutical industry have made mistakes and deliberate ethical transgressions. Both in developing countries and developed countries, he describes how pharmaceutical companies bribed country officials, tested dangerous drugs, used unsafe manufacturing practices and misleading marketing practices. Braithwaite's most interesting contribution to this literature is his discussion of drug dumping from industrialised countries to lesser developed countries and the testing of drugs. To this end, Braithwaite identifies a list of ways that a pharmaceutical company exports drugs in order to recoup some of its losses resulting from no longer being able to sell them in industrialised countries, as shown below.

> •**THE NAME CHANGE:** A product is withdrawn from the market of an industrialised country after unfavourable publicity and/or adverse reactions. In order to send it to a market in a developing country, its name is changed and it is remarketed.
> •**THE LAST MINUTE PULLOUT:** A drug being tested does not look as though it will be licensed by the drug regulatory body, so the drug company withdraws its application, and then labels it 'for export only' so that they can sell it in a developing nation.
> •**DUMP THE WHOLE FACTORY:** Closing down production of a hazardous chemicals in a industrialised country in order to move closer to a market in a developing country and to avoid problems in export and regulation.
> •**THE FORMULA CHANGE:** Slightly changing the formula of a drug in order to avoid spectrometer detection in exporting.
> •**THE SKIP:** Some countries will not license drugs that have not been licensed in other countries so to get around this, the company will export a previously banned drug to a lax country such as Guatemala and after its license is awarded, re-export it into the target country
> •**THE INGREDIENT DUMP:** Exporting a drug's ingredients separately, and then reassembling them once they reach their market.

Source: Braithwaite, 1984: p. 259

One of the more commonly cited examples of drug dumping is the case of A.H. Robin's Dalkon Shield and Upjohn's injectable contraceptive, Depo-Provera. Depo-Provera is a drug that was denied a license or testing in the US by the FDA due to its unpleasant side effects. The Dalkon Shield is a intra-uterine device (IUD) that was recalled by the FDA in 1973 who deemed it dangerous due to the fact that it was responsible for the deaths of seventeen women, over 75 cases of uterine puncture and several ectopic pregnancies (no sample size was given). After this, Dalkon Shields were sent to over 40 developing countries. Of course, one could argue that even with these side effects, if these developing countries needed this contraception, these side effects could be overlooked. Pregnancy itself is risky state. The ethical problem of whether the need for contraception was worth the risk of using these devices is not discussed by Braithwaite. Issues such as the likelihood of the survival of the

mother and child through pregnancy, the survival of the child later and its burden to society are all issues that must be considered before making accusations. (Ironically, the US government Office of Population in conjunction with US Development Aid bought several of the Dalkon Shields in order to help population control at a 48% discount because the devices were unsterilised, further compounding the device's use in the context of a developing country)

Another way of dumping drugs mentioned by Braithwaite, is the exporting by pharmaceuticals companies of drugs right before these reach their date of expiration. This is compounded by the actions of developing countries who are prone to miscalculating their needs in drugs. Drugs are over-ordered such that many are stored for long periods of time before they can be transported to where they are needed and expiration is not uncommon before they reach their final destination. Some drugs past their expiration dates are no longer effective or become poisonous. The antibiotic tetracycline deteriorates into a toxic substance once past its date of expiration. In some cases, if a drug does not deteriorate into a poisonous substance, but simply starts to become less active, it is still damaging. An antibiotic beyond its date of expiration may not only be ineffective against a disease it is meant to cure, but in the case of infectious diseases, allows for a greater potential prevalence and infection rate added to resistance to that antibiotic. Of course, this is not the case for all drugs. Some drugs remain effective after their expiration date and given a choice between these drugs and no drugs, developing countries must accept them. It is important, however, to eliminate the export of drugs that will become dangerous after expiration. Also, those individuals treating patients with these drugs should be made aware that the drugs are less effective, and doses should be adjusted accordingly. Far more knowledge of drugs is therefore, necessary in this case, requiring knowledge not only of the drug's normal action, but its action after expiration.

Attempts by the WHO to control the inappropriate export of dangerous drugs and expired drugs was strongly opposed by the United States. Any actions that the WHO took had to be considered in the context of its impact on US funding to the WHO. Discussions about restricting imports of dangerous drugs was moved to the UN General Assembly which developed Resolution 37/137 asking the General Secretariat to make a Consolidated List of banned and extremely restricted drugs (Micklitz, 1988). This was supported in 1983 by the Council of Europe's Recommendation 969 on the Sales of European Pharmaceutical Products in Countries of the Third World which recommended that drugs to be exported from Europe undergo the same restrictions of domestic drugs. It further suggested that European countries should help the WHO efforts in drug rationalisation in developing countries (Micklitz, 1988) The Banotti report of 1986, criticising the export of banned or unregistered European products, caused the European Parliament to adopt the report's recommendations and in 1988, the European Commission started the process of solidifying this (Burstall and Reuben, 1990).

This was further supported by the EEC Treaty which insisted that these banned and restricted drugs were 'dangerous chemicals' under which this treaty carefully regulated the import and export. Furthering this attempt to regulate exports, the WHO has developed a standardised method of assessing the quality of those drugs moving in international markets.

3-3:9d Chetley

Finally, literature attacking the drug industry came to its peak when in 1990, Chetley published a book entitled *A Healthy Business? World Health and the Pharmaceutical Industry* which was a very acid attack on the activities of pharmaceutical companies. In this book, he highlighted the pharmaceutical industry as a profit motivated industry, and attacked the industry because of its focus of trying to cure diseases primarily affecting industrialised countries. He portrayed pharmaceutical companies as driven by unbridled ambition, often at the cost of the welfare of those in low income countries. He also stated that the prices of pharmaceuticals are inordinately high, and although these companies justified this as covering the costs of R and D, he stated that much of the price of items goes to cover other costs. He cited that 15-20% of each sales dollar of pharmaceutical products was for promotion which is higher than expenditure on research and development . Furthermore, this author wrote that the R and D in developing countries did not serve them that well because very little drug development was specific to these countries' needs (Chetley, 1990).

3-3:10 Past Drug Testing in Developing Countries by Transnational Pharmaceutical Companies

Another area of contention is in the testing of drugs. In 1964, the Helsinki Declaration, published by the World Medical Association, directed that all drug testing must occur under the *explicit informed and voluntary consent* of those tested (Smith and Quelch, 1991). Despite this, several very dangerous drugs have been tested in developing countries where many pharmaceutical companies can take advantage of what Braithwaite refers to as the 'least resistance to early marketing' (Braithwaite, 1986). What this essentially means is that those used to test drugs in developing countries are less likely to sue a country for injury due to poverty and laws, and similarly, laws governing 'informed consent' are less likely to be observed. It also has been suggested by many that there is an unspoken lower value of human life for those in developing countries such that the drug testing and killing of those in industrialised countries is thought to be worse than the drug testing and killing of those in developed countries. Such claims as these are debatable, and more optimistically, this testing could be explained by the fact that fewer statistics and information on those who die from testing in developed countries exist and this is why these countries are chosen, not because of differing valuations on human lives. Testing these drugs in developing countries also proves to be cheaper than

in industrialised countries and pharmaceutical companies can easily weed out chemical compounds from new drug applications (NDAs) to the FDA.

Unfortunately, not all ethical principles on the preservation of human life are followed and often very dangerous drugs are tested in developing countries at the expense of those tested. Balasubrahmanyan (1986) reports that in 1985, in Patancheru, India, a research site was established to test Schering A.G.'s injectable contraceptive Net-Oen. Many local women brought to be tested did not know that the drug was experimental, or that there were side effects to the drug. Those paramedics left to find volunteers for injection did not explain about the drug, nor did they distribute the drug's local-language information pamphlets describing the drug and its side effects because they feared that they would not be able to find anyone willing to try the injection. Once informed about the possible dangers of the drugs by Balasubrahmanyan and a women's activist group, only five of the thirty who were brought to the village to be tested stayed to be injected. One woman who refused to be injected was threatened by a doctor who suggested that she might have difficulty obtaining treatment at that health centre if she needed it in the future. Likewise, a women with who was still breast-feeding a child and a very young girl, both of which the drug is contraindicated, were brought in for testing. Ironically, those who warned the women who were to be tested were accused of jeopardising the family planning programme and impeding the liberation of women over their own bodies.

The testing of contraceptives is one of the more common forms of drug testing in developing countries. However, this evidence must be considered with the fact that this is in part, due to the tremendous pressure for family planning in developing countries. Nevertheless, it does not explain the testing of dangerous contraceptive drugs for which little is known and whose information is dependent on the reaction of those being tested: largely uneducated, poor women. The following list describes some incidences of testing that has occurred in developing countries over the past forty years.

1953	**Searle** test oral contraceptives in Puerto Rico. (Braithwaite, 1986)
	Johnson and Johnson and **Syntex** test oral contraceptives in Puerto Rico, Mexico and Haiti (Braithwaite, 1986)
1960	**Syntex** and **Merck** (Germany) test low-dose oral progesterones in Chile Braithwaite, 1986)
1970s	Various companies test intra-uterine devices in Columbia, Iran, Korea, Taiwan and Thailand (Braithwaite, 1986)
1980s	**Upjohn's** Depo-Provera is tested in Brazil, Thailand, Chile, Philippines, Sri Lanka, Hong Kong, Egypt, Honduras, Peru, Mexico, Pakistan and South Africa. (Duggan, 1986)
	Schering A.G.'s testing of the injectable contraceptive Net-Oen in India on women who have not given "informed consent" (Balasubrahmanyan, 1986).

From these examples, one can observe the strong role that those in developing countries have in drug testing of the drugs of transnational pharmaceutical companies. Transnational pharmaceutical companies have tested contraceptives and other drugs on citizens of developing countries without their informed consent and without revealing the dangers of drugs. Undoubtedly, this behaviour is exploitive.

3-3:11 Incorrect Claims in Promotional Media in the Past

In many developing countries, pharmaceutical literature and information is the most available form of information about drugs that the doctor, health worker and pharmacist receives. Although this has the potential to correctly educate many in this area, it also has a great potential for damage if this information is flawed. Those health personnel that receive incorrect information about drugs, without counteracting evidence, are likely to act on this information. The damage of this flawed information depends on the extent of the misinformation and the relative danger of the drug used. In the past, incorrect drug claims for drugs in developing countries on the part of the transnational pharmaceutical companies were common, with the suspected intent of increasing its market and hence, profit, for particular drugs. The following are but a few examples.

The product Orgabolin, an anabolic steroid, was marketed by the Dutch company Organon in Bangladesh, India and Thailand for retarded growth in children, writing that the drug "ensures normal growth, stimulates appetite, promotes optimal weight" when the drug has never been formally indicated for treating malnutrition and under nourishment (Van der Geest, 1988). The danger with this drug is that it can also cause liver damage and female virilisation. Organon, in response to this criticism, claimed that it: (1)was very careful to ensure the safety and information about its drugs, (2) it admitted its mistake in its advertisement of Orgabolin, (3) the company assumed that the drug would only be taken under a doctor's prescription and that (4) there is a difference between the public and private sector of medicine (suggesting its use was designed for the private sector) (Van der Geest, 1988). Indeed, these points of defence, especially the third, suggest that the pharmaceutical company had no knowledge of the conditions of drug availability in developing countries. More than likely, this is not true, but instead, such claims suggest that the pharmaceutical company simply treats the marketing of drugs according to similar conditions in industrialised countries, or more likely, use this as an excuse for any marketing failings. Unfortunately, this appears to be a common excuse given by transnational pharmaceutical companies in defence of their marketing activities.

Trisha Greenhalgh reported that Merck was promoting Encephabol (pyritinol derived from vitamin B_6) as a brain tonic that "improves the uptake and utilisation of glucose in the brain",

recommending it for "strokes, organic brain syndrome of the elderly, post concussion syndrome, perinatal distress (and) learning disorders" (Greenhalgh, 1986: p. 1319) Also, in 1985, it was discovered that Glaxo was marketing a compound called Almacarb for the purpose of healing gastric and duodenal ulcers in Bangladesh when it has never been indicated as such by any pharmaceutical source (Srinivasan, 1986). In India, Merind marketed the anti-allergic drug Periactin for use in increasing appetite which is only one of the drug's side effects and not designed for this use (Srinivasan, 1986) In Pakistan, Birley (1989) reports erroneous claims on benzodiazepines such as Sandoz's Restoril with the claim that "Restoril (temazapam) patients do not experience drug dependence", and Parke-Davis's Verstand (prazepam), cited as a product advantageous for those patients with a history of drug abuse. Such claims go directly against warnings on benzodiazepines in the *Physician's Desk Reference* that says, "Withdrawal symptoms (of the barbiturate type) have occurred after the abrupt discontinuation of benzodiazepines" (*Physician's Desk Reference*, 1992). He says that Roche makes the claim that its drug "Lexotanil (bromazepam) resolves anxiety and *relieves the strain on the heart*" when in fact this drug is only used for short-term treatment of anxiety according to *MIMS* in Britain and nothing is mentioned about its calming effects on the heart. Almost comically, Birley aptly states that "If these claims are correct, then British doctors and their patients are missing out on a therapeutic revolution." (Birley, 1989: p. 220).

3-3:11a Past Statistical Claims

Mismarketing in order to influence health personnel to prescribe drugs is also executed with the misuse of statistical claims. Cesar Victora (1982) studied 350 advertisements and promotional materials sent to four doctors in Pelotas, Brazil over 6 months, and made some rather interesting observations on the use of misleading statistics. He claims that many pharmaceutical companies used biased sampling, no control groups, small experimental groups, non-significant differences, flawed comparisons and misleading graphs. Biased sampling, for instance, is illustrated by an advertisement for the antibiotic phosphomycin which claimed that it was 100% effective for chronic urinary tract infections. However, small print showed that this information was based on a sample size of only eight patients who were tested for sensitivity to the drug in order to remove any patients that were phosphomycin-resistant. Victora also observes comparisons of efficacy of drugs that are pharmacologically distinct and the use of graphs that greatly distort the actual effectiveness of one drug over another. In addition, the authors cite data quoted out of context, with no information about the source, and studies lacking a visible control group (Victora, 1982).

3-3:12 Past Problems with Detailmen

Misinformation from pharmaceutical companies was also propelled with the use of drug salesmen, also known as detailmen. Drug companies, adjusting to the situation in developing countries where labour as an input to marketing is comparatively cheaper and more effective than medical journal advertisements, sends out a veritable army of drug sales representatives to doctors and pharmacists to market their products. The large ratio of detailers to doctors is illustrated in Table 3-5 and is striking when comparing it to ratios of 1:10 or 1:20 which are common in industrialised countries (Lexchin, 1992).

Table 3-5: The Ratio of Detailers to Doctors in Developing Countries

Country	Ratio	Source
Bangladesh	1:7	(Melrose, 1982)
Brazil	1:3	(Silverman et al., 1982
Colombia	1:5	(Silverman et al., 1982)
Congo	1:9	(*Lancet*, 1990a)
Ecuador	1:8	(Silverman et al., 1982)
Guatemala	1:3	(Silverman et al., 1982)
Indonesia	1:2.5	(Silverman et al., 1982)
Mexico	1:3	(Silverman et al., 1982)
Philippines	1:2.5	(Silverman et al., 1982)
Nepal	1:3	(Melrose, 1982)
Tanzania	1:4	(Yudkin, 1978)

Adapted from: Lexchin, 1992: p. 420

This proliferous use of so many drug salesmen, just by number and the fact that doctors have very little access to other medical information gives drug detailers the potential to be very persuasive drug marketing tools.

Such use of drug salesmen is very effective as it adds a personal touch to sales giving the prescriber the opportunity to interact with the seller of a drug and develop a more personal relationship with the salesman. The problem is that because the level of education that individuals reach is generally lower in developing countries, the pool of labour that a pharmaceutical company uses is likely to be less educated and need a greater amount of training in drugs as compared to recruited representatives in an industrialised country. Unfortunately, the education of developing country detailmen is sadly neglected, leading them to give incorrect information. This lack of education mixed with the large enthusiasm to sell drugs, not to mention sometimes incorrect information from the pharmaceutical companies themselves, has lead to broad and incorrect claims and recommendations of various drugs' uses.

The number of incorrect claims and information about various drugs is so numerous as it would be difficult to list them all. Indeed, pharmaceutical companies, lacking the proper social controls in

developing countries in the late 1970s and 1980s, became heavily entangled in the unethical behaviour of making exaggerated claims either through ignorance or more likely for the purpose of increasing profits.

3-3:13 Past Controversy over Gifts and Bribes

A further area of criticism aimed at the pharmaceutical industry was it's frequent practice of giving gifts to doctors and pharmacists as well as larger bribes to governments. The practice of small gifts is used universally by pharmaceutical companies as a marketing tool. Doctors frequently receive small items such as pens displaying the company name, paper pads with the company logo and various other small items as well as free samples of drugs. Often, in developing countries, samples to doctors were so proliferous that these doctors would turn and sell them to their patients for a profit. However, in the late seventies and eighties, it was observed that doctors were receiving gifts that were a great deal more valuable than either pens or paper. Transnational pharmaceutical companies were giving doctors expensive dinners at fine restaurants, all-expense paid trips to medical conferences in exotic locations, and more commonly in developing countries, items such as bicycles, televisions and in some cases, even the services of prostitutes (Medawar, 1979, Silverman, 1982, Smith and Quelch, 1991). This practice was severely criticised by consumer groups and other interest groups because of the motive behind these gifts which undoubtedly had the potential to influence a physician to prescribe a product to a patient for reasons other than medical. Critics considered these gifts as bribery on the part of pharmaceutical companies and found them entirely unacceptable because they are an impediment to rational prescription.

Large bribes to countries are another topic for scrutiny in the unethical behaviour of pharmaceutical companies. Most of these bribes occurred in the late seventies and the early eighties. Bribery as a practice is difficult to prove, but extremely damaging once discovered. Guha (1986) reports a few examples of these.

> "•A US $960 000 bribe of the Italian government on the part of 12 drug companies in order to back an industry sponsored bill
>
> •Merck gave US $2.3 million to a foreign government through its Swiss subsidiary Merck Sharp and Dohme and listed it as promotional expenditure
>
> •American Home Products in 1976 spent US $3.4 million for approval of their drugs in 41 countries
>
> •Parke Davis paid US $2.6 million in 14 countries to hasten drug approval
>
> •Pfizer bribed US $264 000 employees of the government of three foreign countries.
>
> •Roche gave US $14 000 to two Kenyan government officials for purchasing their tranquillisers and anti-bacterials in a bulk amounting to 10 years of need."
>
> Source: Guha, 1986: pp. 224-225

Reports of such practices are seldom observed anymore, possibly suggesting that such activities are far less common.

3-3:14 Recent Activity and Change

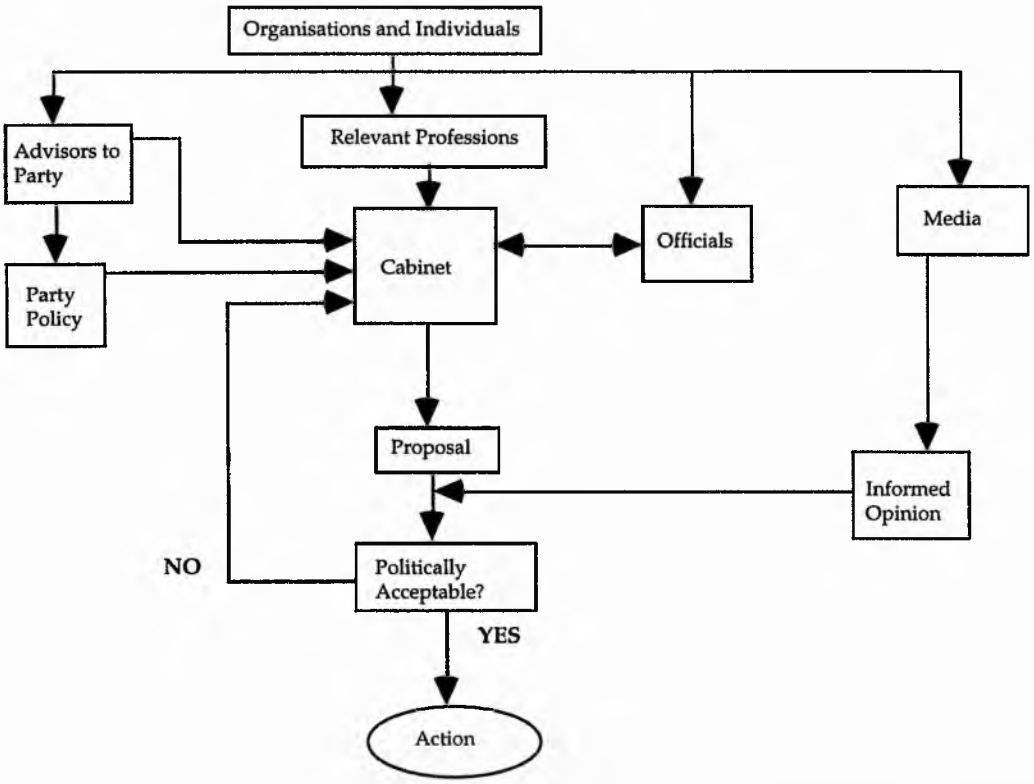
An additional problem in marketing that has hampered drug utilisation is the inappropriate labelling of drugs. In 1993, the US Office of Technology Assessment evaluated the labelling of drugs sold by US-based pharmaceutical firms in four developing countries: Brazil, Kenya, Panama and Thailand (US Congress Office of Technology Assessment, 1994). In this study, 241 drugs were surveyed and of these, 66% of them were incomplete in providing a physician information on their safe and effective use. One example of inappropriate labelling included a magnesium containing antacid (which has known laxative properties and is dangerous to infants in large quantities) indicated for the regular use in infant formula to stop it from souring. Other examples included a drug combination of a corticosteroid, an antihistamine and an antipsychotic recommended for itching without information on the side effects of steroids, and an antinflammatory that was recommended for pain and inflammation without a note of the drug's serious effect in stopping the production of white blood cells. This more recent report suggested that progress in marketing activity regulation of and by transnational pharmaceutical companies still had potential for improvement.

3-3:15 Consumer Groups and Extremists

There are many means for influencing official policy regarding the pharmaceutical industry and consumer policy. A map of government influence has been delineated by Burstall and Reuben (1990), in the Figure 3-3. In attempting to influence the cabinet of a government, consumer groups can either go to party advisors, those in relevant professions influencing the cabinet, party officials, or they can try to influence public opinion through the media. Such a chart as this does not just apply to the governments of states but also global governing bodies such as the WHO. It is through these mechanisms that many proposals shaping the regulation of pharmaceuticals are developed.

Actions to influence the WHO regulation of drugs have been successful. Through the influence of external groups and on its own accord the WHO has made the regulation of drug promotion a strong priority. In order to improve the regulation of drug marketing, the WHO developed the Ethical Criteria for Medicinal Drug Promotion in 1988. This was a comprehensive description of the ethical marketing of drugs, carefully defining ethical considerations required in promotion, advertising medical representatives, free gifts, symposia, export of dangerous drugs and most other information media. The aim of this criteria was to make physician prescribing as objective as possible and make drug information as complete and correct as possible.

Figure 3-3: The Influence of Outside Organisations on Government Policy



Source: Burstall and Reuben, 1990

Such actions have been strongly supported by many critics of the pharmaceutical industry. Some of these critics not only question the nature of the pharmaceutical industry but question the very principals of capitalism, whereas others choose to focus simply on regulation rather than revolution. Despite this discrepancy, many influential consumer groups have developed to regulate drug marketing, notably two, the Bureau Européen des Unions des Consommateurs (BEUC) and Health Action International (HAI). BEUC, founded in 1962, primarily limits itself to marketing activities affecting the consumers in the EC whereas HAI focuses more on global issues, especially those affecting consumers in developing countries. HAI was formed in 1981 for monitoring drug marketing in developing countries. It is run from both Hague in Europe and Penang Malasia and its most visible members are Oxfam, the Bundeskongress Entwicklungspolitische Aktionsgruppe (BUKO), the Dutch International Group on Women and Pharmaceuticals (WEMOS), and the Medical Lobby for the Appropriate Advertising (MALAM) (Burstall and Reuben, 1990).

In the defence of some transnational pharmaceutical companies, Braithwaite traced their reform efforts after much criticism came to light about their subsidiaries in developing countries. He suggested that often subsidiaries of developing countries are portrayed as the perpetrator of many of

these activities and it is the pharmaceutical company's powerful regulatory bodies, made up of "crusaders for the consumer interest", that attempt to change the marketing activities of these subsidiaries with powerful zeal (Braithwaite, 1986: 255). Braithwaite portrays subsidiaries in developing countries as disobedient children that do not necessarily obey their parent companies since these subsidiaries erroneously conclude that they must market their products in a less than honest way in order remain competitive. However, not all poor marketing in the past can be blamed on the subsidiaries of transnational companies. Some companies, by their inaction, allowed these practises to continue. In addition, many companies have had a much stronger role in the marketing of their products in developing countries than they would otherwise admit as is suggested with Searle's marketing of Lomatil, described above.

3-3:16 Ethical Considerations: The Appropriate Place of Pharmaceutical Companies

Pharmaceutical companies are somewhat insulated from consumer groups and consumer reactions since it is the doctor who prescribes drugs in industrialised countries. This is especially true in sub-therapeutic markets where a pharmaceutical company dominates the market with the intellectual rights to a key product, or in the case where a doctor is made to prescribe according to a strict formulary. This can hinder consumer actions in boycotting a drug because a patient, even if he or she is aware of the activities of a pharmaceutical company and wishes not to consume its products, must still convince his or her doctor not to prescribe them. This can be difficult if the doctor is given no other options in what drug to prescribe, or if the patient desperately needs the drug for his or her welfare. In developing countries, information and drug supplies can be so limited that even if a patient or doctor is informed about the poor marketing activities of a drug company, it is unlikely that he or she will stop consuming that company's products as they need whatever drugs that these individuals can obtain and do not have the luxury of choice.

Consumer influence on prescribing is just one manifestation of influencing pharmaceutical companies. Indeed, the methods of social control of pharmaceutical companies lie in three areas, legislation, market forces and moral obligation, as is illustrated in Table 3-6 (Smith and Quelch, 1991). All of these methods of control are flawed and therefore, the combination of all three is needed for the social control of firms. The over-emphasis on one such as legislation over market forces will eventually reduce the incentives on the part of drug firms to produce drugs, and likewise, an over-dependence on moral obligation will not ensure that adverse side effects, contra-indications as well as the proper recommendations for each drug will be disclosed. Hence, a balance between all three of these must be found for each country and internationally for regulating the activities of transnational pharmaceutical firms.

Table 3-6: Methods for Social Control of the Pharmaceutical Industry

Method of Control	Type of Power Exerted	Vulnerability	Examples
Legislation (government intervention)	Coercive Force Condign	Overloaded Limited Effectiveness Threat to Market System	FDA Criminal Prosecution
Market Forces	Remunerative Inducement Compensatory	Insufficient	Profit from successful ventures Consumer Activism
Moral Obligation	Normative Manipulation Conditioned	Unequal Inadequate	IFPMA Code Voluntary Disclosure of drug Risks

Source: Smith and Quelch, 1991: 123

The influence of pharmaceutical companies is undoubtedly important, but what of endogenous regulation in each pharmaceutical company? According to some, the pharmaceutical industry has a social responsibility due to the sensitive and influential nature of their products on health. Others maintain that the pharmaceutical industry is not a charity, but is in fact a free body working toward the goal of profit maximisation and should remain unfettered to pursue this goal with limited criticism. To objectively clarify these opinions, Smith and Quelch (1991) maintain that all business firms can be classified into a model of social responsibility delineated by four levels, as is illustrated below.

> "**1. Profit maximisation and social irresponsibility**
> -Firms may do good through profit maximisation (Adam Smith's "invisible hand") but may also cause harm, would not act to prevent it, and are only doing good as a result of serving their self-interest.
>
> **2. Profit maximisation tempered by the 'moral minimum' operating through self-regulation.**
> -This is avoiding causing harm. Most firms/managers are at this position.
>
> **3. Profit as a necessary but not sufficient goal, with affirmative action extending beyond self-regulation**
> -Some firms/managers make efforts to not only avoid causing harm, but also prevent harm and possibly do good. Johnson & Johnson is the classic example.
>
> **4. Profit as a necessary but not sufficient goal, with social responsibility extending beyond self-regulation and affirmative action to include the championing of political and moral causes unrelated to the corporation's business activities, perhaps even including gifts of charity but only as long as profitability permits.**
> -Gifts of charity here refers to genuine philanthropy rather than that which is primarily PR driven. Few firms reach this position of actively doing good as well as not causing and preventing harm (which many would argue is not a bad thing because of the fairness and legitimacy concerns identified by Friedman). Many firms do not have sufficient resources for the championing of political and moral causes. Classic examples of firms at this position are Ben and Jerry's and the Body Shop."
>
> (Smith and Quelch, 1991: p. 125)

Regarding this model of social responsibility, Smith and Quelch claim that most pharmaceutical companies function on level one, *'profit maximisation and social irresponsibility'* or level two, *'profit maximisation tempered by the moral minimum operating through self-regulation'* when they should at least be on level three, *'profits as a necessary but not sufficient goal, extending beyond self regulation'*.

It is through functioning on this level that consumers get an adequate amount of protection from harmful products. The distinction between levels may not be so very clear-cut with very big firms. Those companies might be functioning on level three in industrialised countries because of strong regulation and a vocal media, but may be functioning on a lower level in developing countries. Merck who has been guilty of some inappropriate actions in the past in developing countries, has recently donated millions of doses of the drug ivermectin for the treatment of onchocerciasis, better known as 'river blindness' (Tanouye, 1992). So, here is a company partially functioning on level four for this charitable contribution for social welfare, but probably only functions on level three in industrialised countries.

3-3:16a Responsibility of the Manufacturer

Expecting that firms to have such a high sense of social responsibility is idealistic and most firms should realistically function on a level where they ensure that their actions will not cause harm. Dukes and Swartz (1988) in *Responsibility for Drug-Induced Injury*, a book for lawyers, manufacturers and health workers, suggest that a drug firm is obliged to provide pharmaceuticals with efficacy, safety, quality, sound packaging and supply, information to official bodies, information to health professionals and the community, warranties and guarantees, limited exposure of non-users, and good research standards. They suggest that the written law does not adjust well to cover all situations and may be outdated, compelling those pharmaceutical companies to observe condign interpretations of current laws and regulations, study and commentary of the current situation by international organisations and 'well-informed observers'. These suggest that drug companies have a responsibility to consider the opinions of critics, consumer groups and legal authorities regarding their activities. The book states that there is never a case where a company can ensure 100% safety or quality in packaging, and that it is from interacting with these bodies that they can better fill their responsibilities in this area.

3-3:17 Summary of Section 3-3

Drug Production is primarily driven by the desire to make profits. It should not be assumed that the activities of this form of free enterprise will subscribe to a moral standard. Past activities on the part of local drug producers and the transnational pharmaceutical industry in some instances have been inappropriate. In addition, drug quality has also suffered, especially in those drugs locally produced. However, some critics of the industry's behaviour often ignore how essential is this industry to health care delivery as well as its substantial work in promoting appropriate products. The actions of the pharmaceutical industry can serve health care delivery as long as it is well regulated. It is a balance of

the consumer, government and market forces that must ultimately influence the behaviour of these producers.

Section 3-4

CONCLUSION TO CHAPTER THREE

Drug therapy can be a cost-effective method in health care delivery and notably the treatment of infectious disease. Nevertheless, the area of drug utilisation is convoluted by the inability to regulate and manage these drugs' uses. Such overwhelming need and high impoverishment in these countries, makes the concentration on the regulation and control of drugs unfortunately a lesser priority as compared to other needs in the infrastructure. Developing countries, which have few resources for increasing health status, must have the very best management of drugs in health delivery in order to maximise the utility it gains from its investment. As compared to an industrialised country, a developing country must be more resourceful, more able to adapt to difficult situations and more able to deal with widespread infectious disease in order to avoid unnecessary deaths. The small amount of funds that requires such resourcefulness is the same reason for the lack of such expertise in order to accomplish this. Drugs that are greatly needed to treat diseases are mismanaged: over-supplied in some instances and completely absent in others. Information, which is necessitated to manage and dispense these drugs is difficult to obtain, unregulated and often of poor quality. The process for changing this is indeed slow, but nevertheless, it is not impossible. Better education of health personnel and patients, better regulation of drugs and better management of health care institutions will improve health in developing countries along with the cooperation and regulation of pharmaceutical companies as well as the guidance of donors, NGOs and the WHO. The lack of these in the past has resulted in a mismanagement of drugs, causing widespread harm. Hopefully in the future, the imperative of these elements will continue to be realised so that improvements in the standard of health delivery with drugs will perpetuate. Following this, includes improvements in health care delivery for drugs that treat infectious bacterial diseases. This is expanded in Chapter 4.

CHAPTER FOUR

ANTIBIOTICS: THEIR UTILISATION AND ASSOCIATED HAZARDS

So far, health care delivery, infectious disease and the utilisation of pharmaceuticals have been discussed in order for an understanding of the influencing factors and the context in which the cost of antibiotic resistance is to be assessed. This chapter attempts to give the reader a background on the utilisation of antibiotics itself, and some theories on the impact of bacterial resistance on the cost of antibiotic treatment. Section 4-1 will discuss the mechanisms of resistance and its association with antibiotic abuse. Section 4-2 will present examples of poor antibiotic prescribing and an economic model of the use of antibiotics and related resistance. Finally, Section 4-3 will illustrate the unique problems of antibiotic utilisation in developing countries that contribute to greater resistance and higher costs in treating infections. This chapter is integral to understanding the rise of bacterial resistance to antibiotics and its potential cost in developing countries. Those factors applying to antibiotic resistance such as basic resistance mechanisms and inappropriate use are later shown more specifically to apply to resistance of tuberculosis bacteria to treatment.

Introduction

Many people are familiar with Kermit the Frog from a children's show responsible for making half a generation of British people omit the letter 'u' from the word colour. Nevertheless, what most people do not know is that the originator of this character, Jim Henson, died from an infection that was completely resistant to antibiotics. Indeed, Jim Henson was an unfortunate victim of the poor management of antibiotics, which causes an increased incidence of resistant micro-organisms.

Imagine a world without antibiotics. Diseases seldom seen today in industrialised countries, such as typhoid, dysentery, tuberculosis, meningitis, syphilis, bubonic plague, cholera and a myriad of other infectious diseases, would once again be a prominent part of everyday life. This may seem preposterous, but it approaches the cold truth that there are now versions of all of these diseases that few or no antibiotics can cure. Furthermore, these diseases do not lie dormant in laboratories, but are

passed from person to person, contributing to greater morbidity and mortality. An acrid reminder of this occurred between 1972 and 1973, when a resistant typhoid epidemic in Mexico was responsible for the deaths of some 20 000 people (Braithwaite, 1984). Resistant infections are no longer an obscure topic for scientific discussion, but a consequential global threat.

In 1994, the global market for antibiotics was worth US $18 billion (SCRIP Reports, 1995). This is one of strongest therapeutic groups due to its imperative role in curing infections. It is impossible to discuss antibiotics without incorporating resistance. Certainly, drug resistance is the driving key to R & D in the market because it is the primary determinant of an antibiotic's effectiveness. Resistance to a particular antibiotic is primarily dependent on the intensity of use of that antibiotic. This is further accentuated by the inappropriate use of antibiotics through sub-therapeutic doses, length of treatment, and irrational prescription. Some antibiotics, which should be reserved for their specific action against life-threatening diseases, are instead used on general infections when other antibiotics will do. The cost of this resistance proves to be high. The cost of treating anti-infective resistant infections can be five to ten times the cost of treating anti-infective susceptible infections (Phelps, 1989). Added to this, antibiotic use and resistance has a negative externality contributing to an overall pool of antibiotic resistance that grows with the use of these drugs. Irrational use is common in industrialised countries but it is, nevertheless, felt quite acutely in developing countries. Developing countries lack the ability to regulate their antibiotics and therefore antibiotic use is uncontrolled. This uncontrolled use has made developing countries one of the greatest beds of resistance and many outbreaks of resistance have originated in these areas.

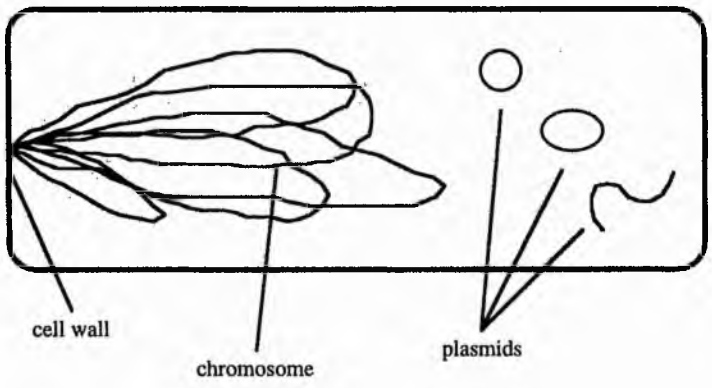
Section 4-1

MECHANISMS OF ANTIBIOTIC RESISTANCE

This section describes how antibiotic resistance develops in bacteria and how the inappropriate use of antibiotics accentuates this. Throughout the human body there are many kinds of small organisms called bacteria (singular bacterium). Most of these bacteria are essential to maintain a healthy existence. Some bacteria, however, are quite virulent and when introduced to an individual, can start to multiply and interfere with the body's regular cell functions, resulting in infections and disease. It is these infections that are treatable with antibiotics, which work in several ways to destroy bacteria. However, a bacterium can develop the ability to withstand the attack of an antibiotic so that the antibiotic has no effect on it. Once this occurs the bacterium is termed as *resistant.*

In general, there are two ways in which a bacterium can become resistant. The first may be referred to as *endogenous resistance*. This occurs through exposure to a particular antibiotic which causes a bacterium to mutate in order to develop a resistance to that antibiotic. In contrast is the second way, which may be referred to as *exogenous resistance* and occurs through the exchange of genetic material between bacteria in the same environment. Genetic material simply refers to chains of molecules called genes within the bacterial cell (see Figure 4-1) which contain various instructions telling a cell how to function.

Figure 4-1: A Simple Bacterial Cell



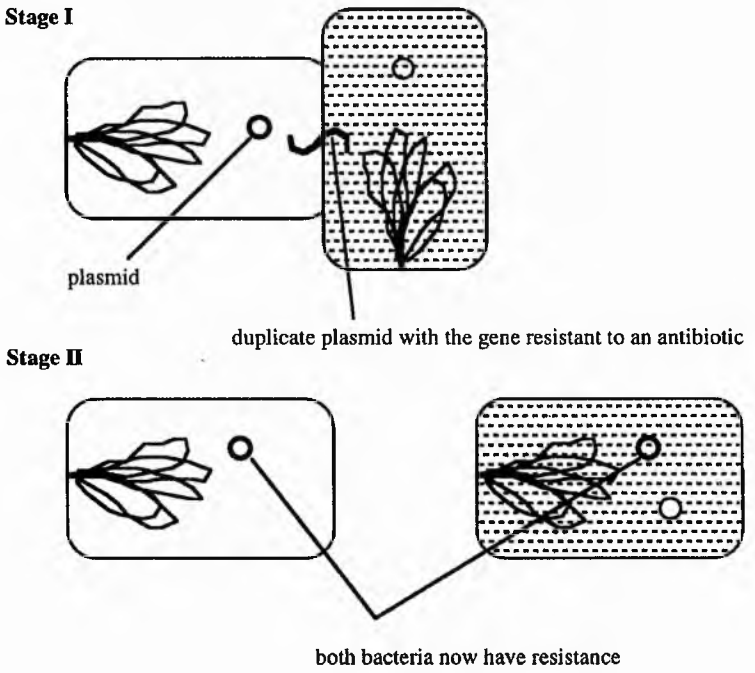
4-1:1 Endogenous Resistance

Endogenous resistance occurs in bacteria because of natural mutation of bacilli in every bacterial colony. This resistance was first detected in the early uses of penicillin when bacteria were observed to be able to live and grow in increasingly high concentrations of the drug. These resistant penicillin mutants had stronger cell walls than their susceptible counterparts, making it difficult for penicillin to

penetrate them (Levy, 1992). Nevertheless, this kind of resistant was thought to be easier to treat and less threatening in most bacteria than exogenous resistance.

Endogenous resistance is still observed in bacteria in modern times. Like exogenous resistance, one of the determinants to this resistance is exposure to an antibiotic. In every bacterial population there are some mutations which are simply more resistant to antibiotics. Often, through sub-therapeutic doses of antibiotics, all antibiotic-susceptible bacteria are killed, picking out or *selecting for* the mutants which then remain and multiply. It is a type of 'survival of the fittest' occurrence whereby natural resistance helps to perpetuate a population. Nevertheless, the likelihood of the development of this kind of resistance is strongly dependent on the size of a bacterial colony.

Figure 4-2: The Transference of Resistance Between Bacterial Cells



4-1:2 Exogenous Resistance

The second type of resistance in bacteria is exogenous resistance, which can be more virulent in many cases. This type of resistance occurs when bacteria receive their ability to resist antibiotic attacks from the free floating genetic material of other bacteria. Genetic material in bacteria consists of two types: a long chain of genes that remains with the cell, called the chromosome, and much shorter chains of freely moving genes known as plasmids that can be duplicated and transferred to other bacterial cells. These plasmids are of great importance because it is though them that resistance can be passed from one bacterium to another. In essence, a gene containing the instructions for a

bacterium to become resistant to a particular antibiotic will reside on a plasmid and can be duplicated. These duplicate plasmids may then move into other cells thus enabling these cells to become resistant. Figure 4-2 depicts this process.

To illustrate this process of transference, suppose a bacterium that resides in the intestine contains a gene with the instructions for resistance to the antibiotic penicillin, and happens to meet a more virulent bacterium, such as dysentery. The dysentery bacterium can then receive a duplicate gene form the intestinal bacteria rendering it resistant to penicillin. Nevertheless, one might question the threat of one bacterium resistant to an antibiotic such as penicillin in an infection characteristically containing several million bacteria. The problem occurs once this population is exposed to the antibiotic to which it is resistant. The antibiotic will kill every cell of bacteria that is susceptible to it, leaving only those resistant bacteria behind. Once this has occurred and there are only the bacteria with the resistant genes left, the antibiotic has selected for the resistant bacteria. This bacteria can now multiply faster in this environment since there are fewer other bacteria to compete with. Correspondingly, it can remain impregnable to any further treatment from that antibiotic.

Once an infection has become antibiotic-resistant, it can be passed to other individuals in this resistant form. In this situation, the individual that has been exposed and develops a resistant infection also cannot be treated by the respective antibiotic. In this way resistant infections can become predominant.

4-1:3 The Effects of Transferred Resistance

What can be concluded from these two methods of resistance development is that individual exposure to antibiotics can be the cause of resistance. The problem arises from repeated exposure to various antibiotics, there can develop a disease strain that is resistant to several different antibiotics characteristically used to treat it. This can make its treatment very expensive and difficult, often resulting in patient fatality. Furthermore, there are few new antibiotics coming onto the market. Antibiotics are chemicals that originate from a few basic chemical types or 'families', most of which have been completely exhausted.

Indeed, the mismanagement of antibiotics is common. Many doctors, can feel pressurised to prescribe an antibiotic for the common cold virus to which antibiotics are ineffective, or for use in the treatment of acne resulting in prolonged and unnecessary use. Also, insufficient exposure to antibiotics is also a determinant of resistance: due to the lack of education, many people who receive antibiotics stop taking them once they feel better, failing to complete the necessary prescription. Hence, the inappropriate and inefficient use of antibiotics can cause unnecessary resistance.

4-1:4 Summary of Section 4-1

There are two methods for the development of resistance, endogenous or naturally occurring mutation, and exogenous resistance, through the exchange of genetic material between bacteria. The mechanisms of antibiotic resistance are a unique and worrying occurrence especially where resistance can be easily transferred from one type of bacteria to another type of bacteria in the same environment. To fight such resistance, serious consideration needs to be taken concerning the consumption of antibiotics. Certainly, many antibiotics might be considered one of the most valued scarce resources if actions are not taken for their better regulation.

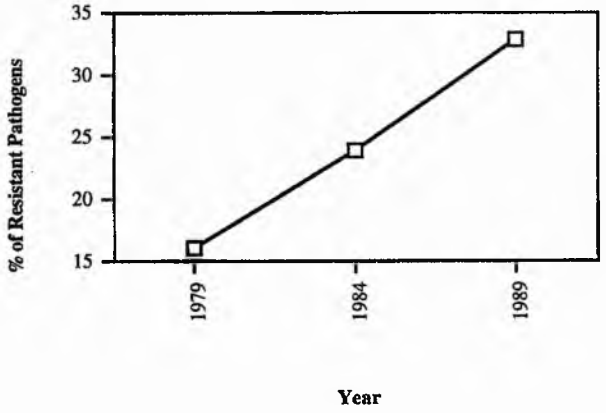
Section 4-2

ANTIBIOTIC UTILISATION AND COST CONSIDERATIONS

In this section there is an overview of the significance of antibiotic resistance. It additionally contains a presentation of an economic model showing how inverse demand curves for a given antibiotic are affected by increasing resistance to it. Theories on how bacterial resistance to antibiotics influences the cost of treatment are also presented in this section. This information will be further expanded in later chapters when it is applied to tuberculosis.

Antibiotics have served as a comparatively cheap health intervention in the treatment of bacterial infections that once caused widespread morbidity and mortality. Antibiotics are a relatively 'hassle free' method of treating infections, giving them their often referred to name in developing countries of the 'magic bullet'. Nevertheless, this highly efficient cure has been threatened by the growth of bacterial resistance to antibiotics. Bacterial resistance can grow quickly and move with ease. Indeed, the growth of resistance has many implications. It makes the treatment of bacterial infections far more difficult and in some cases impossible. Often more expensive antibiotics must be used, and in the case of serious resistant infections, hospital stays during treatment increase. This, of course, drastically increases the cost of treating such infections and therefore, has a strong economic impact on the cost of interventions.

Figure 4-3: Percentage of *Salmonella* Isolates Resistant to One or More Antibiotics in Three Prospective Studies



Source: Cohen, 1992

4-2:1 The Appearance and Growth of New Strains of Resistance

Resistance is continually growing and new strains of resistance are discovered every year. Cohen (1992) for example, reports US Center for Disease Control (CDC) results of three prospective studies of *Salmonella* isolates' susceptibilities to 12 antibiotics. New resistance is a function of antibiotic use whether it is appropriate or inappropriate. As illustrated in Figure 4-3, this report shows that in 1979 16% of isolates were resistant to one or more antibiotic, in 1984, 24% were resistant and in 1989, 32% were reported resistant to one or more antibiotic. Each year greater degrees of resistance are observed. Resistance is not particular to older antibiotics but it is indiscriminate. The more a drug is used on an antibacterial population, the more likely it is that resistance will develop. Levy (1991) charts outbreaks of resistance as observed in Table 4-1.

Table 4-1: Outbreaks of Resistant Pathogens in the 1980s

Country	Year	Manifestation of Resistance
Central and South America	1985	Co-trimoxazole resistant *E. coli*
North America	1985	Tc^r resistant *Mycoplasma* and *Ureaplasma*
Argentina	1984	Multiresistant *S. aureus*
	1988	Penicillinase-producing *N. gonorrhoeae*
Australia	1985	Multiresistant *S. aureus*
Australia, US, France, Belgium, Japan	1986	Tc^r *C. perfringens*
Bangladesh	1983	Multiresistant *V. cholerae* El Tor
Brazil	1989	Resistant urinary tract isolates
Bulgaria	1990	Multiresistant *S. sonei*
China	1986	Gentamicin resistance
	1988	Resistance in hospital isolates
Chile	1985	Ap^r Cm^r *H. influenzae*; multiresistant *Shigella* sp. ; Pn^r Tc^r resistant *S. Pneumoniae*
Finland	1988	Trimethoprim Resistance
GDR	1987	Multiresistant *S. aureus*; multiresistant *Enterobacteriaceae*
Guatemala	1989	Resistant *S. pneumoniae*
India	1983	Multiresistant *S. typhimurium*
	1984	Multiresistant *S. typhi*
India, West Bengal	1985	Multiresistant *S. dysenteriae* type 1
Iraq	1988	Resistant enteric pathogens
Philippines	1989	Resistance to new ß lactam antibiotics
Spain	1988	Resistant pneumococcus
Sri Lanka	1987	Trimethoprim resistance
Sudan	1987	Multiresistant *Enterobacteriaceae*
Tanzania	1983	Multiresistant *V. cholerae* El Tor
U.S.	1985	Multiresistant *Mycobacterium tuberculosis*
	1986	Penicillinase producing *N. gonorrhoeae*
	1986	Tc^r *N. gonorrhoeae*
	1987	Vancomycin resistant *S. haemolyticus*
	1988	Trimethoprim resistant *E. coli* in day care centres
	1988	Penicillinase producing *enterococci*
Former U.S.S.R.	1989	Resistant *P. aeruginosa* in hospitals
Vietnam	1989	Multiresistant *Shigella* sp.
Various Countries	1985	Co-trimoxazole resistant enteric pathogens
Zaire	1983	Multiresistant *S. dysenteriae*

Source: Levy, 1991

Resistance has become a powerful threat, in some cases, challenging doctors' abilities to treat common diseases. The two most clinically significantly observed incidences of resistance are

vancomycin resistant *Enterococcus faecina* and penicillin resistant *Streptococcus pneumoniae* (Bartlett and Froggatt 1995). The first is resistance that threatens patients in intensive care units because it is usually transferred nosocomially (hospital aquired). Other drugs that exist to treat this have not proved particularly effective. This resistance is relatively recent, having first been a problem in infections in 1988, nevertheless, it has started to grow at an alarming rate. Frieden *et al.* (1993) report that of 361 patients with vancomycin resistant *enterococci* (VRE) who were identified at 38 hospitals in New York, that 93% of VRE patients' infections were obtained nosocomially and 83% of these patients were administered vancomycin or a cephalosporin 30 days before VRE was detected. The hospitals in this study experienced a rise in VRE from 1 in 1989 to 38 in 1991. Penicillin resistant *S. pneumoniae* has also caused many problems in treatment and completely changes the approach to the infection's treatment.

Recent reports of the degree bacterial susceptibility suggest that resistance is a notable problem. Shehabi (1995) reports in Jordan between 1978-1989 that 52-90% of *S. typhimurium* isolates were resistant to one or more antibiotics. Kanavaki *et al.* (1994) report in Greece that of 1 002 isolates of *S. pneumoniae* from patients with community acquired pneumonia, 14% were resistant to penicillin, 20% were resistant to erythromycin, 26% were resistant to tetracycline and 1% were resistant to chloramphenicol.

Significant resistance has also appeared in rare infections in the immunocompromised, which are responsible for high death rates. Spencer (1995) observes resistance of *Stenotrophomonas* (Xanthomonas) *Maltophilia* and *Burkhoderia* (Pseudomonas) *Capacia* as a serious threat in nosocomial infections in immunocompromised cancer patients. Indeed, although a 7% resistance is observed in the UK, a 40% resistance is observed in the US. Fatal deterioration of patients in hospital because of these infections is very significant as far as the impact of resistance and its associated economic costs.

Indeed, antibiotic resistance is observed in most environments. It has appeared in animal livestock and in drinking water. Holmberg *et al.* (1984) identify 18 individuals in the midwest of the US who were infected by ampicillin-, carbenicillin- and teracycline- resistant *Salmonella newport*. 13 of these patients who were infected with this *S. newport* had consumed a hamburger from the same herd of South Dakota beef cattle, which had been administered sub-therapeutic chlortetracycline for growth promotion. Another example occurred in a ground water drinking supply in the US. Mckeon, Calbrese and Bissonnette (1995) found that of susceptibility tests to 16 antibiotics of 250 coliform and noncoliform bacteria from untreated ground water, all non-coliforms and 87% of coliforms were resistant to at least one antibiotic.

4-2:2 Inappropriate Use of Antibiotics

With such a significant amount of antibiotic resistance to so many pathogens, the use of antibiotics cannot afford to be anything but rational and appropriate. The inappropriate use of antibiotics for the treatment of viral infections, or infections where they will not be effective, is a common phenomenon in both developing countries and industrialised countries, propelling the growth of resistance. Hogerzeil (1995) reports on the irrational use of antibiotics in teaching hospitals spanning from 1977-1991. He maintains that teaching hospitals, which are designed as role models for medical students, could possibly be propagating bad habits in student learning due to irrational antibiotic prescription procedures. In Table 4-2, one can observe irrational prescribing behaviour in six countries, occurring in a wide range of departments. This suggests that inappropriate use of antibiotic in a hospital context is not an isolated phenomenon.

Table 4-2: Inappropriate Use of Antibiotics in Teaching Hospitals

Country	% Inappropriate Use	Type/Department	Source
Canada	42%	Surgical Ward, Parenteral Antibiotics	Achong, Hauser and Krusky, 1977
	50%	Gynaecology Ward	
	12%	Medical Ward	
USA	41%	All Inpatients	Maki and Schuna, 1978
Australia	86-91%	Prophylaxis	Mashford and Robertson, 1979
Canada	30%	Paediatric Medical Cases	Schollenberg and Albritton, 1980
	63%	Paediatric Surgical Cases	
Australia	48%	All Departments	Harvey, 1988
Kuwait	39%	Paediatric Inpatients	Najdi, *et al.*, 1988
Australia	64%	Patients Treated with Vancomycin	Misan, *et al.*, 1990
Thailand	91%	All Departments	Aswapokee, Vaithayapichet and Heller, 1990
South Africa	54%	Gynaecology Inpatients	Till, *et al.*, 1991
	22-100%	Unrestricted Antibiotics	
Thailand	41%	All Departments	Udomthavornsuk *et al.*, 1991
	79.7%	Surgical Prophylaxis	
	40.2%	Documented Infection	

Compiled By: Hogerzeil, 1995

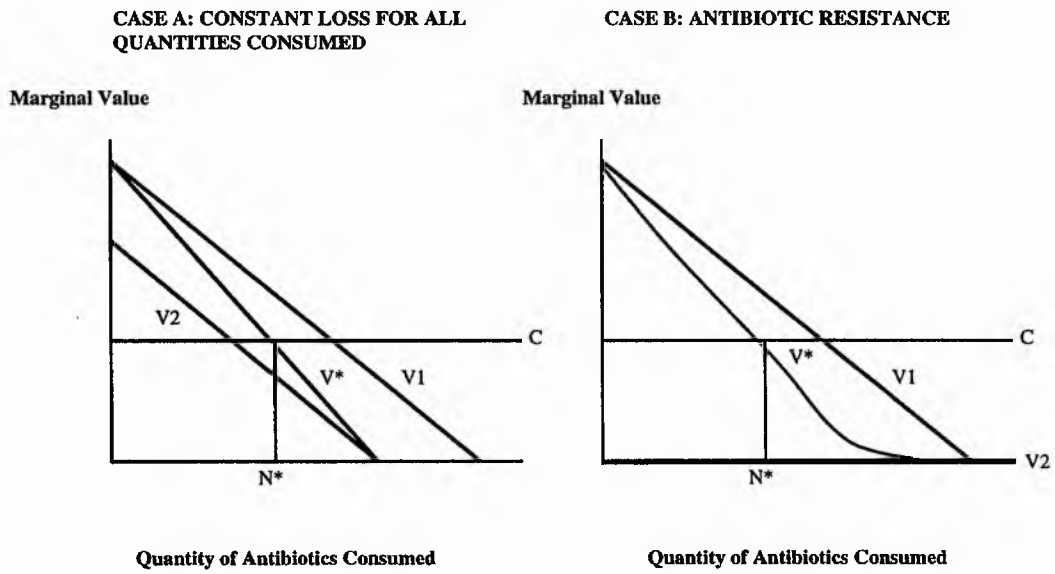
Efforts to curve inappropriate antibiotic use have only been somewhat successful. One of the most interesting cases of this occurred in Australia. Here there has been a large problem in a highly resistant form of *enteroccus* in hospitals which has become quite a threat in nosocomial infections. In an effort to change the prescribing behaviour of doctors, relevant to antibiotics, the *Antibiotic Guidelines* were brought out in 1977, supported by a strong marketing campaign (Harvey *et al.*, 1986). This marketing campaign later in 1985 involved pharmaceutical-style marketing material and representatives to educate doctors in antibiotic prescribing. This approach was deemed to be effective in the short run, but the positive effects were diffused over time. Cost savings from better antibiotic prescription were observed to greatly outweigh the costs of this educational campaign (Landgren *et al.*,

1988). Nevertheless, although some progress was obtained in prescribing behaviour, many doctors still prescribed antibiotics counter to the *Antibiotic Guidelines*. In a study by Harvey (1990), a sample of G.P.s' prescribing behaviour was compared to the recommendations of the *Guidelines*. In this sample 50% of G.P.s prescribed norfloxacin for acute urinary uncomplicated urinary tract infection when its use is not recommended for this. Another 43% of 2342 prescriptions to treat tonsillitis were for amoxycillin and co-trimoxazole which is also counter to the *Antibiotic Guidelines*.

4-2:3 Economic Loss from Resistance

Bacterial Resistance creates two potential losses to the overall economic well being of society. The first represents the direct loss to the consumer due to inappropriate use. This is loss that a given consumer experiences because those antibiotics that a consumer has used inappropriately will no longer be useful in treating future infections that he or she might experience. The second form of loss is indirect loss experienced by all users of antibiotics in a society. As the overall use of antibiotics rises, so does the overall growth of resistance, therefore increasing the transference of resistance and making antibiotics less potent in fighting infection in future antibiotic users. Antibiotic use creates a negative externality whereby one individual's use allows for greater future bacterial resistance that will be experienced by others. The negative externality of antibiotic use according to Phelps (1989) is such that each 10% increase in use will result in a 1-10% increase in resistance.

Figure 4-4: The Expected Value Demand Curve for an Antibiotic



Source: Phelps, 1989

4-2:3a The Impact of Resistance in the Expected Value Demand Curve for Antibiotics

Phelps (1989) has derived a model for the impact of resistance on the demand for antibiotics. In this model, shown in Figure 4-4, demand for an antibiotic is strongly affected by the level antibacterial resistance to it. Phelps presents two incremental value (inverse demand) curves (V^*) for a given antibiotic. V_1 represents the inverse demand curve if patients were certain that their infection was sensitive to the antibiotic. In contrast, V_2 is the curve representing the case if patients knew that their infection was resistant to that antibiotic. V_2 in *Case A* reflects the 'placebo value' of taking antibiotics, where V_2 in *Case B* does not take into account the 'placebo value' and therefore V_2 is equal to the horizontal axis. This is because V_2 in this second case has virtually no value to patients. In actuality, patients do not know for certain whether or not their infection will be susceptible to an antibiotic and therefore, Phelps takes the weighted average of V_1 and V_2 to derive the actual expected value demand curve for the antibiotic, represented by V^* in Figure 4-4. Demand for the antibiotic will occur at the point where the demand curve V^* and private marginal cost intersect which is at quantity N_1. The probability of resistance (P) is expected to rise with the intensity of an antibiotic's usage. In fact, each subsequent dose of antibiotic increases the probability of resistance. Therefore N, which represents the quantity of antibiotics used, is a determining factor of V_1, V_2, P, and ΔV. Hence, Phelps defines the expected gain from any antibiotic as

$$V^* = V_1(1 - P(N)) + V_2 P(N)$$

Where

V_1 = the inverse demand curve if patients were certain that their infection was sensitive to an antibiotic.

V_2 = the inverse demand curve if patients knew that their infection was resistant to an antibiotic

ΔV = V_1-V_2 = the difference in value of an antibiotic in the case of resistance

P = the probability that a bacterial colony is resistant

C =the drug cost per treatment

From this, the overall welfare gain (W) net cost to society for N doses of an antibiotic is

$$W = \int_0^N \left[V_1(x)(1 - P(N)) + V_2 P(N) - C \right] dx$$

Where

V_1 = the inverse demand curve if patients were certain that their infection was sensitive to an antibiotic.

V_2 = the inverse demand curve if patients knew that their infection was resistant to an antibiotic

$\Delta V = V_1 - V_2$ = the difference in value of an antibiotic in the case of resistance

$P(N)$= the probability of a resistant bacterial colony as a function of the aggregate consumption level N

C=the drug cost per treatment

Here the area from the V^* curve to C in Figure 4-4 is calculated for consumption N.

The optimum use of an antibiotic is found by identifying the point of maximum expected gain, or where $dW/dN=0$ and therefore, where $V^*(N)=V_1(N)(1-P(N))+V_2(N)P(N)$ or

$$\frac{dW}{dN} = V^*(N) - C - \int_0^N \Delta V(x) \frac{dP(N)}{dN} dx = 0$$

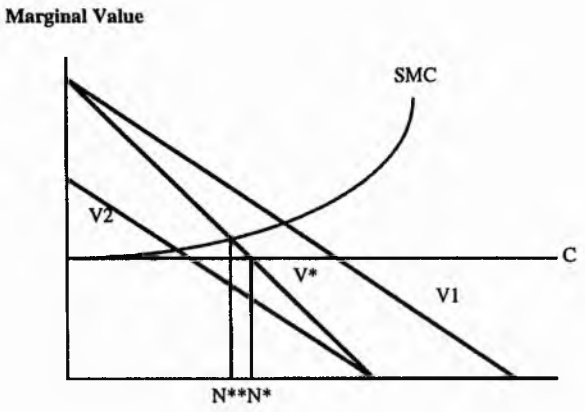
In order to find optimum use in this equation, N is substituted for N^*, the optimum use of the antibiotic in question. In *Case A* in Figure 4-4, ΔV is constant and in order to find the point of maximum expected gain, the equation changes to

$$V^* = C + \Delta V \frac{dP(N^*)}{dN} N^*$$

and dP/dN is calculated at N*.

According to Phelps, these equations predict that increasing antibiotic use until expected incremental benefits V^* equal incremental costs will achieve an optimum.

Figure 4-5: The Private and Social Optimum of Antibiotic Usage



The private cost, in this case is represented by C. These dynamics can be seen in Figure 4-5, where the private optimum N^* makes expected marginal value V^* equal to the private cost C. N^{**}, the social optimum illustrates the negative externality of increasing resistance. SMC is equal to the social marginal cost which is equal to the sum of the private cost C and the negative externality from use. The distance of the SMC curve over the private cost C is dependent on the size of the negative externality. By looking at Figure 4-5, one can see the negative externality between N^{**} and N^*. Efforts to move N^* back to N^{**} will represent lost welfare experienced by the individual. Possible methods to limit the size of this externality and motivate the individual to use antibiotics more carefully might include a tax on antibiotics, a subsidy for not using antibiotics, or an educational programme for individuals as an attempt to improve health so that overall demand for antibiotics will decrease in the long run. Nevertheless, each of these have their associated costs.

4-2:3b Unrecognised Costs

Aside from these costs, according to Phelps, an unrecognised cost arises from the fact that resistance in the individual can last for years after the initial antibiotic use. Such latent resistance may not affect the individual or society until many years later. This time period is represented by T years. Therefore, if resistance lasts for T years, in year one, the unrecognised costs are represented by

$$= \sum_{t=1}^{T} N_t \Delta V_t \left[dP_t / dN_1 \right] / (1+r)^t$$

Where

Nt = the rate of antibiotic use in year t

dPt/dN_1 = rate from at which drug administration in year 1 affects the probability of resistance in year t.

r=the discount rate

These are a representation of the social costs of using antibiotics. Phelps estimates that these costs in the United States alone range from US $75 million and US $7.5 billion. These costs are expressed in the cost per single treatment and can be seen in Table 4-3.

Table 4-3: Annual Unrecognised Costs of a Single Treatment of Antibiotics for Given Various Rates of percentage Change in Resistance

	Percent Change in Resistance Rate Due to a 1 Percent change in Antibiotic Use (US$)					
		0.1	**0.25**	**0.50**	**0.75**	**1.0**
Loss in Expected Value of Antibiotics Due to Resistance	100	0.50	1.25	2.50	3.75	5.00
	250	1.25	3.12	6.25	9.37	12.50
	500	2.50	6.25	12.50	18.75	25.00
	750	3.75	9.37	18.75	28.15	37.50
	1000	5.00	12.50	25.00	37.50	50.00

Source: Phelps, 1989

4-2:4 Comparative Costs Between Resistant and Susceptible Infections

According to Phelps, the size of the negative externality from antibiotic use is dependent on the pattern of use. This refers to the type of antibiotic that is used, the patients chosen for treatment and the disease that it is used to treat. Costs might encompass just the substitution of the ineffective antibiotic for one that the bacterial infection is susceptible. Unfortunately, the antibiotic substituted is usually more expensive than the initial choice. Vancomycin, a last line drug used to treat life-threatening resistant staphylococcal infections proves to be more toxic and more expensive than other antibiotics that treat susceptible staphyloccal infections. For instance, Phelps claims that tobramycin is ten times the cost of gentamicin, and hence, gentamicin becomes the first choice for treating susceptible infections. Certainly, if drugs are the only cost incurred in resistance, the difference in the costs between these two drugs is ΔV. In such cases it is obvious that a health facility is going to rely on the cheapest drug to which an infection is susceptible. However, when this drug is no longer effective, the facility must find an alternative drug which usually proves to be more expensive.

Costs from resistance can be quite high and are determined by several factors. These factors include the increase in death rates from infection, the failure to cure an infection, extra hospital days, increased doctor and nurse time, surgical procedures, the cost of more expensive antibiotics (both for society and the individual), spread of the resistant infection to other individuals in the environment and

indirect costs of lost productivity from extra hospital stay and extra time spent with a debilitating infection. Holmberg, Solomon and Blake (1987) estimate from CDC data on resistant nosocomial infections, that the hospital stay for resistant infections is invariably at least twice as long as susceptible infections. Hence, an extra hidden cost to hospital treatment can manifest itself in resistant nosocomial infections. Resistant infections have the tendency to proliferate in health care environments and often manifest themselves in nosocomial infections (nosocomial infections are not always resistant, as some writers believe, but refer to infections that develop in a hospital or health care facility).

All of these costs are primarily a result of the intensity of use of an antibiotic. Nevertheless, antibiotics are undeniably one of the most effective treatments known to man. Until the costs of resistance outweigh the benefits of greater cures, antibiotics will continue to be used, and therefore, resistance will continue as an effect of antibiotic use. Supporting this, Liss and Batchelor (1987) estimate that the overall incidence of mortality from both antibiotic resistant and antibiotic susceptible infections appropriately treated with antibiotics is low. They further observe that benefits from treatment outweigh any social cost, including resistance. However, in the case of the inappropriate use of antibiotics, the ensuing resistance is altogether unnecessary. Just monitoring this use in industrialised countries is not sufficient: inevitably, the resistance that occurs in developing countries has a strong impact on industrialised countries. Sherrard and Forsyth (1994) found that 30% of isolates of *N. gonorrhoeae* from epidemiological and microbiological laboratory data confirmed that infections between 1983-1992 originated in the Philippines. The authors observed that although the first cases of resistance that were observed came from the Philippines, resistance in gonorrhoea was now endemic to Australia.

If resistance should indeed prove to be a real problem in the treatment of many diseases, it is possible that the cost of automatically using a combination of antibiotics to treat a disease may prove less costly than the subsequent resistance arising from therapy with only one drug. Nevertheless, new antimicrobial agents are likely to be less costly than antibiotic combinations (Neu, 1985). The problem is that the development of new antibiotics has diminished.

4-2:5 Summary of Section 4-2

The inappropriate use of antibiotics is closely linked to the growth of needless resistance. The current growth rate of resistance is certainly alarming, especially in cases of VRE and penicillin resistant *Streptococcus pneumoniae,* which are responsible for significant morbidity and mortality. With each individual consumption of antibiotics, there enlarges an already existing negative externality of antibiotic use, as delineated by Phelps (1989). This negative externality has its associated economic

costs. The cost of treating resistant infections far outweighs the treatment of susceptible infections and therefore great savings could be achieved by limiting these resistant infections.

Section 4-3

THE PROBLEM IN DEVELOPING COUNTRIES

This section illustrates the specific problems of antibiotic resistance in developing countries. It shows the free availability of antibiotics to an individual, problems contributing to their inappropriate use and the incidence of antibiotic resistance of various diseases in developing countries. Possible strategies to specifically control and improve the usage of antibiotics are then presented. The problems contributing to antibiotic resistant diseases will be later applied to tuberculosis along with many of the mentioned strategies for decreasing resistance.

One of the areas with the largest incidence of antibiotic resistance is developing countries. This can be attributed to the free availability of antibiotics and the lack of their regulation. In most developing countries, it is possible to walk into a pharmacy and buy most reasonably priced antibiotics. Also, there is a lucrative black market trade in drugs, thus increasing their availability. In such an environment where antibiotics are so freely accessible, their frequent and unnecessary use is inevitably leading to a greater incidence of resistant infections. This is accentuated by the lack of education and the lack of funds available for health care which in turn results in individuals taking antibiotics indiscriminately to 'cure' problems such as a headache or sexual impotence (Kunin *et al.*, 1987, Ferguson, 1988, Medawar, 1976, Kapil, 1988, Lansang *et al.*, 1990).

Resistant manifestations of bacterial diseases render these diseases more difficult to treat, necessitating longer treatment and less success. More time and resources have to be spent treating these diseases in place of other health care needs. Following this, antibiotic resistant diseases financially drain these countries' already strained health budgets, making available health care all the more feeble. In developing countries, resistant infections incur the cost of the initial antibiotic(s) used before resistance was detected, the cost of newer more expensive antibiotics subsequently needed and the extra cost of treatment in terms of hospital resources and doctor, nurse and patient time.

A further problem causing resistant strains in developing countries is the ineffective use of antibiotics to treat a disease. In both clinical situations, often the wrong antibiotic or antibiotic combination, such as a broad spectrum or an antiquated antibiotic, is used to treat many infections to which they are ineffective. This less than ideal use can be dictated by cost constraints or misguided choices. In some situations, greater resource drain and extra time and misery could be averted through the use of a slightly more expensive but more cost-effective antibiotic.

4-3:1 Unconstrained Availability

As previously discussed in Chapter 3, like other drugs, many antibiotics can be bought on the street or in pharmacies by any individual who has the means to pay for them in developing countries. In Thailand, the *APUA Newsletter* (1990) observed that 75% of antimicrobials are purchased through non-institutional channels: 50-60% through drug stores and 15-25% through clinics in the private sector. Lansang *et al.*, found that of 1608 antibiotic transactions, 66.3% were made without a prescription. These were most commonly for respiratory tract infections (20.2%), tuberculosis (8.8%), 'prophylaxis' (8.6%) and gastrointestinal infections (8.3%). In addition, the therapeutic dosage period was in question as nearly 90% of purchases were for 10 or fewer pills or capsules. Obaseiki-Ebor, Akerele and Ebea (1987) in Nigeria discovered that of 500 patients, 73% consumed antibiotics before seeking the care of a doctor. Of those antibiotics purchased, ampicillin was used in 80% of cases, succeeded by tetracycline (60%), co-trimoxazole (40%), chloramphenicol (35%), oxytetracycline (30%), dihydrosteptomycin (30%), spectinomycin, (20%) and erythromycin (10%) (Often more than one antibiotic is purchased). This availability is not just taken advantage by residents of developing countries, those in industrialised countries also rely on self-medication obtained in developing countries. In Ciudad Juarez, Mexico, Solis (1993) reports that hundreds of Americans cross the border from Texas to purchase prescription drugs in pharmacies. Here the lure to individuals is that they can buy Mexican drugs unrestrained for a fifth of the cost of pharmaceuticals in the US. 25% of 800 El Paso residents questioned admitted to buying drugs in Ciudad Juarez. Individuals who are displeased that they have not received an antibiotic from an American doctor will cross the border and buy them. For example, in one instance, after receiving aspirin for her feverish 4 year old daughter, a woman rushed her daughter over the border to buy a US $2 package of ampicillin.

4-3:2 Myths Perpetuating Inappropriate Use

The incorrect belief that antibiotics are a miracle cure for most illness perpetuates. Many times as a result of this belief, compounded with the inappropriate marketing of antibiotics, antibiotics are consumed for the wrong reasons. Haak and Hardon (1988) observed in Africa that a common feature of antibiotic drug therapy is for a patient who has previously had a successful cure from an antibiotic to ask for more of it as a preventative measure against future illnesses. Burghhart (1988) found in India that penicillin was used by ayurvedic healers in a myriad of strange capacities. Similarly, Higginbotham and Streiner (1991) observe in one study that no matter what the illness, individuals will purchase an antibiotic due to these drugs' effectiveness in previous illnesses. In Upper Volta, the antibiotic-containing substance *tupaye* can be found in markets all over the country. *'Tupaye'* is a term

meaning 'it heals everything' and is used for treating all ailments from toothache and backache to malaria (Cannon, 1995).

4-3:2a Diarrhoea

This widespread inappropriate use of antibiotics is most acutely felt in the case of diarrhoea. Although many antibiotic medicines are available for this condition, the best recommended treatment with it is ORS. The following quote captures this.

> As the boat drew in to the shore we heard a strange sound from the bank. A woman was crying. We found her with a dead baby in her arms, and a collection of medicine bottles beside here. She had spent all her money on these expensive drugs. She could not understand why they had not saved her baby. This Bangladeshi woman had never been told what was obvious to the doctor that found her. The baby had become severely dehydrated with diarrhoea. Her death could have been prevented with a simple home-made solution of water, salt and sugar. No amount of medicine could have kept her alive. (Melrose, 1982).

Today diarrhoea is a disease that is the largest killer of children under three in the world (Cannon, 1995). Where ORS is the accepted treatment, antibiotic-containing medicines still proliferate. There is the psychological view in consumers that if a medicine contains an antibiotic, it must somehow be better. These antibiotics are not just harmful because they stop the use of ORS, but they can contain dangerous antibiotics. Indeed, this is not an uncommon phenomena and antidiorrhoeal preparations are more likely to resemble 'antibiotic cocktails' with combinations, for instance, of chloramphenicol and streptomycin (Srinivasan, 1988). Supporting this, in the 1980s, Health Action International (HAI) found that one in four antidioarrhoeals in Pakistan and India contained streptomycin, one in three in the Philippines contained sulphonamides, one in four in Africa contained neomycin (an antibiotic associated with the risk of deafness and serious intestinal problems) and surprisingly, one in ten in India contained chloramphenicol (Cannon, 1995). Chloramphenicol is especially dangerous, nevertheless, it has remained a popular drug in some developing countries, especially India. Greenhalgh (1986), in a study of 2 400 patients' medical consultations in India, found that chloramphenicol amounted to 11% of all prescriptions and was the most common antibiotic bought without a prescription.

4-3:2b Cultural Attitudes Towards Antibiotics in Developing Countries

Kunin *et al.* (1987) summarise cultural attitudes towards antibiotics maintaining that poor antibiotic use is propagated by several beliefs: (1) there is a 'pill for every ill' (2) antibiotics are 'wonder drugs' and can cure a myriad of ailments (3) the effectiveness of a drug is related to how fast is works (4) antibiotics cure illnesses more quickly than other drugs with fewer complications (common belief of clinicians as well as the patient) (5) injections are more potent and effective than pills or liquids.

4-3:2c Antibiotic Marketing

The marketing of drugs can perpetuate the popularity of antibiotics. For instance, Osifo (1983) observed that a Nigerian affiliate of Burroughs-Wellcome had five more indications and fewer adverse reactions and warnings on its product package inserts for Bactrim than was observed in the *Physician's Desk Reference* (*PDR*, 1992). The Thamlikitkul (1990) reported that in the *Thailand Index of Medical Specialities* July 1988 issue, antibiotics were incorrectly recommended for ten different indications as seen in Table 4-4.

Table 4-4: Inappropriate Indications for Antibiotics Appearing in the *Thailand Index of Medical Specialities*, July 1988.

Indication	Drugs Inappropriately Advertised
Gonococcal infection	Gentimicin, chloramphenicol, erythromycin, amoxicillin, penicillin V, co-trimoxazole, rifampicin
Pharyngitis, tonsillitis	Kanamycin, chloramphenicol, cloxacillin, co-trimoxazole, oflaxocin
Central nervous system	Amikacin, tetracycline, lincomycin
S. aureus infection	Penicillin V, penicillin G, ampicillin
Non-specific urethritis	Ampicillin, oxacillin
Biliary tract, respiratory tract and urinary tract infection	Rifampicin
Prophylaxis of cholera	Penicillin V

Source: *APUA Newsletter*, 1990

4-3:3 Sub-therapeutic Doses and Compliance

Another problem contributing to resistance occurs from patients receiving sub-therapeutic dosages of antibiotics. This can happen either because the patient is given too short a treatment, the patient does not comply with the treatment, the patient only buys a few pills and does not receive enough of the treatment, or the patient takes clinically unrecommended antibiotics on a regular basis as a prophylaxis. This kind of antibiotic use causes resistance in two ways: through selecting naturally resistant mutants in a bacterial population, as in the cases of some *Mycobacterium* diseases, or through selecting bacteria with resistant plasmids, as in the case of *Salmonella* strains. Treatment times for many antibiotics can differ and some must continue for long periods of time. Many patients, once they feel better, fail to finish their treatment. In addition, some patients can only afford to buy one or two pills, and therefore, manage to only kill part of their bacterial infection. Also, it is not uncommon, where antibiotics are freely available, for patients to take a regular dose of penicillin or tetracycline just to 'make sure they don't get sick' (Levy, 1992). Antibiotic prophylaxis in prostitutes in order to avoid cases of gonorrhoea or syphilis is also a common phenomena. This kind of prophylaxis is likely to have contributed to the quick growth of resistant forms of gonorrhoea.

4-3:4 Abuse and Inappropriate Choices

Antibiotic resistance becomes especially significant when resistance develops in an infectious disease that only one or a few antibiotics which can treat. Chloramphenicol, usually reserved for cases of typhoid fever, has been inappropriately used for all kinds of infections and indications. Consequently, chloramphenicol resistant typhoid has developed which is difficult to treat with other antibiotics. Rifampicin which is reserved to treat life threatening bacterial meningitis and tuberculosis is another case. Rifampicin, could be considered the most powerful new antibiotic to treat tuberculosis and meningitis, but has been used in other indications such as urinary tract infections, gonococcal infections and eye infections (Thamlikitkul, 1990).

Another problem facing developing countries is the choice of antibiotics for use in treating infections. Often developing countries cannot afford more expensive antibiotics and therefore must rely on cheaper alternatives that are not necessarily as effective in curing an infection. In some cases, the length of antibiotic treatments and resistance are heavily correlated. For example, it is possible that a shorter but more effective treatment might have greater compliance, and therefore, will have less associated resistance. Also, if the treatment is poor or relies on a combination of older, substandard antibiotics for treatment, compounded by long treatment periods, resistance becomes more significant because it leaves fewer drugs to treat these infections. This is indeed the case for tuberculosis. Conversely, an extra financial burden is imposed on developing countries when sometimes more expensive antibiotics are used instead of cheaper, equivalent alternatives. In essence, each antibiotic must be carefully considered according to its ability to cure an infection, and its appropriateness in curing that infection in light of alternatives and its relative cost. Finding these alternatives involves the evaluation of each disease and treatment, which takes time, education in cost optimisation and patience.

4-3:5 Damaged and Poor Quality Antibiotics

Individuals who often have to take drugs that are damaged, past their sell-by date, or in poor supply present a further problem. Poor conditions in the transport and storage of antibiotics can allow them to be damaged by heat or humidity. Also, due to the poor management of drug supply, antibiotics are often ordered and stored for too long or they are obtained from pharmaceutical companies when they are too close to their expiration date. These all cause anti-infectives to be far less effective. In an article that appeared in the *Essential Drugs Monitor* (1991b), the stability of drugs during international transport was measured, including work on the stability of antibiotics under high temperatures. 11 essential drugs were sent through in three shipments by sea from the UNICEF warehouse in Copenhagen through Lagos and Mombassa and by land to Kampala and then to

Bangkok. Three sea routes taken accounted for 35 (50%) of 70 countries served by UNICEF and 40% of all drugs dispatched in 1987. In this study, the temperature and humidity in test packs were measured every three hours. Temperatures on the trip varied between -3.5°C and 42.4°C with a relative humidity of between 20-88%. Temperatures inside of the test pack averaged 10-26% higher than these outside temperatures. This is far higher than the WHO set standard of 15-25°C for the storage of drugs. Although the three antibiotics, ampicillin, tetracycline and procain penicillin in the study, did not show signs of instability, the article concludes that humidities, rather than temperature during storage have a large impact on antibiotic de-stabilisation.

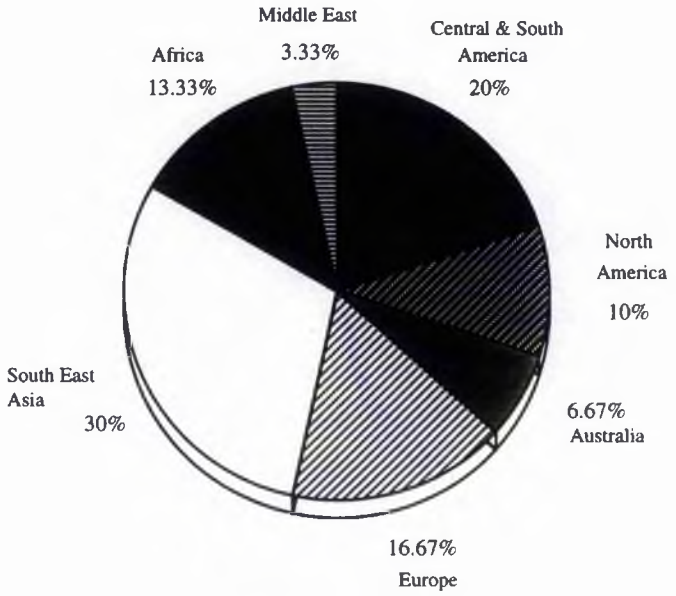
Drugs can also be of poor quality which affects their effectiveness. One of the best examples of this occurred in Jakarta with the sale of ampicillin. A domestic version of Beecham's ampicillin, Penbritin 250 was being sold in similarly marked capsules, but instead of 250 mg inside of them, they had been diluted to 80 mg. Where a doctor might recommend 8-10 capsules per day of the 250 mg version for infections, an individual buying this black market version would have had to take 25-50 capsules per day to get the same effect. Unfortunately, this was not readily evident from looking at the capsule (Silverman, Lydecker, Lee, 1992).

4-3:6 The Incidence of Resistance in Developing Countries

Antibiotics are used with great intensity in developing countries. In Africa, antibiotics are the leading therapeutic group, accounting for as much as 35% of drug sales (SCRIP, 1995). Globally, antibiotics are an extremely important, cheap and effective health care intervention for treating many diseases. This could be said to be especially true in developing countries where malnourishment, poverty, poor living conditions and poor sanitation mean that more individuals in developed countries are susceptible to bacterial infections than those in industrialised countries. Outbreaks of antibiotic resistant bacterial diseases are more commonly observed in developing countries. In fact, data from the Association for the Prudent Use of Antibiotics (APUA) between 1983 and 1990 (Levy, 1991) show that incidences of new strains of resistant infections arose in developing countries approximately 60% more frequently than in developed countries. Although most data for this resistance are unrecorded in developing countries, the percentage of outbreaks per area are shown in Figure 4-6. Population, of course, must be taken into account when looking at this figure.

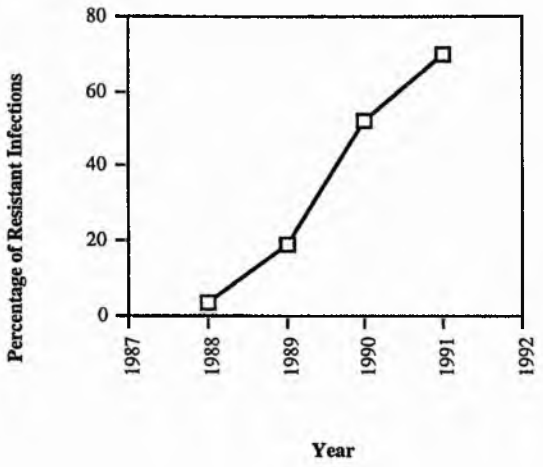
Antibiotic resistant rates are continuing to grow at an alarming rate. The impact of antibiotic resistance in developing countries has been very strong as shown by the following examples. As shown in Figure 4-7, in only three years, incidents of resistant typhoid in India have increased by more than *five times.*

Figure 4-6: Areas Where Antibiotic-Resistant Disease Strains Originated Between 1983-1990



Adapted From: Levy, 1991

Figure 4-7: Growth of Ampicillin and Co-Trimoxazole Resistant Typhoid in India



Adapted from: Sharma, Prakash and Pillai, 1985; Prakash and Pillai, 1992

Table 4-5: Prevalence of Resistant Gonorrhoea in Asia and Africa

Area	Prevalence of Resistance (%)
Asia	
Hong Kong	47.8
Republic of Korea	46
Thailand	42
Philippines	30-40
Malaysia	37.2
Singapore	33.5
Indonesia	25
Japan	16.1
Africa	
Nigeria	56
Kenya	41
Ghana	36
Zambia	25.1
Central African Republic	9.1

Source: O'Brien *et al.*, 1987

In addition, Cannon (1995) reports that of the 248 reported cases of typhoid in the UK in 1991, 50 (20%) were resistant to chloramphenicol and the majority of these were also resistant to ampicillin and trimethoprim. The majority of these resistant cases had returned from Pakistan or India, where resistant typhoid is common and chloramphenicol is the drug of choice in its treatment (as is also the case in industrialised countries due to the serious nature of the disease). Ries (1991) reports of a 1991 epidemic of *S. dysenteriae* in Burundi which proved resistant to all antibiotics available in the country.

Knapp *et al.* (1991) report that data from the Gonoccocal Isolate Surveillance Project show that between 1988 and 1990 gonorrhoea resistance to penicillin grew from 3-10% and resistance to tetracycline grew from 4-6%. The prevalence of penicillin resistance in Asia is reported by O'Brien *et al.* (1987). In Table 4-5, one can observe that resistant gonorrhoea in developing countries averages at approximately 34.6% and is at its highest (56%) in Nigeria. Matamoros *et al.* (1993) observe that in Costa Rica in 1985, gram negative bacteria were resistant to ampicillin in 68-97% of all isolates. Such resistance caused the Costa Rica Pharmacotherapeutics Committee to remove the most commonly used form of ampicillin from their formulary. Teixeira *et al.* (1995) found in their study in Brazil of 5 large teaching hospitals and 1 community hospital, 85 of 152 isolates of *Staphylococcus aureaus* were resistant to methicillin, penicillin, erythromycin, gentamicin, cephalothin, and oxacillin; and 74% of these 85 isolates were also resistant to chloramphenicol, sulfamethoxazole-trimethoprim, ciprofloxacin and clindamycin. Most of these resistant isolates were only susceptible to vancomycin.

Resistant cholera is another challenge in developing countries. Cholera is a diorrhoeal disease that strikes very quickly and can prove deadly. In Peru in 1992, a multi-drug resistant form of cholera known as 'El Tor' caused 3 000 deaths. Also in Pakistan and Bangladesh, 'Bengal' a strain resistant to co-trimoxazole, caused 100 000 cases and 1 500 deaths (Cannon, 1995).

4-3:7 Strategies for Developing Countries

Without a doubt, prescribing behaviour and antibiotic use can be changed. This power lies within the doctor and the patient. Regarding doctors, one form of educational media with the greatest impact is the personal visit from an antibiotic education representative. Schaffer *et al.*, (1983) showed in Tennessee that an informational campaign to physicians with a poor history of antibiotic prescribing, reduced antibiotic prescribing by 18% in the number of doctors, 44% in patients per doctor and 54% in the number of prescriptions per doctor. Reaching patients is more complicated and is likely to be more expensive. Industrialised countries remedy this problem by simply making antibiotics unavailable to the patient unless obtained through a prescribing agent. However, until developing countries limit the availability of antibiotics, antibiotic misuse will persist. Imperfect as this situation appears, individuals can still be educated. Education of pharmacists is a very important step to educating patients on proper utilisation, because this is commonly the point of purchase of antibiotics. Other education is difficult because many patients in developing countries cannot afford magazines, newspapers or television. A search for each country must be made to find whatever informational media to which a patient is exposed. This might range from billboards to educational posters in bars and other areas of social gathering.

It is clear that developing countries need a more effective strategy for the management of antibiotics. This strategy includes the following components: (1) greater regulation to control antibiotic administration and to restrict black market availability on the street (2) better drug transport to decrease the incidence of expiration and assure their arrival in the places they are most needed (3) more secure drug storage to eliminate drug theft (4) closer governmental inspection of the antibiotics purchased internationally to ensure that products are not likely to be beyond their expiration date when a patient receives them (5) more careful government policy for the purchasing of drugs to be sure that what is actually ordered is what is actually needed, thus eliminating some of the large stores of unnecessary drugs that sit unused (Foster, 1993) (6) quality control of the antibiotics produced domestically to ensure that those available meet international standards of antibiotic quality (7) closer analysis of each treatment regimen for each disease to secure the implementation of the most effective and efficient treatment and (8) better education for doctors, pharmacists and patients both so that doctors and pharmacists are more aware of the correct antibiotic to give for each condition, and so that patients know to complete their entire treatment as well as not rely on antibiotics for inappropriate purposes.

4-3:7a Influencing Doctor Prescribing Behaviour

In the case of doctor intervention (8 above), there are several approaches that can be taken toward changing prescribing practices. Avorn *et al.* (1987) gives a precise breakdown of the types of influence that can be used to change prescribing practices (reproduced in Figure 4-8). Here, influence is separated into three distinct strategies: re-educative and persuasive strategies, facilitative strategies and power strategies. Re-educative and persuasive strategies attempt to influence the doctor through education with media with lectures, drug information cards, audits on prescribing behaviour and guidelines. As mentioned earlier, this approach has been somewhat successful in Australia. Facilitative strategies involve specifically targeting drug programmes, diseases and patient populations using specialists in this area to, for instance, test for resistance or estimate the likelihood of resistance. Power strategies refer to enforced restriction. This involves the use of formularies such as essential drugs, control of drug representatives and marketing and special approval for various antibiotics. All these approaches should prove effective and any country that attempts to improve its antibiotic use should try to implement as many of these strategies that are within its means.

Figure 4-8: Strategies for Changing Prescribing Practices

Re-educative and Persuasive Strategies
Staff conference
Lectures by recognised authorities
Drug information bulletins
Feedback of prescribing data (audits)
Audio-visual programs
Independent printed drug information
Guidelines (requires feedback loop)
Laboratory sensitivity tests
Restriction of reports on selected agents unless requested, Information feedback to guide drug selection

Facilitative Strategies
Clinical-specialist consultations
Clinical microbiologists, Clinical pharmacists
Joint specialist programs with clinical microbiologists/pharmacists co-operation
Target drug programs
Target diseases and target patient programs

Power Strategies
Control of contact between pharmaceutical representatives and prescribers
Registration in hospital, Appointments, Entry into patient-care areas, Displays, Samples/gifts
Sponsoring, Advertisements, Literature,
Formularies
Effective Drug and Therapeutic Committee, Generic prescribing (encourage bid purchasing), Exclusion of inferior or marginal products, Limit therapeutic duplicates, Review of new drugs via comparative drug monographs, Require written justification for additional requests
Restriction on use
Approval of specialists for controlled agents, Approval of Drug and Therapeutic Committee recommendations, Written justifications before dispensing (review these at a later date), Satisfaction of criteria for use, Automatic stop orders, Require consultations after first doses of certain drugs

Source: Avorn *et al.*, 1987

4-3:7b Levels of Antibiotic Regulation Enforcement

Although the above strategies are ideal in industrialised countries, they must be evaluated according to the means of a developing country. Each country has its own system of antibiotic regulation enforcement. As shown in Table 4-6, Simon, Folb and Rocha (1987) classify these according to major categories: complete, partial, minimal, and none. Countries such as the United States where drug regulation is quite stringent will undoubtedly come under the category of complete antibiotic regulation enforcement. Countries such as Brazil and Mexico will fall in the category of minimal regulation. Nevertheless, the majority of low income countries, such as Bangladesh and Ethiopia, are more likely to fall in the enforcement category of 'none'. These categories dictate the environement to which antibiotic measures must be adapted. Although it would be ideal to change the very infrastructure of drug distribution and enforcement, this is unrealistic in the short run. Those countries that have a very poor enforcement of drug regulations, must work within their means to educate doctors and patients on the dangers and proper use of antibiotics. Highly elaborate monetary

intensive antibiotic prescribing behaviour schemes are a lure for developing countries but will prove useless under their limited drug delivery systems.

Table 4-6: Application in Practice and Enforcement of Compliance with Regulations

Complete	Tightly controlled availability; regulations rigorously enforced
Partial	Incomplete enforcement of controls associated with limited availability of antibiotics to the public for other reasons, such as economics and/or logistic factors
Minimal	Incomplete enforcement of controls associated with widespread availability of antibiotics as a result of failure to apply regulations in practice and absence of other constraining factors
None	No restrictive legislation; widespread availability

Source: Simon, Folb and Rocha, 1987

Certainly, a complete list of these changes might seem expensive, but many are not outside the financial realm of most developing countries. Angunawela, Diwan and Tomson (1991) in a study of 15 outpatient health care institutions in Sri Lanka, found that those in a control group that did not receive any information on correct prescribing of antibiotics wrote more prescriptions for antibiotics than a group that received information on correct prescribing. Information for prescribing emphasised the use of penicillin for common infections, contraindications of tetracycline for children and the improper use of antibiotics for viral infections. Each attempt to change antibiotic utilisation requires that there be a little more care in the handling of antibiotics. Although this may seem a little more costly, the benefits in terms of fewer antibiotic resistant infections, lower morbidity and mortality, reduced drug costs, averted treatment costs and reduced adverse side effects would outweigh the costs of these reforms in absolute terms.

4-3:8 Summary of Section 4-3

Developing countries have a poor system of antibiotic regulation. This is compounded by perpetuated myths of exaggerated antibiotic effectiveness and damaged and poor quality antibiotics rendering the consumption of antibiotics in sub-therapeutic doses. The effects of this improper use of antibiotics has been such that there is a higher incidence of resistance in developing countries. Such higher incidence has had a great impact. Resistance in already health constrained developing countries is responsible for morbidity and mortality and the high monetary costs of treating this. Indeed, it is possible to improve antibiotic utilisation in developing countries, but it is considerably complicated by the drug distribution infrastructure. Unless a concerted effort is made to improve drug use, inappropriate consumption and resistance will continue.

Section 4-4

CONCLUSION TO CHAPTER FOUR

Antibiotics are a valuable form of treatment, and undoubtedly, the most effective treatment for a myriad of infections . However, this effectiveness is threatened by resistance. Resistance has caused once inexpensively cured illnesses to be difficult or impossible to treat in some cases. In some cases, inexpensive antibiotics have become obsolete, and therefore, more expensive antibiotics are needed which often are not available or cannot be afforded. The use of antibiotics perpetuates an unavoidable negative externality of resistance. However, this resistance can be somewhat attenuated if care is taken to use antibiotics only when they are absolutely necessary. Indeed, the problem is even more accentuated in developing countries. Here resistance is rampant due to more inappropriate use of antibiotics and poor systems for their regulation. Antibiotics must be carefully evaluated for each disease according to their economic costs, their effectiveness and their role in curing other diseases. Needless resistance is likely to continue in developing and industrialised countries unless measures are taken to rationalise antibiotic use. Should antibiotic resistance continue, it could have potentially serious consequences for future generations. Some bacterial diseases can develop resistance to all known effective antibiotics leaving only surgery or unproven and dangerous drugs for treatment. This is serious when the disease is infectious and deadly. Tuberculosis is one of these diseases and because of sustantial levels of natural mutation on the part of the bacteria, tuberculosis resistance easily occurs. In addition, unlike some bacterial resistance, this is almost entirely due to inappropriate usage of tuberculosis antibiotics, as shown in the next chapter.

CHAPTER FIVE

TUBERCULOSIS

"At the midpoint of the 20th century, tuberculosis was recognised by all as the "White Plague", undeniably the most dreaded enemy of the human race by any measure. Whether measured by prevalence, cost, social consequences, sheer misery or any yardstick, I believe that any observer of the time would consider the bacillus of tuberculosis as the enemy number one of the human race. None of us - myself included - believed that its control could be attained by medical means within this 20th century." (H. Corwin Hinshaw from Ryan, 1992: p. 49)."

"Tuberculosis is still a leading contender for the dubious distinction of being the most important plague of mankind. (Comstock and Cauthen, 1993)."

"The captain of all these men of death that came against him to take him away, was the Consumption, for it was that that brought him down to the grave." John Bunyan, *The Life and Death of Mr. Badman*

In order to find the impact of resistance on the cost of tuberculosis, those elements specific to the treatment of tuberculosis must be described. This chapter traces the trends of tuberculosis infection, the nature of the disease and the difficulty in meeting the challenge presented by drug resistance and HIV combined with TB. In addition, this chapter is intended to give a comprehensive background to the reader so that he or she will be equipped with an understanding of the complex problems arising in TB treatment. Section 5-1 will begin with an overview of tuberculosis including its history, diagnosis, etiological epidemiology, treatment, resistance and the impact of HIV. In Section 5-2, current techniques of controlling tuberculosis will be presented including areas for potential improvement. The effectiveness of tuberculosis control will be illustrated in Section 5-3, highlighting the current global impact of tuberculosis and its changing nature.

Introduction

On the 21st of January, 1992, the *Evening Standard* in London ran the headline "HOSPITAL WARNING AS LETHAL SUPERGERM SPREADS". At this time at least a dozen people were wandering the streets of London with infectious tuberculosis (TB) that could not be treated by any antibiotic (Ryan, 1992). Tuberculosis which was thought by many as a plague of the past once again

was making news. People became aware of the disease along with what many erroneously feared a different 'super-strain' of tuberculosis resulting in widespread alarm. Certainly, tuberculosis is still a dangerous infectious disease. Because it is observed less in industrialised countries than in developing countries, its danger to mankind is not highlighted the way are diseases such as AIDS and heart disease. Nevertheless, it still causes large-scale devastation in developing countries. Its pathogenicity, which is often ignored, should never be underestimated. Indeed, in 1990, tuberculosis killed 2.9 million people, making it the largest cause of death from a single pathogen *in the world* (Murray *et al.*, 1991).

'White Plague', 'consumption', 'pulmonary phthisis', 'The Captain of all Men of Death': since the evolution of man, tuberculosis has been at his or her side, at times taking a startling 20% of lives in cities (Dubos & Dubos, 1987). In the last two hundred years, tuberculosis has claimed the lives of approximately a billion people (Ryan, 1992). Nevertheless, with modern antibiotics it was thought that the battle against this disease was won and it would only be a matter of time before tuberculosis was completely eradicated. It seemed that this prediction would manifest itself as the incidence of the disease fell continuously, starting in the 1950's. This made observed cases of tuberculosis more and more rare. However, this decrease in tuberculosis, quite surprisingly, came to an end when in 1978 its infection rate strangely began to rise. At first, clinicians could find no apparent reason why tuberculosis was on the rise, but they soon were able to link it to HIV (Human Immunodeficiency Virus), responsible for Acquired Immune Deficiency Syndrome (AIDS). It is no coincidence that as the incidence of AIDS increased in the late 1970s, so did the incidence of tuberculosis. However, difficulty in identifying the HIV virus, which was practically invisible until the early eighties, convoluted efforts to explain the rise in TB. Only time has revealed that the synergistic effects of the combination of these two diseases has proven deadly. In addition to this is the growing problem of the rise of multi-drug resistant tuberculosis, such that there is a growing percentage of cases that are failing to respond to conventional chemotherapy. Globally, tuberculosis remains as the leading cause of deaths in adults by an infectious disease (World Bank, 1993). In 1990, approximately a third of the world's population was infected with tuberculosis. Furthermore, of the 2.9 million people throughout the world that died from it in 1990, 40 000 of those deaths came from industrialised countries, leaving a staggering 2.86 million deaths from developing nations (Ryan, 1992). In this decade, it is predicted that 90 million new cases of tuberculosis will be diagnosed and 30 million will die from the disease (*FDA Online Reports*, 1995). This is especially significant because tuberculosis is a *curable* disease.

Efforts to reduce the incidence of tuberculosis have been effective in the past, but the AIDS virus presents a new challenge in treating tuberculosis, therefore representing a new era for this disease. Of all diseases globally, tuberculosis is the most opportunistic infection which will be strengthened by the

increasing prevalence of HIV. HIV patients essentially represent a pool for the TB virus to continue to thrive and move from individual to individual.

Section 5-1

THE NATURE OF TUBERCULOSIS

This section will give a description of tuberculosis, the likelihood of developing the disease, its diagnosis, history and treatment. Also, other problems complicating treatment and increasing its growth such as anti-TB drug resistance and HIV will be presented. This material introduces significant variables that will be later discussed in the context of the impact of TB resistance on the cost of TB treatment in developing countries.

5-1:1 The History of Tuberculosis

Until a cure was found, tuberculosis was a disease that as a killer did not discriminate between the old, the very young, the very rich or the very poor. Many well known people through history such as John Keats, David Herbert Lawrence, George Orwell, Emily Brontë, Frédéric Chopin and Vivien Leigh were taken away in the prime of their career by tuberculosis. Indeed, signs of tuberculosis have been observed in human remains dating as far back as 8 000 BC (Ayvazian, 1993). Evidence from the mummies of ancient Egypt suggest that tuberculosis was a common disease as far back as 4 000 BC, when it proved to be a disease that thrived in the close quarters of the first ancient cities (Ryan, 1992). Tuberculosis has a striking capacity to mutate and it is believed that all the different strains of tuberculosis came from one common parent. Different strains of tuberculosis affect birds and small reptiles and many mammals such as elephants and cattle. For example, transmission of phthisis, a bovine strain of tuberculosis, was such a deadly disease for cattle that from the middle ages to the eighteenth century, it was responsible for large recorded periods of famine (Ayvazian, 1993). Bovine tuberculosis, *Mycobacterium bovis*, is also significant because ingesting milk from infected cattle is one way that humans develop tuberculosis (Snider, 1994).

Until adequate treatment was developed, the more urbanised civilisation became, the more tuberculosis was able to spread. At the turn of the nineteenth century, 7 million people per year were dying from tuberculosis and 50 million had the disease with one half of the population infected (Ryan, 1992). Yet, even late in this century, all that was really known about the disease was that animals could be infected with it from human tissue. It was not until 1882, when Robert Koch developed a staining technique to isolate and identify tuberculosis, that significant progress in treating the disease began. After this discovery, several chemicals were discovered that could safely destroy tubercle bacteria without damaging its human host. In 1935, the drug prontosil was used in the treatment of tuberculosis and soon after, in 1944 there was the discovery of para-amino salt of aspirin (PAS). The most important progress, however, was made with the discovery of streptococcus in 1944. This

completely changed the nature of the threat of tuberculosis due to its increased effectiveness over previous treatments. After this, came the discovery of isoniazid in 1952 and rifampicin and pyrazinamide in 1963 and ethambutol in 1967 (Ryan, 1992). Triple therapy with three of these drugs revolutionised the treatment of tuberculosis and is still the main approach to chemotherapy for tuberculosis today.

5-1:2 Defining Tuberculosis

Tuberculosis (TB) is an infectious disease predominately caused by the bacterium *Mycobacterium tuberculosis*. It infects the individual by entering the body through the lungs where it can multiply and manifest itself as pulmonary tuberculosis in 80% of cases, and extra-pulmonary tuberculosis (tuberculosis that attacks organs outside of the lungs) in 20% of cases. Tuberculosis can attack any part of the body, but pulmonary tuberculosis is the only type of contagious tuberculosis, and hence, its treatment is a pinnacle element in the containment of the disease.

The spread of tuberculosis commences with the coughing, sneezing or laughing of an infectious patient. This activity produces small particles or droplets containing the tuberculosis micro-organisms which can remain floating in the air for many hours. After this, individuals entering the air around an infectious patient can inhale these droplets which may enter their lungs and multiply causing these contacts to be infected. Logically, the greater contact one has with an infectious tuberculosis person, the more it is likely that he or she will become infected. Those that become infected are referred to as positive tuberculin reactors in reference to the protein purified derivative (PPD) skin test or the Mantoux skin test, used to identify those infected with tuberculosis. It should be noted that there is a distinction between *infection* and *disease*: those that become infected may not necessarily develop tuberculosis. In fact, only ten to 20% of those infected will ever develop the disease, the other eighty to 90% will carry dormant tubercle bacilli for the rest of their lives.

5-1:2a PPD and the Mantoux Tests

The existence of tuberculosis infection is usually established by a tuberculin skin test such as the previously mentioned PPD or Mantoux test. The patient's forearm is scratched, punctured or injected in the skin, intracutaneously, with dead tuberculin bacteria. This test is effective approximately three weeks after initial contact with an infectious case. After this period, individuals that have been infected with tuberculosis should have developed some sort of immune response to it so that they will have antibodies that will react to the dead tuberculin. Such reactions are characterised by redness of the skin but more accurately by induration (hardness of the skin) at the point of the test. Indurations are measured 48-72 hours after the test to observe a reaction. Those who are extremely likely to have

been exposed to tuberculosis, or are HIV positive, are considered positive at greater or equal to 5 millimetres induration Those at a moderate risk are considered positive at greater or equal to 10 millimetres induration. Finally, those who are tested and are perceived to be at no risk are considered positive only at greater or equal to 15 millimetres induration (Bass, 1993). These tests can give a false-negative result if the patient has extremely acute tuberculosis, immunosuppression, viral infections, live virus vaccination including Bacille Calmette-Guérin (BCG) vaccines, renal failure or malnutrition. Also, false-negatives can be the result of improper storage, improper dilution, delayed injection after a syringe is filled, subcutaneous injection, and improper or biased interpretation (Bass, 1993). Such tests only establish proof of infection with tuberculosis and are not guarantees of the presence of the disease, nor can they determine with which strain of *Mycobacteria* an individual has been infected. Nevertheless, it is a useful tool in the sense that a negative test could be used as a possible diagnostic determinant in ruling out tuberculosis once the likelihood of false-negatives has been ascertained. If a response to a test can be established in an HIV-seropositive patient such evidence becomes more significant due to the immunocompromised state of the individual.

5-1:3 Diagnosis

Tuberculosis is suspected when a patient experiences a continuous cough that lasts for more than three weeks, chest pain, shortness of breath, sputum production and sputum with blood in it, fatigue, night sweats, fever, malaise and loss of appetite. Most patients are symptomatic but pinpointing the cause of these symptoms, is sometimes difficult in the case of extra-pulmonary tuberculosis.

5-1:3a Smear Microscopy and Culture

At this point in diagnosis, a technique known as smear microscopy is commonly used. If a patient is suspected of pulmonary tuberculosis, the nature of his or her sputum can determine infectious cases of tuberculosis. Also of significance is the amount of sputum that a patient is able to produce, since this can be an indication of the severity of the tuberculosis. Those patients that fail to bring up sputum can have this induced either by inhaling saline mist or with a bronchoscopy. Once sputum is obtained from a suspected tuberculosis patient, it is smeared on a slide, stained using the Ziehl-Neelsen method, and then examined under a microscope. This process serves to determine if the sample contains acid-fast bacilli (AFB) which suggest tuberculosis micro-organisms. If these micro-organisms are detected, the patient is said to be smear-positive, otherwise, the patient is suspected to be smear-negative, meaning that tuberculosis disease could be present, but may be in its early stages. Although smear-positive tuberculosis is the most infectious form of tuberculosis, smear-negative tuberculosis can sometimes be infectious.

This AFB technique of detecting smear-positive tuberculosis is problematic because a positive smear does not mean that it is necessarily *Mycobacterium tuberculosis*. It could indeed be another kind of *Mycobacterium* such as *Mycobacterium avium*. The likelihood of such false results is dependent on the population being tested. Infection with *Mycobacterium avium* is specific to advanced cases of HIV and is commonly observed in industrialised countries. Hence, results from a population with a high incidence of advanced AIDS should be carefully evaluated. In summary, despite its potential to be misleading, this technique is one of the most widely used methods of detecting tuberculosis in patients. In a developing country, having limited funds, this technique of smear microscopy is often the only available form for tuberculosis diagnosis.

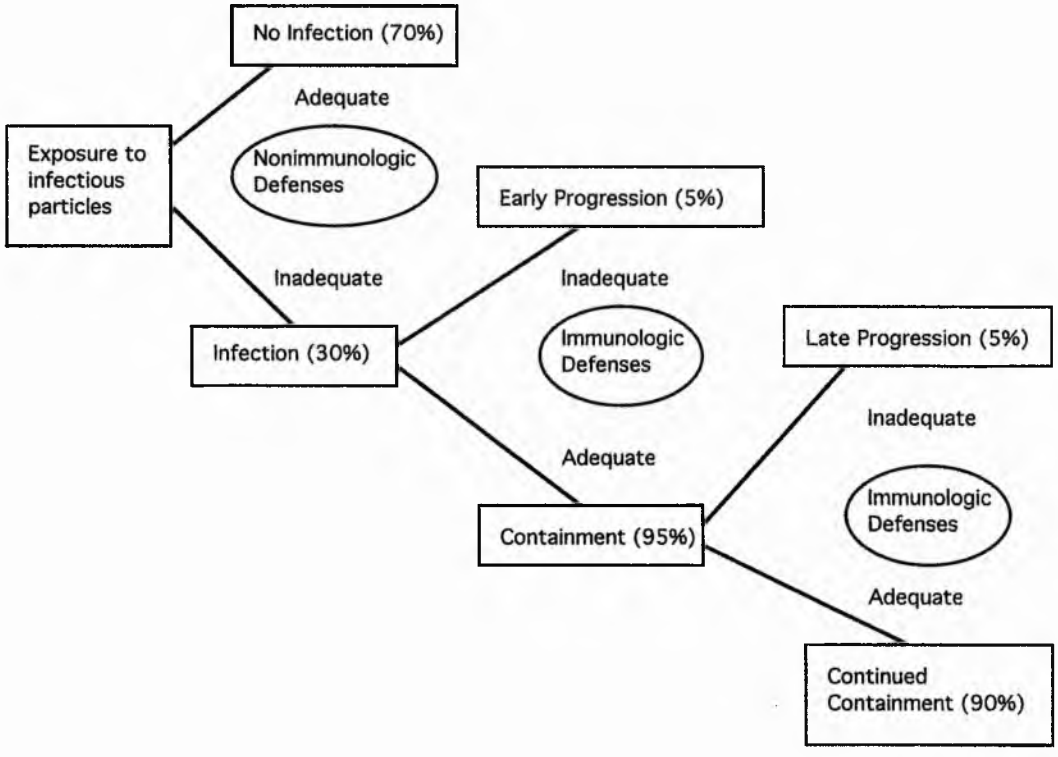
The culture of *M. tuberculosis* is considered to be one of the best ways to diagnose tuberculosis. This technique is very effective and sensitive, only suffering because it is a very slow process due to the slow-growing nature of the bacteria. Faster results can be obtained from using radiometric machines such as the BACTEC (Becton Dickinson, Towson, MD) machine. Such machines operate by detecting the release of gas during growth before any visible growth occurs (Watt, Rayner and Harris, 1993). Also, the use of this machine with inhibition tests allows *M. tuberculosis* to be distinguished from other *Mycobacteria* (Glassroth, 1993). In addition they have the advantage that almost any specimen can be cultured and after it is cultured, it can be tested for sensitivity to various drugs. Certainly, these machines can decrease the time in identifying *M. tuberculosis* to little more than a week, but such machines are often beyond the means of most labs.

5-1:3b Chest Radiographs and Fluid Analysis

Chest x-rays are a less expensive alternative to cultures, but many problems may be encountered when using this method since the x-rays can be difficult to read, even by competent doctors. Nevertheless, some erroneously recommend them over other diagnostic techniques in TB diagnosis (Rossman & Mayock, 1993). There is no chest radiographic picture that is particular to tuberculosis, which will isolate it from the chest x-rays of other diseases. Some chest radiographic patterns are considered suggestive of tuberculosis but they are by no means definite. Before HIV, up to one third of all chest radiographs were considered atypical and this has grown in the HIV era (Khan *et al.*, 1977). AIDS patients have exhibited as many as 59% atypical chest x-rays (Pitchenik and Robinson, 1985). Indeed, Glassroth maintains that, "Among HIV-co-infected persons, virtually any radiographic presentation my be encountered, including a 'normal film.' (Glassroth, 1993: p. 152). With this discussion, it should also be noted that less common media such as computer tomography, ultrasound and magnetic response imaging, are also used, but their ability to provide conclusive diagnostic information is equally limited.

Other methods of detecting the presence of tuberculosis include looking at other body fluids and secretions. Blood changes such as the deficiency in blood cells (cytopenias) or an excess of lymphocytes (products of the lymphoid tissue that function in the immune system) in isolated areas, abnormal levels in serum calcium, and intravascular coagulation (the formation of clots in the blood vessels) are all symptoms of tuberculosis. Urine samples also can show signs of tuberculosis in 20% of all cases. Likewise, signatures of tuberculosis can be found in changes in pleural (lung and thoracic cavity linings), peritoneal (membrane lining the walls of the abdomen and pelvic cavities) and cerebrospinal joint fluids (Glassroth, 1993). In HIV patients, where the diagnosis of tuberculosis proves very difficult due to anergy in skin tests, non-definitive chest radiographs and smear-negative sputum, such analyses of blood and fluids are an important diagnostic process. A final and somewhat inefficient method of diagnosis is through trial and error with treatment. Since tuberculosis is perceived to be quite a substantial social health threat, a lack of definite diagnostic signs of the disease should not necessarily deny a patient treatment. Sometimes it is only through a perceived response to treatment that a definite diagnosis of tuberculosis can be maintained.

Figure 5-1: The Progression of Tuberculosis After Exposure



Source: Hopewell, 1993

5-1:4 Etiological Epidemiology of Tuberculosis

The etiological epidemiology of tuberculosis is defined as the study of the causing and influencing factors of the disease. It answers the questions governing the likelihood of becoming infected with tuberculosis as well as the likelihood of the progression of the infection into disease. As is observed in Figure 5-1 by Hopewell (1993), exposure to infectious particles will result in the infection of only 30% of those exposed. Of these infected, tuberculosis disease will occur in only 10%. This suggests that tuberculosis progresses into a disease in only 3% of those exposed. The likelihood of initial exposure to infectious tuberculosis particles turning into infection is dependent on nonimmunologic defences. Those that are adequate (70%) will not become infected whereas those that are inadequate (30%) will become infected. Of this group, those with inadequate immunologic defences (10%) will either contract the disease right after infection (5%) or much later in life (5%), a phenomenon known as endogenous reinfection. It is because of endogenous reinfection occurring years after initial infection, that the process of tuberculosis eradication in a population is so very slow.

5-1:4a Likelihood of Infection

Tuberculosis is a communicable disease and therefore, the probability of contracting it is highly correlated to the amount of exposure to a human carrier of infectious tuberculosis. This includes the amount of time one is exposed, the amount of contact and the level of 'infectiousness' of the carrier. The more concentrated a population is, the easier it is for the disease to spread. Hence, those in a very densely populated area are more inclined to be infected than those in rural areas. Lowell, Edwards and Palmer (1969) used US Navy recruit testing programs which test for tuberculosis in white males aged 17-21 to illustrate this. Of this group, those living in metropolitan locations all their life had a 4.2% prevalence of positive tuberculin reactivity, whereas those in non-metropolitan locations had a 3.6% prevalence of positive tuberculin reactivity and those on farms had a 2.8% prevalence of positive tuberculin reactivity. Likewise, the greater the contact with a carrier, the more likely is an individual to become infected with tuberculosis. This would explain why those sharing households with infectious individuals are more likely to become infected with the disease. Following this, the greater the crowding in a household, the greater the transmission of infection. In addition, the more advanced and infectious the tuberculosis case, the more likely is the transmission of infection. Grzybowski, Barnett and Stybło (1975) showed in that 62% of those in contact with quite advanced cases of tuberculosis reacted positively to tuberculin reactivity tests suggesting infection, while only 16% of those exposed to a nominal case tested positively (Grzygowski, Barnett, and Styblo, 1975).

The amount of time a carrier of tuberculosis is infectious is also an important element in the spread of tuberculosis. The longer an individual is infectious, the more individuals he or she is likely

to infect. Nevertheless, as compared to other communicable diseases, the risk of infection from a tuberculosis disease carrier is far lower. Comstock and Cauthen (1993) suggest that considering the length of exposure, tuberculosis infectiousness is low per unit of time. These authors also suggest that because of greater potential contact with those with the disease, the risk of acquiring TB increases with age, favours males and non-whites. The likelihood of contracting TB also increases in those who are either voluntarily or involuntarily confined in institutions. In industrialised countries this is especially significant in shelters for the homeless because their lifestyle, as well as such close confinement with others, facilitates a greater spread of infection (Nolan *et al.*, 1991). Hence, environment is a prominent factor in becoming infected with tuberculosis, however, there is also some evidence to suggest that there is an endogenous risk factor in the individual. Indeed, for reasons unknown, some individuals are more likely to be infected with tuberculosis in the same situation than others. It has been suggested by one study that blacks have a greater propensity for becoming infected than whites, but little more is known in this area (Stead *et al.*, 1990).

5-1:4b The Progression of Infection to Disease

The probability that an individual, once infected, will develop tuberculosis is the highest immediately after infection and then decreases with time. Also, development of the disease from infection correlates with age. Those that become tuberculin reactors at a younger age are far more inclined to develop the disease than those who are infected at older ages. In a study of Puerto Rico, Comstock, Livesay and Woolpert (1974) discovered a trend supporting this. Of 82 269 tuberculin reactors from ages 1-18, observed for a time period of 18-20 years, 1 400 cases of tuberculosis primarily occurred either before the age of eight or in between the ages of 13 and 25. Additionally, those that were underweight were far more inclined to develop tuberculosis than those overweight.

Race has little to do with development of disease once tuberculin reactivity has been established. Also significant is the fact that the amount of tubercle bacilli to which a reactor is exposed can determine the likelihood of disease. Those who are exposed to very infectious cases and therefore far more tuberculosis organisms, are at a higher risk for the disease than those reactors who become infected by less infectious cases.

Lastly, the state an individual's immune system affects the likelihood of the progression of a TB infection into disease. Immunocompromised individuals such as alcoholics, the homeless, intravenous drug users, those with HIV or those who are malnourished, all have higher incidences of TB. In addition are those who inhale large amounts of toxic particles such as smokers and mine workers. Incidences of TB have been higher in South African mine workers than in non-mine workers in past studies (Packard, 1989).

5-1:5 Treatment

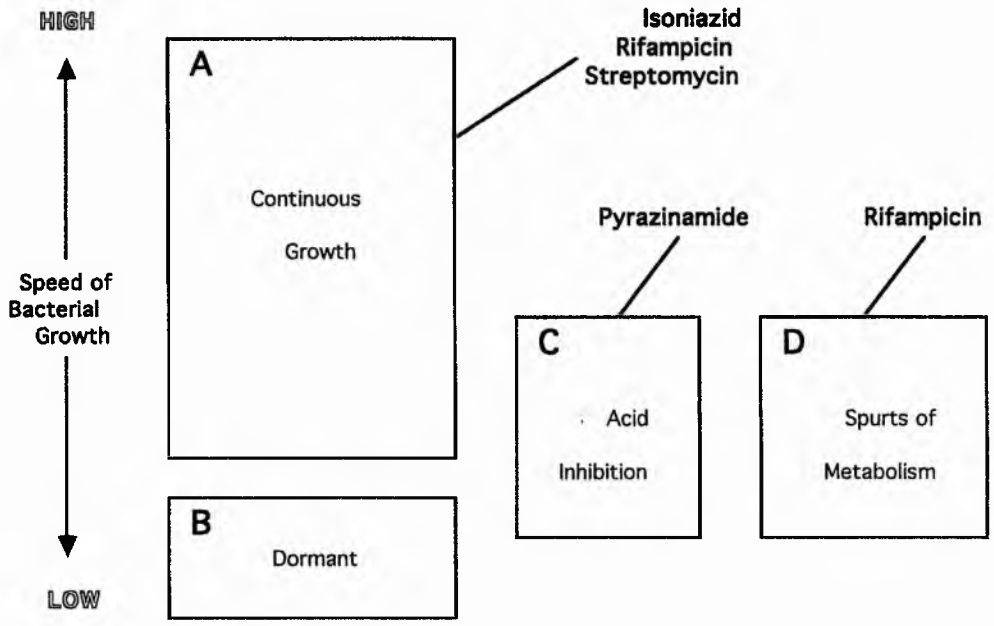
The treatment of tuberculosis is predominantly through chemotherapy with antibiotics, although some experimentation has been performed with passive immunisation or immunotherapy (Stanford, Grange and Pozniak, 1991). The antibiotics that are commonly used are isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), thiacetazone (T) and streptomycin (S). The two most powerful of these are isoniazid and rifampicin due to their ability to completely eradicate or sterilise the bacilli. In order to be effective in the treatment of tuberculosis, chemotherapy must involve a combination of these drugs, be in the right dosages, and must be taken by patients on a regular basis for the duration of the prescribed treatment period. Treatment characteristically involves a more intensive phase in the beginning (usually lasting two-three months) where both more powerful drugs and a greater number of drugs are used to convert a patient from smear-positive to smear-negative TB. After this, a continuation phase is designed to protect against a relapse of the disease (usually lasting 6-18 months depending on the drugs used) where fewer and often less powerful drugs are administered.

5-1:5a Short-Course Chemotherapy Versus the Standard Regimen

In industrialised countries, most treatment relies on an intensive phase with two months of rifampicin, isoniazid, pyrazinamide, and ethambutol and a continuation phase of rifampicin and isoniazid for four months (commonly abbreviated as 2RHZE,4HR) (Omerod, 1990). The exception is for treatment of meningitis, children and some other types of extra-pulmonary tuberculosis. Unfortunately, this proves to be a relatively expensive regimen compared to a 12 month regimen. For developing countries, the International Union Against Tuberculosis and Lung Disease (IUATLD, 1994) recommends the use of either eight month chemotherapy or twelve month chemotherapy (see Chapter 6 and 7 for a comparison of each regimen's effectiveness). Eight month chemotherapy, also referred to as a form of short-course chemotherapy (SCC) includes a 1-2 month daily intensive phase of treatment with 150mg of rifampicin combined with 100mg of isoniazid, 400mg of pyrazinamide and 400mg of ethambutol, and a 3-8 month daily long continuation phase treatment with 50mg of thiacetazone and 100mg of isoniazid combined tablets (2RHZE, 6TH). Twelve month chemotherapy, also referred to as the standard regimen or standard drug regimen (S.D.R.), requires daily treatment with 50mg of thiacetazone and 100mg isoniazid combined tablets for twelve months, and daily streptomycin injections for the first two months (2SHT, 10HT). In conjunction, these drugs not only limit the development of resistant tubercle mutants, but each drug has a particular role in destroying tuberculosis bacteria at a particular phase in its development. As is illustrated in Figure 5-2, rifampicin, isoniazid and streptomycin are some of the most important drugs because they are bactericidal, killing the largest population of bacteria. Rifampicin also kills bacteria that have

inconsistent spurts of growth between dormancy. Those remaining bacteria that are encased in an acid environment are destroyed by pyrazinamide (Mitchison, 1985). In addition to antibiotics, immunotherapy with *Mycobacterium vaccae* has been used in limited cases (Standford, Grange and Pozniak, 1991), but its degree of effectiveness is not widely known.

Figure 5-2: The Effect of Various Drugs on Tuberculosis Bacteria During Treatment



Source: Mitchison, 1985

5-1:5b Side Effects of Drugs

There are inevitably side effects due to treatment with these drugs. These side effects can be minor in nature whereby the patient need only be informed of their possibility, or major, life threatening side effects. As illustrated in Table 5-1, the most encountered side effects to tuberculosis drugs is shown. Major side effects to these drugs include exfoliative dermatitis (a severe form of skin peeling or blistering) from thiacetazone; impaired vision from ethambutol; hepatitis often from isoniazid and less commonly from pyrazinamide and rifampicin; dizziness and teratogenic effects from streptomycin; and shock, purpura and fever caused from pyrazinamide, rifampicin and streptomycin. In those patients that show these major side effects, the drug should never be used again. It is difficult to isolate side effects in tuberculosis because these drugs are never administered alone except in the case of isoniazid prophylaxis. The most critical side effect to isoniazid is isoniazid-related hepatitis. Of 13 838 patients given isoniazid alone, the incidence of isoniazid hepatitis correlates with age: of

those below 20, this was 0%; those 20-34 this was 0.3%; those between 35-49% this was 1.2% and those 50-64 years, this was 2.3% (Kopanoff *et al.*, 1978) (for more information on the incidence of side effects between SCC and SDR, see Chapters 6 and 8).

Table 5-1: Major and Minor Side Effects of Primary Tuberculosis Medications

RIFAMPICIN (R)	hepatitis, flu-like symptoms, abdominal pain, red-orange body fluids, decrease in the absorption of other medicines, shock, purpura (discoloration of the skin of a purple or reddish-brown nature caused by haemorrhage in the tissues), fever
PYRAZINAMIDE (Z)	shock, purpura fever, hepatitis, joint symptoms
ISONIAZID (H)	hepatitis, neurologic reactions, minor skin reactions
THIACETAZONE (T)	exfoliative dermatitis,
STREPTOMYCIN (S)	dizziness, teratogenic effects
ETHAMBUTOL (E)	vision impairment

Source: *PDR*, 1992; IUATLD 1994

5-1:5c Follow-up in Diagnosis

After two months of intensive phase treatment, patients undergo a sputum smear examination. Those found to be smear-negative are placed on the continuation phase. In contrast, those who are smear-positive are given more of the intensive phase treatment for another two weeks and then have their sputum rechecked. If it proves positive, the intensive phase is given for another two weeks and the patient's sputum is checked again. After this point, regardless of sputum conversion, the continuation phase commences. At five months, all patients are again given a sputum examination and those who are sputum positive are pronounced as treatment failures and are given a retreatment regimen. Sputum is again checked at seven months and those who are sputum negative are given their last month's treatment if they are on an eight-month regimen and are then pronounced cured. If patients are on a twelve month regimen, they continue chemotherapy until the eleventh month when their sputum is again checked and those in this group who are sputum negative are similarly pronounced cured and given their last month of chemotherapy. Those appearing smear-positive at the seventh month or the eleventh month sputum check are diagnosed as treatment failures and must be given a retreatment regimen. Those who miss appointments during the continuation phase have the missed time added on to the duration of their treatment, totalling one year for the eight-month regimen and 15 months for the twelve month regimen. Any patient receiving treatment lasting longer than these limits is classified as a defaulter.

5-1:6 Retreatment: Failure and Relapse

Special consideration must be given to those smear-positive patients who have previously received a month or more of treatment for tuberculosis. These patients usually fall into three categories: relapses, failures and defaulters. Those patients considered relapses are those who become smear-positive after having received treatment and have been diagnosed as "cured" after their treatment. Likewise, those patients who are considered failures are those smear-positive patients who continue to be smear-positive or convert back to smear-positive tuberculosis after five months of treatment.

Relapses after patients have been classified as cured are rare, yet still occur. There are many explanations for relapse, but the majority centre on inadequate chemotherapy stemming from poor patient compliance (Comstock and Cauthen, 1993). Patients failing to take their treatment properly might end up killing part of the tuberculosis bacilli, reducing the colony sufficiently that the patient's results are smear-negative. Nevertheless, the remaining bacilli will then multiply to their previous size or larger. Relapse can be associated with drug resistant bacilli. This is likely due to the lag between a drug's elimination of most of the susceptible bacteria and the time it takes for the remaining drug-resistant mutants to multiply and become dominant.

Those patients who have received retreatment and are still smear-positive are classified as chronic cases. Chronic cases are one of the most dangerous forms of tuberculosis since they are predominantly resistant to H and R and remain reservoirs of infection for the transmission of resistance. Such resistant cases are often incurable and these patients must rely on surgery and treatment with rarer tuberculosis drugs for the rest of their lives. The prognosis of survival for tuberculosis resistant to both H and R is about 40-60%, roughly the same as for those who receive no treatment at all (Bloom and Murray, 1992).

5-1:7 Resistance

Resistance was soon discovered after the introduction of streptomycin. The Medical Research Council of Britain organised a trial in 1944, where fifty-five patients with pulmonary tuberculosis were given streptomycin and compared with a control group of fifty-two patients who were only given conventional treatment at a sanatorium. The initial results of this trial proved extraordinary as most treated with streptomycin had a clear chest x-ray, compared to only eight per cent of those in the control group. Of those in the control group, fourteen died within six months compared with just four in the streptomycin group, but five years later, thirty-five of the sanatorium patients and thirty-two of the streptomycin patients were dead (Ryan, 1992). It seemed that although streptomycin was initially effective, it had a poor ability in completely curing tuberculosis. This drug weakened the disease for a

small period of time until the disease became resistant and then returned in full force, resistant to streptomycin. Such resistance was also observed by Pyle (1947) who traced drug resistance by using only streptomycin on a tubercle population and found that resistant mutants increased from 1 in 88 750 to only 1 in 367 after 15 weeks. Essentially, the drug selected for those mutants that were resistant to streptomycin and then killed the remainder, leaving only streptomycin resistant mutants to multiply. The disease, initially weakened by the decrease in number by the attack of streptomycin, again gained momentum as remaining mutants started to multiply and dominate.

5-1:7a Mechanisms of Resistance

Unlike many other micro-organisms, tuberculosis can only become resistant to a drug through mutation. Resistance occurs through a tuberculosis drug acting as a selective agent on existing resistant mutants in a population. All tuberculosis bacilli populations contain a small number of mutant bacteria that are resistant to various drugs. However, it is only when a single drug is used on the population, that resistant mutants are left to multiply. In this case, the drug is said to have effectively *selected* for the mutants. The size of the overall population of a colony of tubercle bacteria in an individual also determines resistance. The greater the number of bacteria, the greater is the likelihood that there will be resistant mutants. In an average human lung cavity of a TB patient, there exists 1×10^8 tubercle bacteria (Grosset, 1993). This is significant considering the probability of mutants to various drugs in a given population. Rifampicin's probability of resistance is 1 in 10^8 whereas the probability of resistance for Isoniazid, Streptomycin, Ethambutol, and PAS is 1 in 10^6 and that for periphery drugs such as Thiacetazone has a likelihood of resistance of 1 in 10^3 (Grosset, 1993). In contrast, multi-drug resistance tuberculosis (MDR-TB) occurs at a rate of 1 in 10^{14}. MDR-TB is defined by some as resistance to more than one anti-tuberculosis drug but in this thesis will adhere to the stricter definition of resistance to both isoniazid and rifampicin.

A further characteristic predicting the development of resistance is the type of drug used and its effect on the bacterial population. Drugs with a high bactericidal effect are inclined to select for resistant mutants better than those that are less bactericidal. This is due to the fact that a drug that completely removes the susceptible population leaves the resistant mutants no other bacteria with which to compete. For instance, a case of tuberculosis that is only treated with isoniazid, will most certainly gain *acquired resistance* to that drug, rendering it completely useless in the treatment of the disease. Acquired resistance is defined as resistance that develops in the individual from treatment, and indeed, single-drug therapy is the most common reason for its development. Because each drug selects resistant mutants, the combined selection of multi-drug resistant mutants is more difficult because what one drugs selects for, another will eliminate. Grosset (1993) sites as the signature

feature of a mutant resistant to one drug is that it is usually susceptible to other drugs. This does not mean that MDR-TB will not develop. MDR-TB simply takes longer to develop because there is a longer selection process on the part of each anti-bacterial involved. This is illustrated schematically in Figure 5-3: as a susceptible tuberculosis population is treated with a series of single drugs, the population begins to evolve into a multi-drug resistant population. This is why TB chemotherapy must involve more than one drug and often three or four.

As well as acquired resistance, an individual can be infected with a drug-resistant form of tuberculosis when he or she is exposed to an infectious case of tuberculosis that is unsusceptible to one or more drugs. Once the individual has been infected with this unsusceptible bacilli, it will have the potential to multiply into a purely drug-resistant population. This is referred to as *primary resistance* and has a strong clinical significance because it means that immediately one or more drugs will be ineffective in treating the disease.

Figure 5-3: The Development of Multi-Drug Resistant Tuberculosis

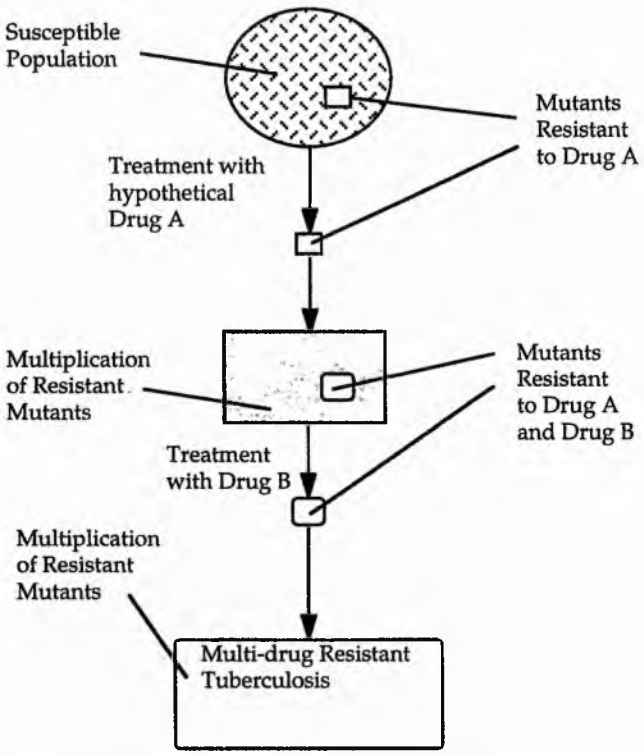


Figure 5-3: The development of Multi-drug Resistant Tuberculosis. A Susceptible population of tuberculosis receives only one drug (hypothetical Drug A) which selects mutants resistant to this population and then these mutants multiply to be treated with a second drug (hypothetical Drug B), further selecting for resistant mutants. The selection and further multiplication of these mutants results in a population resistant to both Drug A and Drug B. Further singular treatment with drugs will select for further resistance in the population rendering a super-resistant population over time.

As the level of primary resistance to standard drugs grows, tuberculosis becomes more and more difficult to treat because the remaining drugs left to treat this resistant TB are far less effective. Therefore, the spread of primary resistance translates to the spread of a relatively untreatable form of tuberculosis. Its growth, in any proportion, represents a major health threat. It is because of this that statistics charting primary resistance are quite significant.

Those patients who cannot be classified as either having primary resistance or having acquired resistance are said to have initial drug resistance where it is unclear whether they have previously received chemotherapy. Patients are sometimes reticent admit to having received previous treatment because of an irrational fear that current needed treatment will be denied. Hence, it can be very difficult to determine the type of drug-resistance experienced by a patient and this serves to skew primary drug resistance data.

5-1:7b Causes of Drug Resistance

The development of drug resistance is dependent on the tuberculosis population, tuberculosis treatment, chemotherapy, drug administration and the patient. Low cure rates for smear-positive tuberculosis regimens serve to make those who would ordinarily die from the disease, develop resistance and survive, thus enlarging the pool of infection (Kochi, 1993). Roughly correlating to this, according to the author Gangadharam (1993), there are five major factors from which drug resistance is attributed: biological, clinical, pharmaceutical, administrative and sociological (see Figure 5-4). (1) Biological factors mainly centre around the favourability of the tubercle bacilli's environment in allowing it to multiply and mutate. An example of this would be if an individual was somehow immunocompromised giving the bacilli a better advantage in multiplying. (2) Clinical factors refer to any element of treatment that interferes with a drug's ability to kill tubercle bacilli and anything that allows for single-drug therapy and the selection of resistant mutants. Often in therapy, resistance arises to one drug and a clinician simply adds another drug to the treatment allowing for a further selection of drug-resistant mutants. (3) Pharmaceutical and pharmacological factors describe anything that weakens the effectiveness of a drug and hence, its ability to fight an infection. This includes any environmental factors that might weaken the action of these drugs causing them to be less effective on the tubercle bacilli. The shelf life of streptomycin, for instance, is three years after its date of manufacture while pyrazinamide, isoniazid, ethambutol and thiacetazone can be used up to five years after their date of manufacture (IUATLD, 1994). A close adherence to the shelf life of a drug is necessary to ensure they will be effective when they are administered. Ineffective doses of drugs have the potential to cause resistance to develop in tubercle bacilli. (4) Administrative factors refer to anything that impedes consistent drug treatment due to a lack of supply. Such examples of

administrative factors would be a patient's inability to receive a regular supply of treatment due to inefficient storage and transport of TB drugs on the part of the health authority. (5) Sociological factors centre around any feature in the patient that impedes treatment. An example of this would be patient default due to difficulty in travelling to a health clinic, or difficulty in affording a full course of treatment.

Figure 5-4: Factors Influencing the Development of Resistance

1. **Biological**
   a. Initial bacterial population
   b. Local factors inside the host favourable for the multiplication of drug-resistant bacilli
   c. Presence of drug in insufficient concentrations
   d. Patient's drug inactivation status

2. **Clinical**
   a. Treatment with single drugs
   b. Inadequate dosage of the drugs
   c. Insufficient duration of treatment
   d. Adding a single drug to a failing regimen
   e. Interference by occult or quack medicine
   f. Interference by other indigenous systems of medicine

3. **Pharmaceutical and Pharmacological**
   a. Insufficient concentration of the pure drug
   b. Inadequate standardisation of the bioavailability of the drugs
   c. Improper storage conditions of the preparations
   d. Improper bioavailability of combined tablet preparations
   e. Confusion created by the trade names of the various preparations of combinations tablets
   f. Improper or incorrect dispensing of the drugs

4. **Administrative**
   a. Insufficient supplies of the drugs
   b Bureaucratic influence in the ordering and supply of the drugs
   c. Substandard drugs purchased because of cost considerations and government regulations
   d. Administrative delays in the release of the drugs from the ports of entry
   e. Administrative controls on the drug dispensing

5. **Sociological (patient's co-operation)**
   a. Non-compliance
   b. Irregularity in drug intake
   c. Premature discontinuation of drug intake
   d. Avoidance of other exogenous infections with drug-resistant bacilli

Source: Gangadharam, 1993: p. 300

5-1:7c Current Levels of Resistance

With the increase in AIDS and tuberculosis there has been a corresponding acceleration of the incidence of resistant tuberculosis. Resistance to the two primary drugs used to treat tuberculosis, isoniazid and rifampicin, has reached record levels, rising to as much as 30% in industrialised countries (CDC, 1993) and between 15% and 39% in developing countries (Khan *et al.*, 1993; Wolde *et al.*, 1990; Mitchison and Nunn, 1986, Ormerod, Harrison, Wright, 1990). Such multi-drug resistance is serious since these are the most effective drugs against TB. MDR-TB patients must rely

on surgical resection and less effective drugs, all of which have lower survival rates. The mortality rate for multi-drug resistant tuberculosis is 40-60%, the same rate as for those not receiving any treatment. For those who are HIV-positive, this figure rises to 80% (Bloom, 1992).

In summary, many factors are responsible for the growth of resistant tuberculosis and if such resistance grows unchecked, it could very well prove be one of the great health threats in the twenty-first century. Most of those factors accountable for drug resistant tuberculosis are caused by human error in consumption, administration or supply of these drugs. An overwhelming problem with tuberculosis is patient compliance since the regimen requires many pills several times a week for such a long period of time. Often those receiving treatment forget to take their pills and in many cases, those receiving the pills stop taking them when they start to feel better, not allowing for their tuberculosis to be completely cleared. Problems in motivating patients to comply with their dosages have been so bad that in areas such as New York, it is cheaper to send out a social worker to police the treatment than it is to deal with resultant patient deterioration from the disease. Even if an individual takes his or her medicines, there is occasionally the problem that a doctor does not prescribe the correct dosages. Again, an awareness and education in the importance of the threat of this illness is a key to instigating better management of its treatment.

5-1:8 HIV and Changing Trends in Tuberculosis

In the US in 1953, there were 84 304 recorded cases of TB from which 19 707 died. In contrast, in 1985, 22 201 were infected with TB and only 1 752 died from it. This illustrates a 33 year trend in the fall in the rate of TB infection, yet recent rises in new cases have threatened to reverse this trend (Murray, 1989). In the United States, new cases of TB increased 18%, from 22 255 to 26 283 between 1984 and 1991 (*FDA Consumer Online Documents* , 1993). After 1985, new cases of tuberculosis continued to increase, rising by 4% in 1989 and a further 9.4% by 1990. Strangely, a pattern was developing where the incidence of tuberculosis, a curable disease, began to rise globally and although some could not explain this, it gradually become linked with the rise of HIV.

It is estimated by the World Bank that 2 million people have already died of AIDS and 13 million are currently infected with HIV (World Bank, 1993). In sub-Saharan Africa, an average of one out of forty has the virus and in cities this rises to almost one in three. Over 90% of these individuals are in their most economically productive years between ages 15-59 (World Bank, 1993). The future situation is bleak as WHO estimates that by the year 2000, 26 million people will be infected with the virus and 1.8 million people per year will die from it.

The nature of tuberculosis is such that once exposed to it the healthy human body can, in most cases, stop its progression into disease. In a healthy human population, only 10% of those exposed to

tuberculosis will ever develop this disease, and the remaining 90% will become carriers of non-infectious tuberculosis bacteria. With AIDS's elimination of an individual's ability to fight disease, he or she becomes more vulnerable to other diseases therein increasing their spread. This is especially true for tuberculosis, and for those with HIV, the progression of TB infection to disease can be 30% higher (Murray, 1989). The annual incidence of TB becomes 8% in this group (McGowan, 1993).

Tuberculosis is such a virulent disease that on many occasions it is the first disease to affect a person with HIV, and indeed, a tuberculosis infection is often the first clue that an individual has AIDS. TB has been increasing in HIV patients. In 4 HIV specialist centers in London (King's, St. Goerge's, South Geng's and St. Thomas's), TB was the second most common AIDS-defining illness, affecting 22% of a total of 86 patients of an African origin (Ofarrell *et al.*, 1995). From October 1990 and July 1991 at the Department of Pediatrics and Child Health in the University Teaching Hospital (OTH), Lusaka, Zambia, of 1323 patients seeking care, tuberculosis was the 5th most common cause of admission. 69% of these TB patients were HIV-seropositive (Chintu *et al.*, 1995). In Tamil-Naden, India, of 100 AIDS patients, at an incidence of 61%, the most common disease between those aged 21-30 was TB (Kumarasamy *et al.*, 1995).

In HIV patients, tuberculosis occurs early on in the stages before AIDS, coming 6-9 months before any other AIDS-defining illnesses (Daniel and Ellner, 1993). Although not conclusive, there now some evidence that a smear-positive HIV patient is more likely to transmit TB than a HIV-seronegative patient. In a study of 436 TB contacts in Spain, twice as many miro-epidemics of TB in intravenous drug users were generated by HIV-seropositive contact cases rather than HIV-seronegative contact cases (Cayla *et al.*, 1996). HIV can also speed up the progression of tuberculosis from years to a matter of weeks. This acceleration of the disease provides a greater pool of infectious tuberculosis resulting in its exponential growth both in those that have AIDS and those that do not. There is also some evidence that TB accelerates the progression of HIV-1-infection (Peterson *et al.*, 1995).

Increases in HIV suggest a greater future burden on highly populated health facilities, which will be to their detriment because of the two-fold problem that HIV will take the time and resources from that allocated for treating other diseases and it will also allow for a greater pool of infectious disease to disseminate. In St. Mary's Hospital in London, of 538 patients with positive Mycobacterial isolates between January 1987 and March 1992, there was a 2.5 fold increase in patients with mycobacterial infection. 57% of these isolates were TB but only 47 patients were known to be HIV positive (Taylor *et al.*, 1995). The National multiple-cause mortality data in the United States shows that between 1987 and 1992, death in HIV-seropositive patients rose from 2.9% to 4.1% (Selik *et al.*, 1995). This would support the conjectures that as TB becomes more prevalant, a greater pool of infection will cause its incidence to rise, and that TB in those with HIV is becoming harder to treat (possibly due to

resistance). Such a problem could be attibuted to the fact that there are not enough existing resources to cover the resource drain of this disease. The present amount of US $200 million in expenditure in developing countries for preventing AIDS is far insufficient as an estimated US $1-2 billion is thought to be necessary (World Bank, 1993).

5-1:8a Characteristics of TB/HIV Co-infection

There are many characteristics of TB-HIV patients separating them from other tuberculosis patients. There is a significant correlation between extra-pulmonary TB and HIV. One third of all HIV-seropositive patients are likely to have extra-pulmonary tuberculosis compared with approximately 18-19% HIV-seronegative patients. Zaire, for instance in 1985, had 47% HIV-extra-pulmonary TB cases as opposed to 33% HIV smear-positive TB cases (Small *et al.*, 1991). In addition, infection with HIV is the most significant known risk factor in activating a latent TB infection, a phenomenon also known as endogenous reinfection. The risk of contracting TB in an HIV-seropositive individual is 7-10% per year as compared to 10% per lifetime in a healthy HIV-seronegative individual. Besides endogenous reinfection those with HIV are more prone to developing TB through exogenous infection. The HIV-seropositive individual lacks the ability to fight TB infection so that it invariably progresses into a disease. Because of such increased vulnerability to tuberculosis, the use of isoniazid preventative therapy and isoniazid prophylaxis is common in those patients who are likely to have been infected or where infection has been established.

In addition to a greater vulnerability to tuberculosis, there is commonly a delay in the diagnosis of tuberculosis in HIV-seropositive patients. The diagnosing of tuberculosis in HIV patients can be difficult because a large proportion of them exhibit anergy (lack of a reaction) to tuberculin skin tests and therefore, evidence of infection in this manner is not an effective method. Chest radiographs and smear tests are likewise undependable and doctors must rely on tuberculosis cultures and blood tests to help them diagnose the disease. HIV patients have atypical sizes of tubercle colonies and they are more likely to be smear-negative than smear-positive. In Zambia, of 109 patients, 66% HIV-seropositive patients proved to have lower grade sputum positive or sputum-negative smear tests, lower colony counts in cultures and longer culturing times (Elliot *et al.*, 1993). HIV is also inclined to render a patient with a negative tuberculin skin test. The greater the progression of AIDS, the less likely the patient will exhibit a positive skin test after tuberculosis infection. In the United States only 39-56% of TB/HIV co-infected patients had a positive skin test, and in Uganda 68% of those TB/HIV co-infected patients exhibited a positive skin test (Ellner, 1990; Vjecha *et al.*, 1991). A negative tuberculin skin test can reflect the fact that an individual's HIV infection is at an advanced stage, suggesting a potentially poorer response to treatment.

Those who are HIV-seropositive will respond to TB chemotherapy similarly to those who are HIV-seronegative. There are some differences in treatment, however. TB/HIV co-infected patients are more likely to die during treatment due to non-TB causes, and are also more likely to die of TB if the disease proves resistant. In a major referral centre in Tanzania, of 157 TB patients, 102 of which were HIV-seropositive, there was a 2% case fatality rate for those with HIV but a comparative 2% for those without the disease (Richter *et al.*, 1995). Of 173 patients with MDR-TB between 1983 and 1993 in New York, 50% were HIV infected and mortality for HIV patients was 70% versus 20% for HIV-seronegative patients. Only appropriate therapy was linked to the survival of these HIV patients (Park *et al.*, 1996).

TB/HIV patients are far more likely to experience adverse side effects to the medicines, especially thiacetazone (Cohn and Iseman, 1993), and they are far more likely to have relapses when treated with the twelve-month regimen. This would suggest the use of short course chemotherapy over the standard regimen in HIV seropositive patients. Also, the use of streptomycin injections, required in the twelve month regimen, can be problematic because often needles and syringes are re-used, which could lead to a spread of HIV to other patients receiving injections. Another problem in the treatment of TB/HIV co-infection is that those with HIV offer an attractive pool of infection for MDR-TB, because of the ease that it can pass from an MDR-TB infected person to an HIV infected person. One study from the CDC (1991) found that all HIV cases of an outbreak of MDR-TB had been in a hospital ward near another patient who was being treated for MDR-TB. This is supported by Edlin *et al.* (1992) and Fischi, *et al.* (1992) who found a similar situation in MDR-TB/AIDS co-infected patients. In addition, regardless of whether an HIV patient already has tuberculosis, he or she can still be exogenously infected by a resistant strain. Such evidence has been proven by a study by Small (1993) who analysed the restriction-fragment-length- polymorphisms (RFLP) (an analysis of changes in bacterial DNA strands) of 17 TB/HIV co-infected patients to find a sudden change in four at the detection of MDR. This evidence suggests a strong potential for MDR-TB to be transmitted nosocomially where treatment of MDR-TB includes aerosol-producing medical practices such as endotracheal intubation, bronchoscopy, respiratory tract manipulation, autopsy and wound manipulation (Jarvis, 1993). The likelihood that MDR-TB can be transmitted so easily among those who are HIV-seropositive has stimulated discussions about isolating them. These means include, for instance, isolating those who are HIV positive and homeless by providing special homeless shelters for HIV positive persons, in order to protect them and limit the spread of this relatively incurable form of tuberculosis (Tynes, 1993). Containing the transmission of MDR-TB/HIV co-infection is extremely critical for HIV patients since the mortality rate of MDR-TB/HIV co-infection is 89% within 16 weeks (*FDA Online Documents*, 1995).

5-1:9 Summary of Section 5-1

As an ancient disease that was thought to be almost eradicated, tuberculosis is still a very real health threat in modern times. It is a disease that has been well studied, revealing detailed information on its diagnosis, etiological epidemiology and mechanisms of resistance. Such information has been an invaluable help in diagnosis, treatment and retreatment of this disease. Nevertheless, erradication of this tuberculosis, due to its close epidemiological tie with HIV still seems a very distant reality.

Section 5-2

Effective Management of Tuberculosis Control Efforts

In this section the management of tuberculosis drug supply, containment, preventative therapy and case holding are explored. Also, this section discusses the costs associated with these control efforts. Sound management in all areas of TB control is an essential element in controlling tuberculosis resistance as will be discussed in further chapters.

5-2:1 Drug Supply

Much of the management of the containment of tuberculosis is dependent on chemotherapy which serves to limit exposure of others to the disease. Any impediments to effective chemotherapy and any delay in getting it will foment greater exposure. Hence, delays in the supply of drugs are significant impediments to tuberculosis control programmes. A balance in future drug supply must be correctly calculated so that precious funds are not spent on drugs that will expire before a patient can use them, but enough must be available so that each patient can finish his or her treatment. This is achieved using estimates of past drug use. In addition, to make use of these estimates requires the availability of an adequate amount of funds to purchase drugs. Those drugs that are purchased must be of high quality so that consuming them does not effectively result in no treatment or resistance. Similarly, even if the correct quantity of drugs is ordered, if they do not reach the patient on a consistent basis, this can also jeopardise a control programme. Drugs should be carefully monitored to make sure that they are not left susceptible to bad weather conditions on delivery docks or left to theft in warehouses. If drugs cannot be delivered regularly to the patient, he or she will receive intermittent therapy also likely resulting in a relapse or resistance.

Excluding non-commercial production and distribution of anti-TB drugs, in 1990/91, the global market for tuberculosis drugs was US $177 million. Drug production is dominated by two companies in the United States and one company in Switzerland (Weil, 1994). This is a large market with a strong, inelastic demand. Cost recovery for TB drugs is usually prohibited because the disease is such a consequential health threat. For this reason, TB drugs are seldom procured by the private sector, but remain the area of the government and external donors. Regarding this, drugs were estimated to represent from 20-40% of all costs of a tuberculosis drug programme (Murray, 1990; Murray, Styblo, Rouillon, 1990). The cost of procuring these drugs including service fees from procurement agencies, port charges, insurance and customs duties can account for as much as 20-100% over the actual cost of each drug (Weil, 1994). Such costs as these accentuate the fact that the current management of tuberculosis drugs in most countries is less than ideal and offers much room for improvement.

5-2:1a The WHO Anti-TB Drug Survey

Illustrating the requirement for better TB drug management, Weil (1994) reports on a WHO anti-TB survey in 1992. This was a study of the 1991 tuberculosis drug use of: 31 of 45 (68%) member states from AFRO (African region), 14 of 36 (38%) from AMRO (American region), 9 of 22 (40%) from EMRO (Eastern Mediterranean region), 5 of 11 (45%) member states from SEARO (Southeast Asian region), and 15 of 23 (65%) member states from WPRO (Western Pacific region). Of these member states, only 70% based their future ordering of drug on their past year's demand. Likewise, 49% of respondents reported experiencing *drug stock-outs* meaning that at some point during the year, some or all of the supply of tuberculosis drugs were exhausted on a national scale. 59% of respondents and 68% of AFRO countries reported that drug supply financing was their greatest weakness to an effective tuberculosis control programme. 39% of respondents indicated that they did not have adequate or stable financing for their 1992 TB drug demand.

Figure 5-5: Percentage of External Aid Received by Respondents on a WHO Anti-TB Study

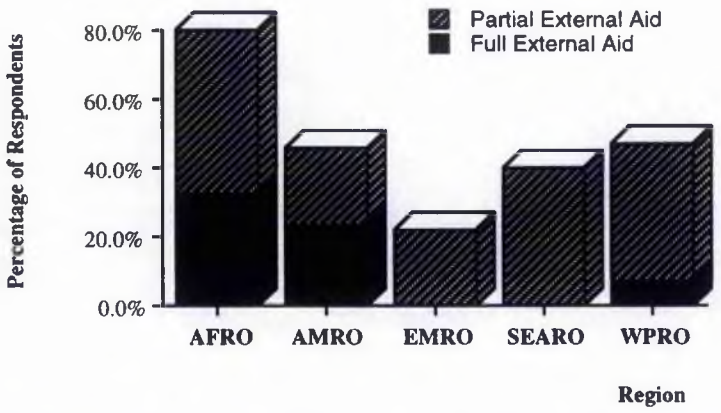


Figure 5-5: PERCENTAGE OF EXTERNAL AID RECEIVED BY RESPONDENTS ON WHO ANTI-TB STUDY. 73 of respondents in this WHO anti-TB study responded to questions on the sources of their funding. This graph shows the percentage of responding member states that experienced full or partial external aid. As can be observed, African member states receive the largest amount of full external and partial external aid whereas Eastern Mediterranean member states receive only a small amount of partial external aid. (Weil, 1994: p. 131)

In developing countries, drug financing for tuberculosis is usually dependent on some form of external aid. The degree of need determines whether this external is full or partial in each country. Figure 5-5 indicates that some member states in some regions received full external aid, meaning that their tuberculosis drugs were almost fully funded by an external body. In the AFRO region full external aid amounted to 32% of all countries that responded to the survey and amounted to 23% in AMRO. A

further 48% and 23% of countries in AFRO and AMRO, respectively, is accounted for by partial aid. Less aid for TB is given in EMRO, SEARO and WPRO, EMRO and SEARO only receiving partial external aid for tuberculosis drugs.

In addition to funding sources, the cost-per-case was surveyed from 52 respondents (19 in AFRO, 12 AMRO, 7 from EMRO, 4 from SEARO and 10 from WPRO), but comparisons of these data are difficult due to variations in the calculation of cost-per-case. As might be expected, AFRO had a low cost-per-case, but SEARO had the lowest cost-per-case range. Discrepancies between a low cost-per-case and a high cost per case reflects each member state's incidence of TB, labour costs, overhead costs, case-load and cost of drug regimens (See Table 5-2 for differences in cost per case).

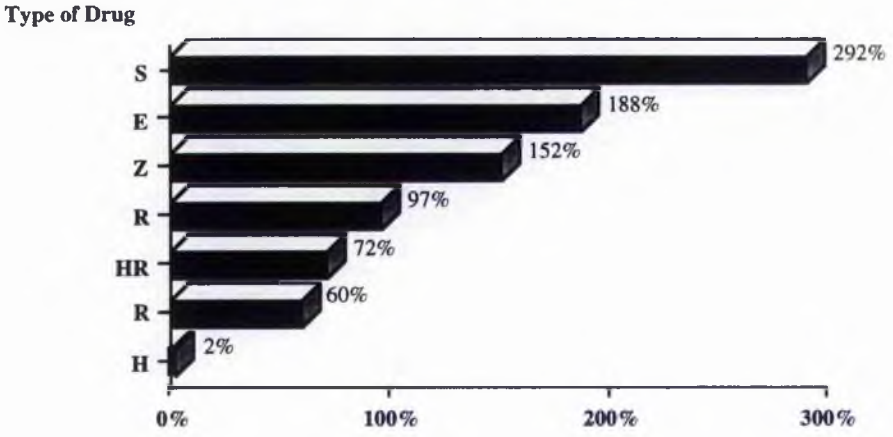
Table 5-2: Cost per Case Range Obtained from Respondents of WHO Member State Regions

Region	Cost
AFRO	$9-$289
AMRO	$12-$667
EMRO	$15-$1142
SEARO	$27-$67
WPRO	$7-$420

Source: Weil, 1994

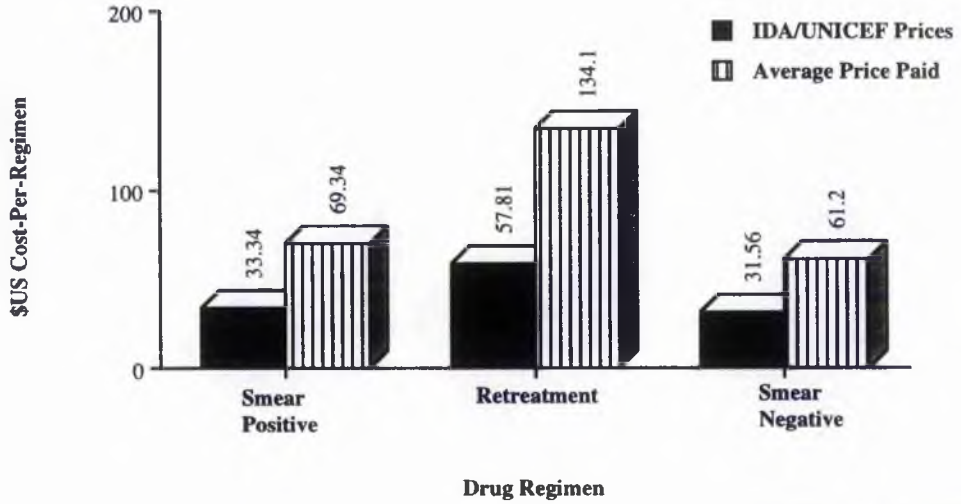
One of the reasons for such a difference in the price per case could also be attributed to the prices that different countries pay for drugs. Such differences are widespread and differ from country to country and are also dependent on the drug chosen. Figure 5-6 shows the respondents' reports on the prices that they paid for their tuberculosis drugs which proved to be much higher than UNICEF or IDA (International Dispensary Associates) prices. Prices for isoniazid (H), the most popular bactericidal drug averages at only 2% over the price, whereas ethambutol, streptomycin and pyrazinamide proved to have the highest average price over its UNICEF or IDA price. It is unknown why there is such a difference in these percentages, but it is possibly due to the fact that there is less of a demand of these drugs over isoniazid and rifampicin which, under ideal conditions, without considering available funding, should appear in every initial drug regimen due to their superior effectiveness (discussed in Chapter 6).

Figure 5-6: Percentage of Average Price over IDA or UNICEF Price



Adapted From: Weil, 1994: p. 129

Figure 5-7: A Comparison of the US $ Cost per Drug Regimen Paid for IDA/UNICEF Priced Drugs and the Average Prices Paid



Smear-positive regimen: 2HRZE/4H_3R_3;
Retreatment Regimen: 2HRZES/1HRZE/5$H_3R_3E_3$;
Smear-negative Regimen: 2HRZ/2H_3R_3 (a three subscript refers to three times weekly)
Source: Weil, 1994: p. 32

UNICEF and IDA prices are lower because they buy their drugs in an extremely high volume. Such a difference between the price paid for drugs over these suppliers is explained by Weil (1994) who attributed it to: (1) those in the government procuring drugs have limited information on suppliers and

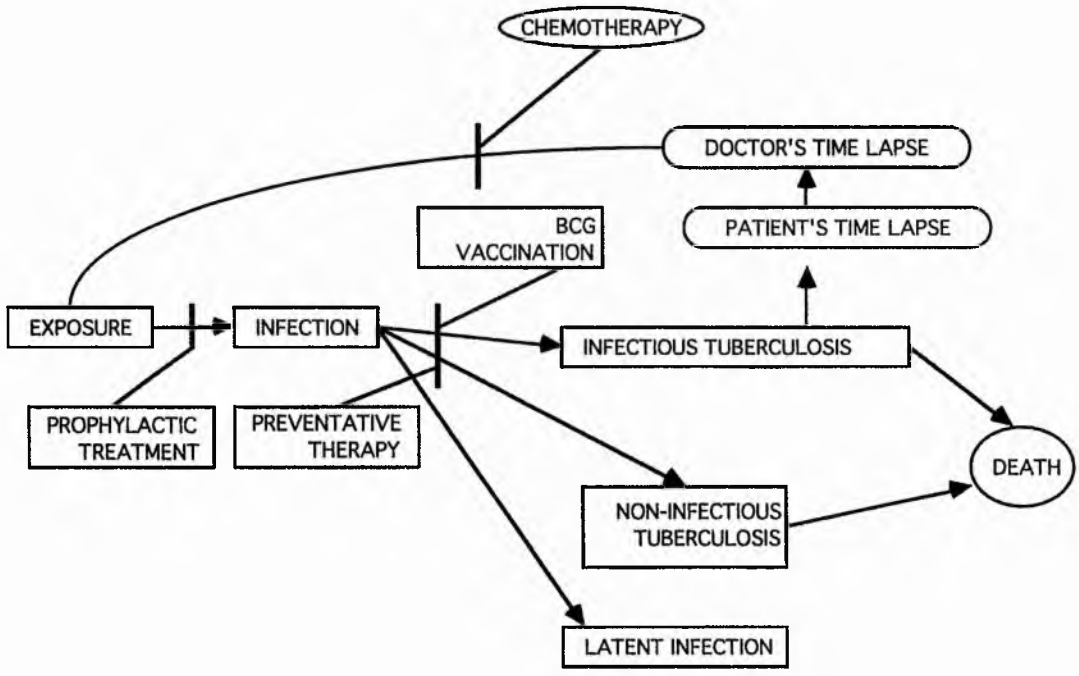
competing prices, (2) under-utilisation of UNICEF and IDA suppliers (3) Funding delays which cause a country to demand emergency drugs resulting in their higher prices and (4) Government-enforced importation limits on drugs to stimulate local drug production of drugs, result in the procurement of higher priced drugs.

The WHO anti-TB survey accentuates such differences in prices which are significant when considering their impact on treatment regimens. As is illustrated in Figure 5-7, with these average prices, treatment regimens become twice the price of those IDA and UNICEF suppliers. Considering drug prices alone, with more efficient procurement, twice as many patients could have been treated for the same amount of money.

5-2:2 Impediments to Tuberculosis Diagnosis and Treatment

Another impediment to effective containment of tuberculosis is dependent on the patient and the doctor. As observed in Figure 5-8, delays in chemotherapy and greater exposure of the population to tuberculosis is partially caused by the time lapse that occurs from when a patient becomes infected with tuberculosis to when he or she seeks treatment, compounded with the time lapse in the doctor's diagnoses between the initial consultation and treatment.

Figure 5-8: Containing the Spread of Tuberculosis After Infection



Source: Reider, 1993: p. 168

Patients often try to deny that they have tuberculosis, which delays treatment. This highlights the importance of case finding in tuberculosis to both stop the spread of infection, and to locate those who have been infected with tuberculosis to ascertain the likelihood of their infection's progression into disease (Reider, 1993). The doctor's role in containment is also essential when considering the importance of a quick diagnosis in stopping the spread of infection. Those doctors trying to diagnose the disease: (1) have problems in identifying tuberculosis due to the often endogenous difficulties in its diagnosis, (2) are unfamiliar with the disease, (often the case in industrialised countries due to its past decline) or (3) do not immediately diagnosis TB/HIV coinfection due its unusual clinical manifestations, a phenomenon that is becoming increasingly common (Kramer, 1990). In one study performed by the CDC in the United States, of 2 000 doctors, 75% misinterpreted a TB test and 27% used an incorrect laboratory test (Cooper, 1993). To avoid these diagnosis delays, further education to doctors and health personnel is necessary so that they are aware of the changing clinical appearance of tuberculosis as well as its growing prevalence. Finally, the lack of patient compliance can be a further impediment to effective chemotherapy. Those patients that default in their course of treatment allow for the tubercle bacteria to continue to grow or become resistant, contributing to greater exposure of others to the disease along with the added danger of developed resistance.

5-2:3 Physical and Technical Tuberculosis Containment Methods

5-2:3a Contact Tracing

All containment strategies are dependent on contact tracing, a term encompassing all elements of tuberculosis control such as prevention, containment and surveillance. Contact tracing usually begins with the presenting case, a patient who appears with some form of tuberculosis. This is more efficient in terms of costs than mass screening because, by definition, contact tracing starts looking for tuberculosis in areas where it is most likely to be present rather than spending resources on screening low risk individuals. From this point, a contact investigation begins with an attempt to find the index case or the person who infected the presenting case. Also, there is a search for all close contacts with the presenting case, defined as those who have spent several hours or days with the presenting case and are likely to infected. In addition, is the location of any other tuberculosis contacts.

According to Etkind (1993) the expediency of this investigation is dependent on the risk factor of the presenting case which centres around three components: person factors, time factors and place factors. Person factors depend on the relative infectiousness of the presenting case as illustrated in Table 5-3. If a presenting case has extra-pulmonary tuberculosis or is smear-negative, the risk of his or her transmitting tuberculosis is low. In contrast if the patient proves to be smear-positive with pulmonary tuberculosis then the risk of transmission is assessed to be quite high. Exceptional efforts

must be given to those presenting cases that prove to have drug resistant or multi-drug resistant tuberculosis as these cases can prove to be the most dangerous to contacts. Time factors focus on the length of exposure of close contacts and tuberculosis contacts. If a presenting case is assessed to be highly infectious, the commencement of his or her symptoms is used as a rough guide as to what time period to focus on in identifying contacts with the presenting case. Place factors involve the environment in which the presenting case met most of his or her contacts. This is significant because if this environment is well ventilated or outside, the risk is low to contacts whereas if it is crowded and poorly ventilated, then the risk is much higher to contacts. Additionally relevant to the place of contact is the relative risk to those contacts. If the patient, for instance, spent a large time in contact with those who are HIV-seropositive such as in an HIV hospice, or if the patient spent a large proportion of time in the presence of children such as at a day-care centre or at a school, then the risk infection must be considered more seriously. Contact tracing is an important tool in the prevention of tuberculosis while proving prove instrumental in case finding. This is a valuable cost-effective method for identifying high risk groups for screening instead of using a wide scale, indiscriminate screening of a population. It is a method that can be applied in both developed and developing countries alike, and a lack of its utilisation would prove detrimental in TB containment.

Table 5-3: Personal Factors of the Presenting Case Influencing Contact Tracing According to Likelihood of Transmission

CLINICAL DATA	HIGH	LOW
TB Disease Location	Laryngeal Pulmonary	Extra-pulmonary Alone
Smear Status	Positive	Negative
Smear Source	Spontaneous Specimen	Induced or Clinical
Chest X-ray	Cavitary	Noncavitary
PPD Result	Large, > 15mm	-
Symptoms	Cough	No Cough
Anti-TB drugs	No	Yes (2 weeks or more)

Source: Etkind, 1993: p. 280

Indeed, contact tracing should concentrate on facilitating patient awareness that there is effective available treatment for tuberculosis and that quick action means less transmission to others. Passive case finding, involving only the patient is essential but not satisfactory. Active case finding on the part of the community is necessary. In order to accomplish this, it is necessary to have a strong community infrastructure with an added awareness of the symptoms and treatment of tuberculosis. Unfortunately,

both in developing countries and industrialised countries, there are many unpleasant cultural attitudes condemning those with tuberculosis such that those who have it will wait until they can no longer function before they seek treatment. Changing attitudes towards tuberculosis can be extremely difficult when shadowed by firmly entrenched cultural beliefs. The patient must be given the incentive to seek treatment and this incentive, such as the need to feel better, must be stronger than any other factors such as his or her shame. Likewise, society must have the incentive to report cases, such as a perception of the benefit of the eradication of tuberculosis. Such needs highlight the key role of education and awareness of tuberculosis in containing its spread.

5-2:3b Environmental Control

On a different level, in containing the spread of tuberculosis, one can focus on controlling the environment where tuberculosis is present. One of the best ways to control the spread of tuberculosis is to limit contact between those with the disease and those who are susceptible to infection. Unfortunately, contact can only be realistically limited after the infectious case of tuberculosis has been identified. The use of facial masks for the patient and encouraging the patient to cover his or her mouth is a common practice and is surprisingly effective in keeping the infection from becoming airborne. This method is commonly used with very infectious cases of tuberculosis in industrialised countries and remains one of the only effective environmental controls within the financial means of a developing country. One of the areas for the greatest amount of concern is containing the spread of tuberculosis in hospitals. In industrialised countries, severe cases of tuberculosis are placed in isolation in hospitals so as not to infect the air of other hospital patients. In the United States, patients are not allowed to leave the area of isolation until they have had three negative sputum smear on three consecutive days. Also, health workers are encouraged to wear respirators when dealing with tuberculosis patients. Another environmental method of control is the use of air disinfection through Ultraviolet Radiation (UV) of 245 nm. wavelength light. Although this method of disinfection is less effective at high humidities, it is still used in many areas in hospitals and even some public institutions such as shelters for the homeless, whereby the upper air in a room is irradiated and then circulated. Effective use of UV radiation can reduce airborne tubercle bacilli by employing approximately 20 air changes per hour (ACH) (Riley, 1993). Air in a room can also be filtered through a container where it is irradiated or where it passed through a high-efficiency particle filter (HEPA). Unfortunately for developing countries, such expensive measures prove to be implausible due to financial constraints.

5-2:4 Prevention

5-2:4a Chemoprophylaxis and Preventative Therapy

Those patients who are found to have been infected by tuberculosis can be treated with isoniazid to take advantage of the delay between infection and disease. Preventative therapy uses one drug, and its strategy in limiting the disease centres around attacking tuberculosis when the population is quite small and the likelihood of resistant mutants is low. Chemoprophylaxis similarly involves giving small doses of an antibacterial to an individual who has not yet been infected with tuberculosis but has had close contact with it in order to prevent infection and disease. The drug of choice for prevention and prophylaxis is isoniazid, quite possibly, the strongest bactericidal tuberculosis drug. Isoniazid is given in dosages of 10mg/kg daily in children and adolescent and 5 mg/kg daily for adults for a minimum of 6-12 months (Geiter, 1993). Patients considered for preventative therapy are often those at high risk for the disease such as those with HIV, intravenous drug users and children (CDC, 1991). Nevertheless, there is some controversy over the risk of isoniazid preventative therapy due to the risk of isoniazid induced hepatitis, usually estimated at around 14-23 cases per 100 000 (Snider and Caras, 1992). There is also the rarer problem if an individual has been infected with an isoniazid resistant form of tuberculosis, in which case the drug will be ineffective. In this case, the individual is given two drugs to which it is assumed that the infection is sensitive. In considering isoniazid preventative therapy, it is important to look at the relevant population that a patient comes from.

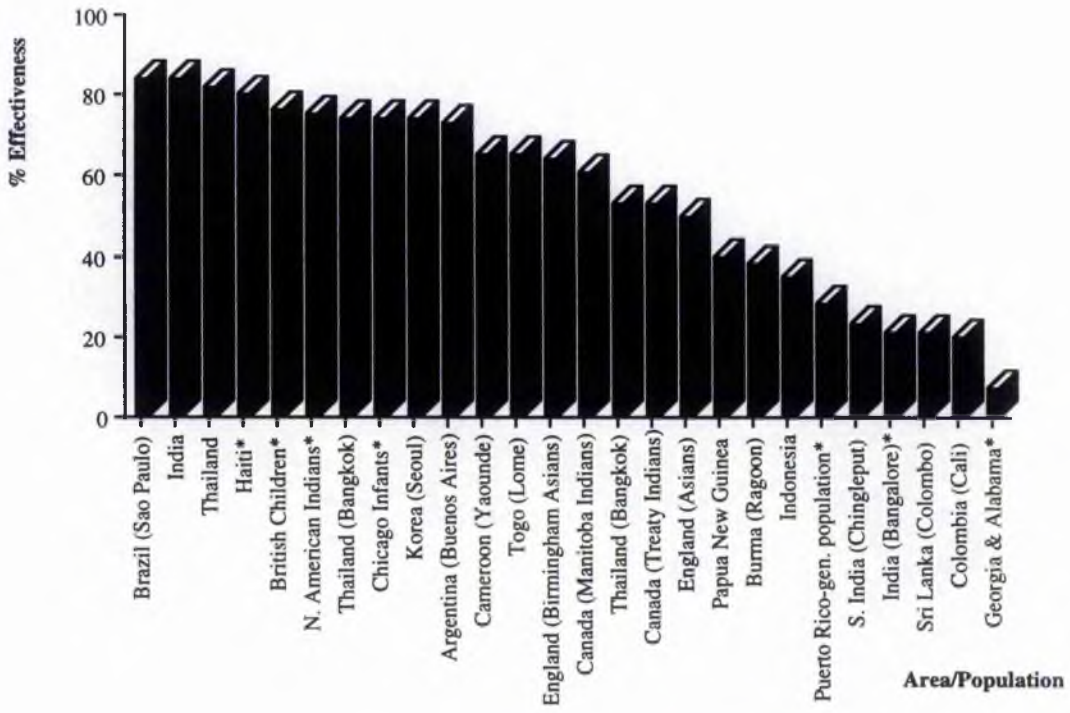
It is difficult to determine which individuals will develop tuberculosis from infection. Those at high risk are obviously strong candidates for care, however, considering that only approximately 10% of those HIV-seronegative that are infected will develop the disease, this prevention inevitably concludes with the unnecessary treatment of 90% of infected individuals. It is therefore necessary to look at the cost of such treatment, not only in monetary terms, but in terms of the patients' quality of life. This treatment must then be evaluated in terms of its overall utility and effectiveness when compared to the opportunity cost of other treatment strategies in an existing tuberculosis control program. In the case of a programme funded by limited means, the opportunity costs of the use of preventative therapy might not be justifiable when they include the expense of drugs to treat a large population of infectious cases of tuberculosis.

5-2:4b The BCG Vaccine

More than seventy years ago, the Bacille Calmette-Guérin (BCG) vaccine was obtained from a virulent strain of *Mycobacterium bovis* and distributed to labs around the world for further attenuation. BCG is a live, enervated vaccine that functions in stopping the progression of tuberculosis infection into disease. This vaccine has been used on the general population of most countries except for the US

and the Netherlands. It is generally thought to be effective, although the level of effectiveness has been difficult to prove and is therefore an issue for controversy. When the BCG was stopped in Sweden, TB increased in children by six times. In contrast, in Chile, it proved only 10% effective and in India, BCG proved 0% effective in a study of 200,000 (Fine and Rodrigues, 1990; Sepulveda, Parcha, Sorensen, 1992). Data from studies on the vaccine's effectiveness have varied from below 10% to 80%, as is seen in Figure 5-9. There are several theories attributing this inconsistency which include the relative natural exposure to *Mycobacterium* bacteria, the effectiveness of BCG on varying stages of disease, physiological, geographical and genetic differences in tubercle bacteria, and the purity of the vaccine itself (Fine & Rodrigues, 1990). Nevertheless, the reasons for the BCG vaccine's effectiveness remain unanswered.

Figure 5-9: The Effectiveness of BCG Vaccination in Various Studies



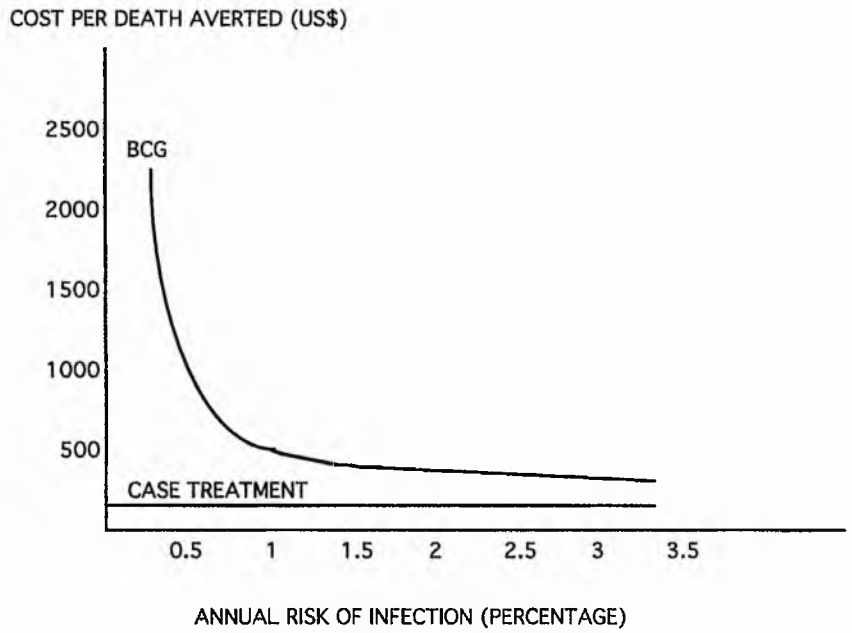
*Signifies those studies that were controlled trials; all others are observational studies.
Data compiled by: Fine, 1994: p. 63

One of the groups that the BCG vaccination offers the greatest protection to is children. There is even some evidence in Zambia to suggest that vaccinating HIV-1-infected children with BCG is advantageous in preventing the disease and has little incidence of vaccine-induced illness (Papaevangelou and Borkowsky, 1996). The BCG vaccination has primarily proven to be effective in

children in preventing non-pulmonary tuberculosis. Hence, vaccination for children is of limited utility in preventing the spread of tuberculosis as it predominantly works to prevent non-infectious forms of tuberculosis. Nevertheless, it is effective in preventing miliary tuberculosis as well as tuberculosis meningitis which young children are more inclined to develop. Therefore, vaccination in a population where there is a high prevalence of tuberculosis should be performed as soon in life as possible (ten Dam, 1993).

BCG vaccinations can be used on a national level for immunisation, but when the risk of tuberculosis infection drops below certain levels, its wide scale use can no longer be justified in terms of protection or cost effectiveness. The author ten Dam (1993) maintains that when the risk of tuberculosis infection drops lower than 0.1% per year, the benefits of BCG vaccinations are outweighed by adverse reactions. In such cases, the author suggests that selective vaccination be used for those in high risk groups. Indeed, the impact of BCG immunisation at high levels of annual risk of infection becomes very cost-effective in terms of the annual cost per death averted. Yet, when the rate of the annual risk of infection drops below 1%, the cost per death averted rises with every death and the intervention becomes less and less cost effective. This is illustrated in Figure 5-10.

Figure 5-10: The Cost-Effectiveness of BCG Immunisation and Tuberculosis Case Treatment as a Function of the Annual Risk of Infection



Source: Murray and Styblo, 1993

5-2:5 Variables Influencing Case Holding

5-2:5a Causes of Patient Default

A cogent element to the successful treatment of tuberculosis is patient compliance. The greatest risk factor for relapse after tuberculosis treatment is non-compliance due to default from treatment (Brenner and Poziak, 1993). Patients who have not complied with treatment for two months or more are considered defaulters, although the term is used loosely for any patient that has failed to comply with treatment for any length of time. There is no cultural or demographic determinant of patient compliance (Sumartojo, 1993). According to Kilpatrick (1987) treatment compliance is dependent on the patient and doctor's understanding of the importance of treatment, efforts of patient and health worker to co-operate, a patient's reaction to the drugs, and lastly, chance. In TB chemotherapy, the patient must take numerous pills each week and must continue this for between eight and eighteen months. In light of this, it is not surprising that patients frequently do not comply with their treatment. Often, once a patient feels better, he or she will stop taking the medication, erroneously thinking that it is no longer important or that he or she is cured. Case holding becomes difficult because modern chemotherapy is so effective, that the patient feels better after a few weeks and simply loses the incentive to take any more medication. Compounding this, if patients live in circumstances whereby they are severely impoverished or suffer from homelessness or drug addiction, it is all the more difficult for them to comply. Unfortunately, these are the circumstances where tuberculosis is most often found, making its treatment and containment complex. If a patient forgets to take his or her drugs, cannot afford to buy the drugs that he or she needs or cannot afford to travel to a clinic to receive the drugs, this obviously impedes his or her treatment. For adequate patient compliance, patients must be given the incentive to take their medicines, be capable of taking their medicine, see the value of taking these medicines and find that taking their tuberculosis medication is not too inconvenient or difficult a task (CDC, 1989). In essence, the patient must view the future benefits of the treatment as greater than its cost. Far too often, default results from patient myopia whereby the patient perceives the cost of having to take such a large amount of pills over such a long time as outweighing the patient's subjective discounting of the future benefits of treatment.

5-2:5b Responsibility of the Health Worker

Special attention in case holding must be given to those patients who are on a retreatment regimen, alcoholics and those with mental or physical problems. No matter from which country a tuberculosis programme is run, there will always be a percentage of patients who are unwilling to take their medication. In considering this, all tuberculosis programmes should have some sort of network whereby a patient's treatment can be closely monitored. There are several ways in which patient

compliance can be monitored, however, few of these are completely effective. These methods include self report, estimates, missed appointments, pill counting, pharmaceutical records, and urine testing (Chaulet, 1987). Blister packs protect pills against heat and humidity damage, but only act as a reminder, not a guarantee that a patient will take his or her medication each day (Fox, 1990). In addition, health worker's estimates of TB patients' medication consumption is flawed. In a study of patients with TB, only 32% of non-complying TB patients were identified, and 8% of those complying with treatment were incorrectly identified (Wardman *et al.*, 1988). Self reporting suffers because of fear of those administering care or an unwillingness or forgetfulness in reporting (Chaulet, 1987). One study in particular showed that 28% of patients lied about taking their medicines (Preston & Miller, 1964). Urine tests are inconsistent in measuring drug intake due to different metabolism rates between patients. In addition, some microelectronic devices attached to drug containers only measure whether a patient has opened them. These containers can be destroyed, lost, left open or repeatedly opened because of curiosity (Sumartojo, 1993). Those in industrialised countries are usually given their medication and then checked by doctors to make sure that they are taking it. Patients who are considered likely to fail to comply with treatment are often monitored with directly observed therapy (D.O.T.), whereby a worker visits the patients, and watches the patient consume each dose of his or her medication (Kenneth, 1992). This form of patient monitoring has become quite popular because it limits default and the cost of hiring a health worker still proves less than the cost of retreatment and the associated potential increased transmission. D.O.T. often takes a slightly different form in developing countries whereby during the intensive phase of treatment (usually the first two months) patients must come to a health facility each day and receive treatment. Those who fail to appear for their scheduled appointments are usually visited by an appointed nurse to discover why the patient is having trouble complying. Unfortunately, these efforts in case holding are quite dependent on the health-care personnel. The nurses that care for the patients must have a genuine interest in the programme and attempt to foster a good patient-nurse relationship. Programmes where apathy is prevalent cannot help but suffer because patients are forgotten about and their treatment is not followed-up. This can result, for example, in patients moving from one health facility to another receiving treatment for a short time and then disappearing.

Another aid to case holding is the use of tangible incentives or gifts to patients which motivate them either by making the process of seeking treatment easier or making their overall quality of life slightly better. Such examples of incentives that have been used in the United States are bus tokens, coats, shoes, a new car battery and gasoline. Psychological explanations for such gifts suggest that rather than bribe the patient to finish treatment, they serve to solidify a strong patient-nurse relationship which is what commits the patient to finishing his or her treatment (Brenner and Poziak,

1993). The nurse almost takes on a maternal role for the patient, listening to problems and establishing trust.

5-2:5c The Use of Hospitalisation for Patient Compliance

As a last resort, hospitalisation has been used in order to ensure patient compliance for the intensive phase of treatment. Usually, hospitalisation is reserved for very serious cases of tuberculosis, whereby the patient's life is in danger. For most tuberculosis cases, ambulatory care (defined as outpatient care) is used where the patient makes daily or monthly visits to a health facility to receive treatment. Hospitalisation proves to be very expensive as it inherently involves not only the drug treatment of patients but the costs of meeting their other needs. This drastic measure undoubtedly helps, however, it is often beyond the means of a developing country. Nevertheless, it could be argued that when compliance falls low enough, hospitalisation might be more cost-effective if it is cheaper than the cost of retreatment and resistance that results from patient non-compliance. The work of Murray *et al.* (1991) concerning Malawi, Mozambique and Tanzania revealed that if hospital admission increased the cure rate by 5%, the cost per case cured would be US $777-2 008. A cure rate increase of 10% would decrease the average incremental cost to US $389-1 004 per case cured. Finally, a cure rate increase of 15%, would decrease the incremental marginal cost per case to the same as the incremental marginal cost of any ambulatory drug treatment for tuberculosis, US $259-669. These results suggest that when hospital admission increases the cure rate of treatment above a certain level, and non-compliance to ambulatory care is high, then the cost-effectiveness of hospitalisation becomes cheaper or equivalent to ambulatory care because it eliminates or greatly reduces default.

5-2:5d Brenner and Pozsiks' Case Holding Model

To illustrate the importance of case holding, Brenner and Pozsik (1993) have developed a model where they studied case holding's effect on the overall containment of tuberculosis. In this model, three examples are studied, (1) those industrialised countries with relatively good case holding, (2) those industrialised countries with less than satisfactory case holding and (3) a developing country . The purpose of the first two examples (1 & 2) in developed countries is to show that where case finding, access to care and efficacy of chemotherapy are all equal to each other, case holding has a strong impact on the overall reduction in the sources of infection: 88% versus only 72%. In comparing the latter two (2 & 3), the industrialised country and the developing country have the same case holding capacity of 80%. The developing country suffers not only from weak case holding but an additional host of other problems. It is shown to suffer because the proportion of cases detected, proportion of those beginning therapy and the efficacy of its chemotherapy are all much lower than

this industrialised country, making its comparative reduction in sources of infection much lower: 38% versus 72%. Murray (1994b) maintains that unless a developing country can maintain case holding at 80%, it is not worthwhile to concentrate on expanding case finding. Hence, in this model, one can observe how important case holding is to the effectiveness of a tuberculosis control programme.

Table 5-4: A Measure of the Overall Impact of Case Finding on the Success of Tuberculosis Control Programmes Under Changing Variables

Measure of Overall Impact		=	Case Finding and Surveillance	x	Access to Care	x	Effectiveness of TB Drugs	x	Case Holding
Reduction in Sources of Infection		=	**Proportion of Cases Detected**	x	**Proportion Beginning Therapy**	x	**Efficacy of Chemotherapy**	x	**Proportion Completing Therapy**
Industrialised Country with good case holding	88%	=	95%	x	99%	x	96%	x	98%
Industrialised Country with less than satisfactory case holding	72%	=	95%	x	99%	x	96%	x	80%
Developing Country	38%	=	70%	x	80%	x	85%	x	80%

Source: Brenner and Pozsik, 1993: p. 186

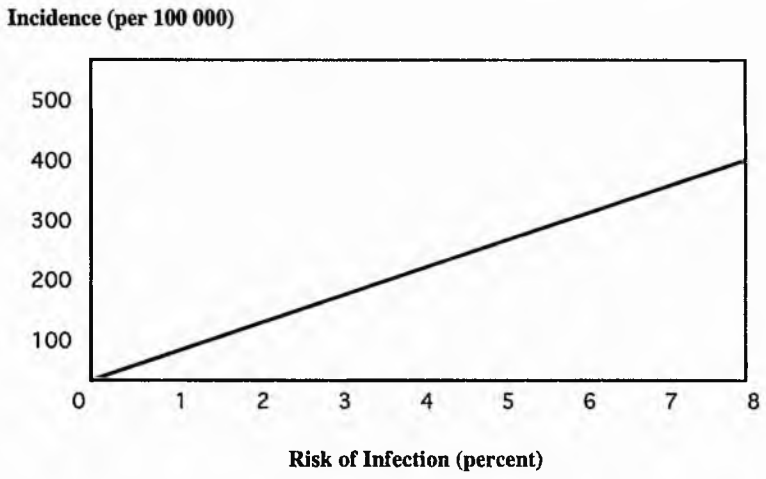
This model also highlights the overwhelming problems facing developing countries. It suggests that their problems not only centre around case holding but also around several other factors by virtue of the fact that there are so many more cases to be dealt with. High levels of case holding are a challenge to maintain and methods to ensure that patients take their medicines on a regular basis are each incomplete by themselves. The best functioning programs are dependent on not one method, but a comprehensive approach to patient compliance. Indeed, comprehensive programmes utilising patient monitoring and observation, verbal commitments, monetary incentives, convenient accessibility to care and caring and understanding staff seem to be the most successful at inducing patient adherence to treatment.

5-2:5e Information Documentation

Case holding is dependent on an accessible record of patients in order to keep track of their treatment progress. It is essential that all information about a patient, relevant to his or her treatment, be recorded. Information such as the treatment regimen, drug reactions, background health information, the patient's address and a contact person are essential as well as an accurate appointment

attendance record. This information must be convenient to record and easy to retrieve and read if required. It can correspondingly be recorded on a computer or on patient treatment cards and a patient register book. In industrialised countries, computer programmes such as EPI-INFO developed by the WHO and the CDC are used to record such information. In developing countries, where the use of computers is often too expensive in health care institutions, the IUATLD has a specific format for the collection of TB information in developing countries including a patient register, patient treatment cards, TB laboratory registers, sputum examination registers, quarterly reports and order forms. Again, the correct recording or this information is strongly dependent on the health-care worker or equivalent. Where there is an overwhelming caseload and little available time or little interest in recording patient information, it will be neglected.

Figure 5-11: The Relationship Between the Annual Risk of Infection and the Incidence of Smear-Positive Tuberculosis



Source: Murray, Styblo and Rouillon, 1993: p. 235

5-2:5f The Annual Risk of Infection and Prevalence

Patient information is not just important for case holding, but on a macro level, serves to predict the future nature of a tuberculosis programme. It functions in determining the incidence of tuberculosis per 100 000 population and the prevalence, which is usually equal to twice the incidence (Broekmans, 1994). It is estimated that for every 1% of new annual infections, there are 50-60 new smear-positive cases of pulmonary and 50-60 new smear-negative and extra-pulmonary cases per 100 000 population (Crofton, Horne and Miller, 1992). Also, the incidence of pulmonary smear-positive tuberculosis is accompanied by a rise in the annual risk of infection as illustrated in Figure 5-11. For each 1% rise in the annual risk of infection there are 49 cases of smear-positive tuberculosis per 100 000 of the population (Murray, Styblo and Rouillon, 1993). Indeed, from these figures, future

drug needs, personnel and facility provisions of the disease and the formation of control strategies are developed.

5-2:6 Costs of Control Efforts

The costs of containment measures for tuberculosis are an essential issue for consideration in any TB programme. Educational means for containment might prove expensive as would screening an entire population for tuberculosis. In all areas of the world, but especially where funds are scarce, economic considerations must be made as to the threat and prevalence of tuberculosis versus the measures taken to contain the disease. If the incidence and cost of treating tuberculosis is low and therefore the risk of successful spread is low, the cost of these measures might not be justifiable. However, in developing countries, where the risk of tuberculosis is significant, as well as the threat of AIDS, remuneration for such expenditures for containment is more than accounted for. In developing countries, where the prevalence of tuberculosis is high the current strategy could be said to be based around case finding and treatment, yet in industrialised countries, where the incidence of tuberculosis is lower, the control strategy takes on a different emphasis of surveillance and containment (Brenner and Pozsik, 1993).

5-2:7 Summary of Section 5-2

It is important to recognise that endeavours to manage tuberculosis involve not one but a combination of several factors. Control efforts should focus on managing drug supplies, information collection and case holding, while concentrating on containment and prevention measures and developing a sound administration infrastructure. The best tuberculosis programmes implement a balanced combination of all these variables, adjusting to the financial means of each country. It is only through the utilisation of all elements of tuberculosis control that efforts to manage this disease will be successful.

Section 5-3

THE GLOBAL IMPACT OF TB

After looking at both the nature of tuberculosis and control efforts in the previous two sections, this section will explore the present global impact of tuberculosis. The changing nature of TB in the HIV era will be discussed as well as costs associated with new cases of tuberculosis. This section will also look at some recent work highlighting tuberculosis as a top disease control priority by the World Bank and conclude with a discussion on future burden and expenditure. In the context of high tuberculosis growth, there is likely to be associated growth in drug resistant tuberculosis.

Tuberculosis has had a striking global impact in the last ten years. A disease that was thought to have been eradicated has been revived by HIV. Evidence of this can be seen from rising rates of new tuberculosis cases and a halt in the overall fall in tuberculosis. From 1955-1985, new tuberculosis cases declined 6% per year whereas between 1985-1992 new cases actually increased by 16% (Yow and Demmler, 1992). This is significant considering that there are available, effective treatments for the disease which should logically result in a fall of the incidence of TB. In comparing figures from 1980-1984, and 1985-1989, it is possible to see that there has been only a 2% fall in tuberculosis in Southeast Asia, only a 1% fall in Europe, and no change at all in Africa (Orr and Hershfield, 1993). Globally, tuberculosis accounts for more than 3% of the total burden of disease (Murray, 1994b), and represents 7% of all deaths and 26% of all avoidable deaths (Murray, Styblo and Rouillon, 1990).

Table 5-5: Incidence of Tuberculosis in Southeast Asia, Europe, and Africa

	Incidence (per 100,000 population)	
	1980-1984	1985-1989
Southeast Asia	87	85
Europe	34	33
Africa	57	57

Source: Orr and Hershfield, 1993

5-3:1 Global Changes in the Annual Risk of Tuberculosis Infection

The epidemiological situation of tuberculosis is such that due to the better quality of care and smaller levels of transmission, its annual decline in industrialised countries is occurring much faster than in developing countries. Kochi (1991) estimates from WHO data before 1991, a decline greater than 10% in developing countries, but a comparative decline of only 0-3% in Sub-Saharan African and the Indian subcontinent, as can be seen in Table 5-6. Logically, the annual decline in the risk of

infection is dependent on the prevalence of TB and the availability of health resources. Area 3 (Middle-income and East and Southeast Asia) and area 4 (Sub-Saharan African and the India subcontinent) both have the same annual risk of infection, but health resource availability is superior in area 3 and therefore it has experienced a greater annual decline in the risk of infection.

Table 5-6: The Epidemiological Pattern of Tuberculosis

Area	Current Annual Risk of Infection	Annual Decline in the Risk of Infection	Health Resource Availability
(1) Industrialised Countries	0.1-0.01%	>10%	Excellent
(2) Middle-income in Latin America, West Asia and North Africa	0.5-1.5%	5-10%	Good
(3) Middle-income in East and Southeast Asia	1.0-2.5%	>5%	Good
(4) Sub-Saharan Africa and the Indian subcontinent	1.0-2.5%	0-3%	Poor

Source: Kochi, 1991: p. 1-6.

5-3:2 Costs

Who could have predicted that HIV would arise and cause cases of TB to increase? Investment in most tuberculosis programs dwindled in the late nineteen-seventies and early nineteen-eighties due to the fact that tuberculosis was perceived to be a disease that was no longer a threat. As is evident, this lack of expenditure caused a greater proliferation of new cases of TB both in developing countries and industrialised countries. Bloom and Murray (1992) estimate that in the United States alone, the cost of new or 'excess' cases of tuberculosis since 1985 resulting in greater transmission is approximately equal to US $340 million, plus an added 4 400 discounted lost years of life, lost productivity, and social production equalling an added US $300 million. The cost of discounted years of life was estimated to be US $20 000 per year, discounted at 3%. These authors estimate that the average treatment cost per patient in the US for TB is US $25 000. Costs are five times higher for resistant cases of TB and ten times higher in terms of the costs of drugs. An outbreak of MDR-TB (see section 5-1) in ten patients in Fort Worth, Texas cost US $950 433 or an average of US $95 000 per patient (CDC, 1990). Likewise, at the Jewish Hospital, Denver (which specialises in treating resistant cases of TB) MDR-TB costs US $100 000-200 000 per patient. Other estimates are that this form of TB can cost up to US $250 000 (*FDA Online Documents,* 1995)

5-3:3 DALY's and TB

Much work has been performed to emphasise the need for better global tuberculosis control. WHO has made tuberculosis one of its top priorities and the World Bank has highlighted the cost-

effectiveness and high cost-utility resulting from tuberculosis control efforts in terms of years of life saved and corresponding disability adjusted life years (DALYs). Short-course chemotherapy for tuberculosis saves more DALYs than almost any other intervention because of the severe impact of the disease (Jamison, 1993). In terms of cost, a disease like diarrhoea will be much cheaper to treat, compared to tuberculosis, but the impact of TB on the life of the individual is comparatively higher. For instance, a £30 tuberculosis drug regimen might allows an individual to live to his or

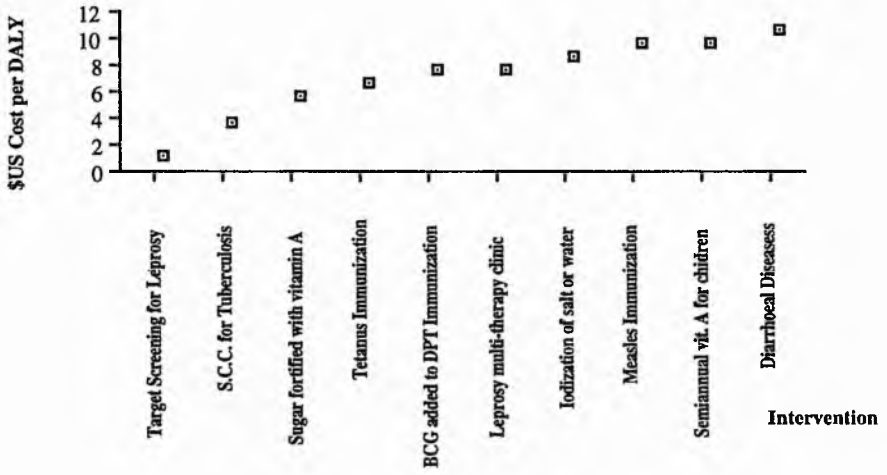
Table 5-7: Cost per DALY Averted for Smear-Positive Tuberculosis Care Under *Hospitalisation*

Country	Cost Per Case	Cost per DALY Averted ($US)
Botswana	367	6.2
Malawi	103	1.8
Mozambique	161	2.7
Tanzania	132	2.2

Source: Murray, 1994b: p. 200

her life expectancy, an extra 50 disease-free years. Similarly, US $100 000 spent on tuberculosis chemotherapy will save 500 patients and avert 35 000 DALYs, whereas the same amount spent on diabetes benefiting the same amount of patients only saves 400 DALYs (World Bank, 1993). To better illustrate this, Murray (1994b) has calculated the potential cost per DALY averted in three states in sub-Saharan Africa.

Figure 5-12: Top Ten Health Interventions in Terms of Cost per DALY Averted



Adapted from : Jamison and Mosley: 1994

The costs per DALY averted in Table 5-7, considering that they include the cost of *hospitalisation*, average at around US $3.22 and roughly correlate with Jamison's (1993) estimate of the cost per DALY for TB of US $3.00. In Jamison's (1993) estimates of the top ten 'cost-effective' interventions,

TB is the second in priority, only lower than the targeted screening of leprosy (another *Mycobacterium* disease). Therefore, TB merits greater attention in disease control expenditure. Indeed, such a low cost per life saved highlights tuberculosis as a focus for funding from health care budgets. However, despite such high returns per dollar expenditure in comparison to other medical interventions, according to Murray (1994b) tuberculosis still globally accounted for approximately 46.5 million disability adjusted life years (DALYs) in 1990. Some of this measure can be attributed to HIV, but not as much as might be expected: a large proportion of it is occurring in those who are HIV-seronegative.

Table 5-8: Disability Adjusted Life Years for Tuberculosis in Selected areas in 1990 (in thousands)

REGION	MALE	FEMALE	TOTAL
Established Market Economies	106	46	152
Former Socialist Economies of Europe	308	53	361
Middle East, North Africa and South-west Asia	2 165	1 880	4 045
India	6 282	4 518	10 800
China	3 469	2 445	5 914
Other Asia and Pacific	5 165	3 771	8 936
Latin America and the Caribbean	1 508	1 061	2 569
Sub-Saharan Africa	7 464	6 209	13 673
Total	26 468	19 982	46 450

Source: Murray, 1994b: p. 195

It is an unfortunate, but valid assertion that expenditure on HIV-seronegative individuals results in better returns than treating HIV-seropositive individuals. This is primarily due to the 100% probability that those with HIV will progress to AIDS and have a drastically shortened life span. Because of a shorter life expectancy, there are fewer years of life gained from TB treatment interventions. Correspondingly, if considering the life expectancy of a patient that already has AIDS into a DALY calculation, DALYs saved for HIV-seronegative individuals are much higher than those gained from HIV-seropositive individuals. This highlights the fact that given the nature of this measure, DALYs for HIV-seropositive individuals and HIV-seronegative individuals can differ. This

assertion is not meant to recommend that empirically HIV patients should be denied treatment because they are economically a greater expense, but only acts as a theoretical caution in calculating DALYs for TB/HIV co-infected patients. Indeed, such economic considerations must indeed be kept in check by the moral obligations of a society.

5-3:3a Global Burden of Disease According to HIV Status

Current TB increases cannot be only attributed to those already affected by HIV. As can be seen from Table 5-9, only 3% of the burden of disease in DALYs was attributed to HIV in 1990, and this is expected to rise to only 10% in 2000 (Murray, 1994b).

Table 5-9: Disability Adjusted Life Years According to Type and HIV Status in 1990 (in thousands)

HIV-status	Smear-positive	Smear-negative	Extra-pulmonary	Total
HIV negative	22 5528	18 248	4 280	45 057
	48.5%	39.3%	9.2%	97.0%
HIV-positive	697	543	154	1 394
	1.5%	1.2%	0.3%	3.0%
Total	23 225	18 790	4 435	46 450

Source: Murray, 1994b: p. 196

5-3:3b Priorities in Tuberculosis Control

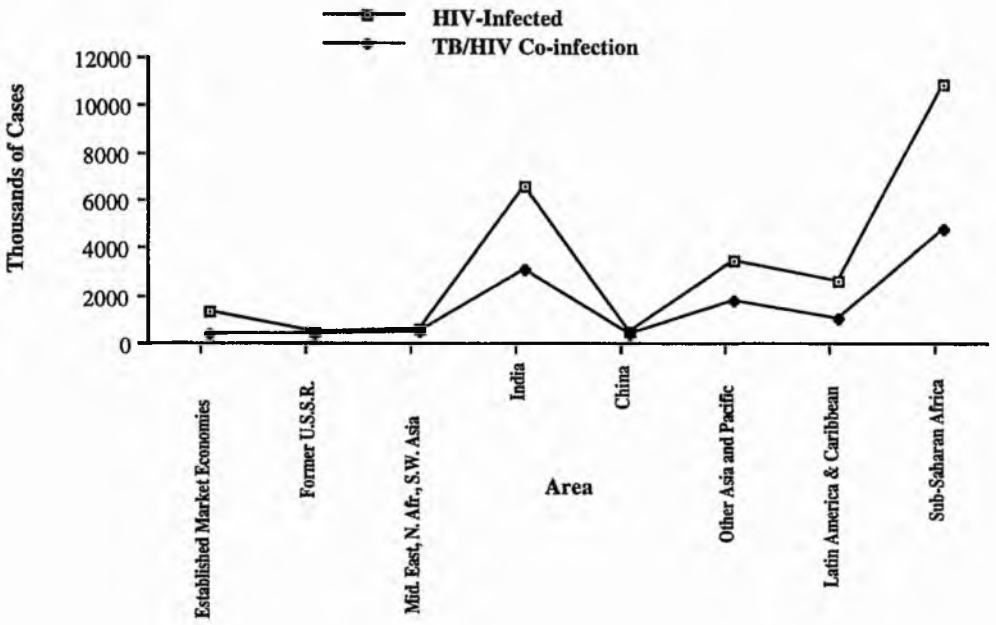
Because there are so many smear-positive patients and they are the infectious cases of TB, this is usually the focus for tuberculosis control programmes since it is the most effective form of treatment in terms of cost and utility due to lives saved and spread containment. Smear-positive tuberculosis in 1990 accounted for 48% of global TB burden. Murray, Styblo and Rouillon (1990) estimate that for every DALY averted by a smear-positive, HIV negative, patient's treatment, four are averted over the next two decades. In contrast, treatment of smear-negative patients under an 80% case detection rate is predicted to reduce only 25% of global TB burden. It is estimated that TB treatment of those who are smear-negative is 3.5 to 8 times the cost of treating smear-positive TB. Nevertheless, treatment of smear-negative patients still proves to be beneficial in terms of cost-utility as it remains low compared to other health interventions. Treatment of smear-negative patients is also significant because they often turn into smear-positive cases as their disease progresses. In contrast to smear-positive and smear-negative, HIV-seronegative cases, concentration on smear-positive HIV patients is estimated to reduce current burden at most, by 10% (Murray, 1994b). According to Murray (1994b) those interventions for tuberculosis that prove to have the highest cost per DALY averted can be prioritised starting as follows below.

(1) S.C.C. for HIV-seronegative, smear-positive TB cases
(2) S.C.C. for HIV-seropositive, smear-positive TB cases
(3) S.C.C. treatment, HIV-seronegative pulmonary TB cases
(4) S.C.C. treatment of HIV-seropositive pulmonary TB cases
(5) chemoprophylaxis of close contact cases
(6) chemoprophylaxis of high risk contact cases

5-3:4 New Expenditure and Future Burden

Murray (1994b) estimates that in countries in different regions of the world, cost-effective tuberculosis control can be achieved with an expenditure of 8.4% of the public health sector budget and US $0.86 per capita expenditure in sub-Saharan Africa, 1.7% of the public health

Figure 5-13: Predicted TB/HIV Co-Infection by the Year 2000 (in thousands of cases)



Mid. East=Middle East, N. Afr.=North Africa, S.W. Asia=South West Asia
Adapted from: Murray, Lopez and Jamison, (1993)

sector budget and US $1.65 per capita expenditure in Latin America and the Caribbean, 4.5% of the public health sector budget and US $0.60 per capita expenditure in India and 2.4% of the public health sector budget and US $0.94 per capita expenditure in other parts of Asia and surrounding islands. The estimate for sub-Saharan Africa is based on that for a country that spends US $10 per capita on health. This amount ($0.86) might seem an extraordinarily high estimate for this, but it reflects the immense burden that this area experiences from tuberculosis. Indeed, tuberculosis treatment is under-funded in

virtually all parts of the world. Globally, the current estimate of expenditure is US $300-500 million per year when in fact US 1.75 billion dollars should be spent per year, representing a 1.25 billion dollar gap.

The contribution of HIV on tuberculosis is expected to continue as is suggested by rates of co-infecton. Figure 5-12 illustrates the projection of both HIV and TB/HIV co-infection in 2000: as HIV grows, so are expected cases of TB/HIV co-infections. This suggests that unless more money is spent for tuberculosis control, the number of new cases of tuberculosis will continue to grow.

5-3:5 Criticisms of DALY Derived Conclusions on TB

When considering the conclusions of DALYs, it must be remembered that this measure is conceptually and methodologically flawed (see Chapter 2 for a more complete description and criticism of DALYs and their related methodology) and it is possible that their conclusions may not be entirely correct in their portrayal of the burden of disease. For instance, it is highly possibly that in calculating the burden of disease of TB due to HIV, these authors may have grossly underestimated it because of the fact that it can be difficult to identify HIV in TB patients.

In addition, one criticism of DALYs when considering their role in prioritising treatment is that they are a measure that includes the assumption that a government has taken the entire responsibility for all of its citizen's welfare or has the financial ability to do so. Hence, strictly speaking this is an approach that is highly dependent on the health care system available. If a country's health care is primarily provided through private sources, then the DALY becomes less relevant. Although much of TB treatment is provided for by the government because of its perceived critical health threat, many countries lack the financial resources or the incentive to make it a top health priority. Therefore, despite the fact that the use of DALYs concludes that TB is a highly cost-effective intervention, investment in its cure may not always manifest. Indeed, it is unlikely that the message of DALYs will have much of an impact on already economically over-burdened developing countries (Kibuga, 1994).

5-3:6 Summary of Section 5-3

The total burden of disease accounted for by tuberculosis still proves to be quite great. Although this disease accounted for 46.45 million DALYs in 1990, treatment for this disease represents one of the most cost-effective interventions available to both industrial and developing countries. Efforts to discount tuberculosis as an HIV disease are convoluted with the fact that a supposedly very large proportion of cases are HIV negative. Nevertheless, this disease's relationship with HIV cannot be ignored, proven by projected cases of TB/HIV co-infection which are expected to rise significantly. Poor records of funding for this disease suggests that such rises in TB will cause growing numbers of

future cases in both HIV positive and HIV negative individuals. Such a rise in cases will sadly result in a greater future morbidity burden if imperatives to treat it are ignored.

Section 5-4

CONCLUSION TO CHAPTER FIVE

Tuberculosis remains one of the world's greatest health threats and still encompasses a disproportionate amount of the global burden of disease, considering it is a curable disease. Methods for the treatment of tuberculosis rely solely on drug treatment that is almost 25 years old, although the impact of the disease has changed in the era of HIV, proven by the rise in new TB cases. The synergistic effect between HIV and TB has caused the largest growth of new cases of TB in the age group of 15-45, the most economically productive part of an individual's life. Discounted as an disease of the past, tuberculosis is not a prominent health priority in many countries. This is despite the fact that TB treatment is considered one of the most cost-effective interventions. Undoubtedly, tuberculosis will continue to grow due to its movement with HIV. A lax attitude to this health threat, compounded with the lack of education of doctors and health authorities in recognising the disease will allow the disease to thrive unnoticed. Until greater attention is focused on the threat of tuberculosis, tuberculosis cases will continue to have the unfortunate feature of being one of the greatest causes of death from a single pathogen in the world. As discussed in Chapter 6, most of these deaths are likely to occur in developing countries, who experience the greatest burden of this disease.

CHAPTER SIX

TUBERCULOSIS IN DEVELOPING COUNTRIES: THE IMPACT OF CURRENT MANAGEMENT AND EXPENDITURE

Introduction

The IUATLD (1994) cites tuberculosis as the greatest single cause of death for those aged between 15-40 in developing countries. Over 3 million new cases of smear-positive TB occur in developing countries per year. Using this number, if there are 1.2 cases of smear-negative pulmonary TB and extra-pulmonary TB for every smear-positive case, this means a total of over 6 600 000 new cases of TB per year. From these new cases, 10-14% will be infected per year and 0.6-1.2% of these will progress into disease (Murray, Styblo, Rouillon, 1990). The annual risk of infection (ARI) in developing countries ranges from 1.0-2.5% (Cauthen, Pio, ten Dam, 1988), whereas in industrialised countries it averages to be far less than 1% (Styblo, 1989). Compounding this is the burden of HIV. In 1992, there was an estimated 4 million people who had TB/HIV co-infection and 95% of these were in developing countries (Narain, Raviglione, Kochi, 1992).

After defining tuberculosis and discussing the techniques of its management in Chapter 5, this chapter will familiarise the reader with the complex problem of tuberculosis in developing countries and present an analysis of existing literature concerning the impact of past expenditure on tuberculosis treatments. It will also present the methodology used in this thesis.

In order to answer the question of the impact of resistance on the cost of tuberculosis treatment in developing countries, it is important to know the particular challenges that developing countries face in containing tuberculosis. Also, past studies on those variables affecting the cost of treatment as well as the cost-effectiveness of treatments are integral to discussions on resistant TB's impact on cost. Section 6-1 will focus on developing countries and methods in which they manage tuberculosis as well as challenges that they face and the success of their tuberculosis programmes. Section 6-2 will give a comparison of various TB treatments and review methodology and past literature on the cost-

effectiveness of these treatments. TB in developing countries is such a major health threat that expenditure for its treatment must be carefully considered.

Section 6-1

TUBERCULOSIS IN DEVELOPING COUNTRIES: THE NEED FOR BETTER MANAGEMENT

Problems in the treatment of tuberculosis that are common in industrialised countries are accentuated by the circumstances in developing countries. In developing countries, tuberculosis treatment is complicated by widespread ignorance of the disease, poor drug supplies and a greater incidence of HIV. This section shows how TB treatment can be standardised in developing countries with a national tuberculosis programme. This section also presents some of the specific challenges that developing countries face in containing tuberculosis such as TB resistance rates and TB/HIV co-infection. TB resistance is shown to be higher in developing countries, and reasons for this are explored. Hence, variables determining TB resistance, specific to developing countries, are also discussed. These variables will be further discussed in following chapters studying TB in Ethiopia.

6-1:1 Problems in Treating TB in Developing Countries

As a result of ignorance, those under care fail to comply with drug treatment, doctors fail to recognise and diagnose this disease and treatment is substandard and inconsistent. In addition to this problem, drug supply is limited such that, in some countries, it is difficult to get the required drugs needed to treat the disease. Those working to treat TB must often face extremely remote conditions with rudimentary medical support. In contrast to this is urban areas of developing countries where drugs fail to be well regulated in pharmacies, and can be purchased on the black market, making them quite freely available. This is particularly significant because, for treating other infections, there are usually drugs that are cheaper and equally effective to TB drugs. Such use of these drugs, especially rifampicin, results in both resistance to the drugs and a shortage of them in tuberculosis programmes (*Research in Microbiology*, 1993). Hence, a schism has formed among developing countries. Those with very low incomes have problems in getting the correct supplies and drugs. In contrast others higher income developing countries face different problems of managing existing drug supplies in order to avoid the frivolous use of TB drugs and therefore its associated drug resistance. Added to this is the more fundamental problem which relates to the actual treatment regimens used. Many countries lack the funding to afford more modern drugs and are therefore confined to using drug regimens which are less effective. In addition, such problems are also accentuated by the large incidence of AIDS, poor nutrition and poor sanitation that have caused the growth in an infectious pool of tuberculosis and its subsequent transmission (Murky *et al.*, 1993).

6-1:1a The Comparison Between Developing Countries and Industrialised Countries

Tables 6-1 and 6-2 present data on tuberculosis infection in developing countries and the incidence of smear-positive TB between 1985 and 1990. From these tables, it can be observed that areas with a high concentration of developing countries have greater degrees of both tuberculosis infection and incidence of smear-positive TB than in those areas with a high concentration of industrialised countries.

Table 6-1: Estimates of Tuberculosis Infection in Developing Countries, 1985-1990

Area	% Risk of Infection	Annual % Decrease in Risk
Sub-Saharan Africa	1.50-2.50	1-2
North African and Western Asia	0.50-1.50	4-5
Asia	1.00-2.00	1-3
South America	0.50-1.50	2-5
Central American and the Caribbean	0.50-1.50	1-3

Source: Cauthen, Pio and ten Dam, 1988.

Table 6-2: Estimated Incidence of Smear-Positive Tuberculosis in Developing Countries, 1985-1990

Area	Cases			Incidence (per 100 000)
	Low	Midpoint	High	
Sub-Saharan African	342 921	591 445	839 970	117
North African and Western Asia	52 592	145 640	238 687	54
Asia	1 141 877	2 298 393	3 454 909	79
South America	57 937	160 440	262 943	54
Central American and the Caribbean	30 022	83 138	136 266	54
Total	1 625 349	3 279 056	4 932 775	79

Source: Murray, Styblo and Rouillon, 1993: p. 235

It is interesting to note that sub-Saharan Africa, almost entirely composed of developing countries, has the highest case fatality rate and the lowest average detection rate, as shown in Table 6-3. Also, new cases of tuberculosis in 1990 rose the most in the Eastern Mediterranean, Western Pacific and African Regions. African regions also had the highest ratio of deaths to new cases as shown in Table 6-4.

Table 6-3: Estimated Cases of Tuberculosis Detected and Case-Fatality Rates in Developing Countries, 1990

Area	Cases Detected	% of Total Cases Actually Detected	Case Fatality Rates	
			Low	High
Sub-Saharan Africa	325 132	25	39	47
North African & Western Asia	222 686	69	26	29
Asia	2 572 809	50	32	37
South America	221 856	62	28	32
Central America & the Caribbean	62 054	34	38	45

Source: Murray, Styblo and Rouillon, 1993: p. 238
Authors base their assumption of fatality on a 15% death rate from standard chemotherapy

Table 6-4: Estimated New Tuberculosis Cases and Deaths Occurring in 1990 by Region

Region	New Cases	Deaths	Ratio of Deaths to New Cases
Europe and other industrialised countries	410 000	40 000	1: 0.09
Eastern Mediterranean	594 000	160 000	1: 0.26
Western Pacific	2 560 000	890 000	1: 0.34
Southeast Asia	2 480 000	940 000	1: 0.37
Americas*	560 000	220 000	1: 0.39
Africa	1 400 000	660 000	1: 0.47

*Americas exclude the United States and Canada. Industrialised countries include Japan, US, Canada, Australia and New Zealand
Adapted from Kochi, 1991: p. 1-6

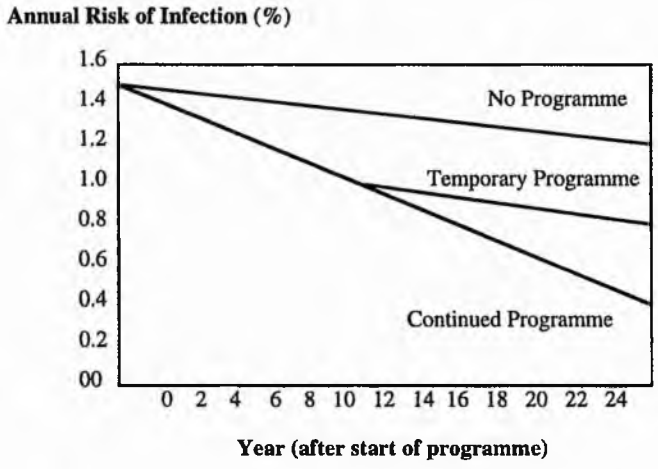
Greater annual risk of infection, mortality rates and incidence of TB, and high incidences of HIV in developing countries predictably cause TB to have a greater cost on the social and economic structure of these countries. In developing countries, there was an estimated 10.6 million deaths of those aged 12-54 in 1990 and 18.5% of these were from tuberculosis (Murray and Feachem, 1990). The fact that tuberculosis affects individuals in this age group means that the disease affects those when they are the prime economic and social contributors to society. This is an age range where an individual has the most responsibility in work and raising children. Because TB strikes this age group, the effects of morbidity and mortality from TB have both significant direct and indirect effects. For example, children whose parents die are far more likely to die during childhood (Greenwood *et al.*, 1987), and this is undoubtedly true for those children whose parents die from TB.

6-1:2 Treatment Programmes in Developing Countries

In 1991, the WHO designed a strategy for tuberculosis control in order to achieve several goals on the path to eradication. Among these was a global 70% smear-positive detection rate and a cure rate of 85% of smear-positive cases by 2000. This is a very ambitious target and may become little more than an unmanifested desire in many developing countries. The ability of different countries to achieve this target has and will vary according to available resources and level of priorities placed on treating tuberculosis over other health care interventions. One method that has proven cogent in achieving greater detection and cure rates has been the standardisation of treatment on a national scale and a firm commitment by a country's government to effectively reduce the incidence of TB.

In many developing countries, efforts to establish a national tuberculosis control program (NTP) have been effective in improving the treatment of the disease. NTPs are essential for treating tuberculosis because they represents a commitment on the part of a developing country to fight the disease, and it is a start in standardising all TB treatment. An NTP educates health workers on the symptoms and diagnosis of TB, it provides standard, effective treatment guidelines, and it gives health workers information on case holding and case finding.

Figure 6-1: Effects of a National Tuberculosis Programme on the Annual Risk of Infection



Source: Murray, Styblo and Rouillon, 1993: p. 254

As is observed in Figure 6-1, without an NTP, treatment of tuberculosis results in only very small changes in the annual risk of infection. Likewise, those temporary initiatives, whereby the country finds it can not longer fund its national tuberculosis programme, will assume the same gradient as those countries with no programme after falling during the enforced NTP period. It is only with a consistent programme that a country can maintain a consistent fall in ARI. With a consistent programme, the annual risk of infection should decrease by 6% per year (Murray, Styblo and Rouillon,

1993). This analysis does not, however, take into account the large scale effect of HIV. In such instances, there will be perceived benefits, but they will be somewhat abated.

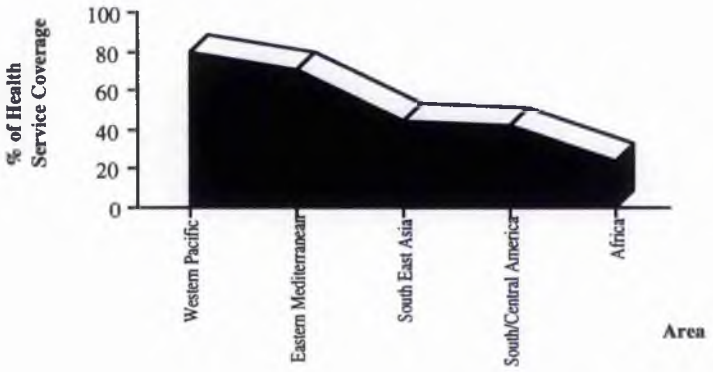
6-1:2a NTPs Improvements in Tuberculosis Treatments

Past efforts in developing countries in controlling tuberculosis have suffered because health workers were unfamiliar with the disease and persisted in treating patients with only one drug or a creative mixture of several drugs and consistency of treatment regimens was often lacking, taking no logical pattern. For example, one doctor might administer a rifampicin and ethambutol regimen for one month and then an isoniazid and ethambutol regimen for four months while another doctor at the same health centre might administer an isoniazid and thiacetazone regimen for two months and then just isoniazid for twelve months. Additionally, diagnosis has also been poor in the past. Doctors, for instance, unfamiliar with tuberculosis and depending on chest x-rays, often would diagnose false-positives and false-negatives. NTPs were established to change such practices with various uniform procedures in TB treatment.

An effective NTP in a developing country is dependent on several components which will predict the success of any programme. (1) A control programme is dependent on the proficiency of the health care staff administering treatment in health care facilities. Health workers must be aware of the fact that a patient's life depends on correct treatment, and this should be communicated to the patient. Overworked staff or poorly educated staff are ill equipped to give good treatment to patients. The caseload in developing countries, especially in hospitals, continues to increase. For example, hospital admissions for TB patients in Uganda increased two-fold between 1985-1989 (Okat-Nwang, Wabwire-Mangen, Kagezi, 1993). Incompetence in the past has resulted in patient default with no follow-up, whereby the names and progress of individual treatment have been lost. Also, poor staff support of a country's NTP can result in inappropriate treatment. In past instances patients with pneumonia and even cancer that have erroneously been diagnosed as TB and continually treated for years. It is the responsibility of health staff, for instance, to make sure that patients do not miss appointments, are taken off treatment that causes severe drug reactions, are quickly hospitalised and are not placed on monotherapy (therapy with only one drug) or continuous phase treatment instead of intensive phase treatment. (2) The role of case finding of clinics offering ambulatory care for tuberculosis is extremely important. An outpatient health facility is an essential key to case finding because it is the primary receiver of infectious cases of tuberculosis. With so many cases presenting themselves, the opportunity arises to trace any close contact the patient had with others, to discover those who infected him or her. It is not uncommon, for example, for a mother to come into a clinic seeking care, and subsequently, a clinic's search will discover that many of her children also have

tuberculosis. (3) NTPs can also instil population confidence in health care facilities by virtue of their greater effectiveness in curing patients. A belief that a health care facility can cure a patient is extremely important. In some cases, individuals with tuberculosis put a greater trust in cultural remedies and beliefs and are unlikely to seek treatment at a health care facility until the disease progresses into its advanced stages. (4) Laboratory staff must be competent in detecting tuberculosis. It is important that they use the correct procedures in identifying tuberculosis, or a large proportion of cases that are smear-positive go unnoticed, depriving the doctor of one of the most effective diagnostic tools for infectious tuberculosis. This includes the proper collection of a sputum sample from a patient as well as staining techniques and analyses. Some patients give saliva samples rather than sputum samples. It is the job of the laboratory staff to make sure that they are analysing sputum rather than saliva or the smear is likely to be negative despite a patient's smear status. Poor laboratory techniques can greater jeopardise the diagnosis of tuberculosis. In rural Nepal, for example, case-finding was only 7% due to poor sputum preparation (Weakliam and Hamlet, 1994).

Figure 6-2: Health Service Coverage for Tuberculosis in Selected Areas (1988-1989)



Adapted From: Kochi, 1991

(5) It is also important that a health care facility is able to give a population access to health care. If a patient cannot readily get to an area where he or she can be treated, the individual is unlikely to persist. Patients, for example, might travel from a rural area to an urban area and stay with friends or on the street when his or her tuberculosis is quite severe and after receiving a month of treatment, and feeling better, will go back to their rural location, motivated by an impending harvest time or a family's dependence. This point highlights the fact that one of the great problems with tuberculosis control programmes in developing countries is that access to health services diagnosing and treating

tuberculosis is not available to the entire population, and in some areas, covers less than half the population. Poor roads, extremely rural conditions, strong cultural beliefs in traditional healing and the lack of funds to treat tuberculosis all impede health services' efforts to penetrate areas with a high prevalence of tuberculosis. As suggested in Figure 6-2, between 1988-1989, areas such as the Western Pacific had coverage of 88% in contrast with Africa, which has experienced a pathetic coverage of only 24%. With such poor access to health services to treat tuberculosis, it is no wonder that the incidence of the disease is so high in these low coverage areas. (6) NTPs are also effective in recording information on patients. Past treatment of patients has been incomplete where either no information or only incomplete information on the patient was taken. Some countries in the past, have had TB facilities which were overloaded with tuberculosis patients. Treatment in these cases was haphazard and patients would arrive, receive a diagnosis a small amount of drug treatment and then disappear. Indeed, all patient statistics must be recorded, including patient progress and adverse drug reactions to keep track of patients and their response to treatment. Over the period of treatment, patients are classified according to six distinct categories of treatment: *cured*, where the patient has received a full course of treatment and has had two negative sputum smears; *treatment complete,* where the patient has received a full course of treatment, but his or her smear status is unknown; *failure*, where the patient has had a positive sputum smear after the fifth month of treatment (this might also includes chronic cases) and must start a retreatment regimen; *died* where the patient has died during chemotherapy either due to tuberculosis or unrelated causes; *default* where the patient has not complied with treatment for more than one month; and *transferred out*, where the patient has moved out of the treatment area. Recording a patient's statistics and progress means that the correct treatment appropriate to the patient can be given, and a patient can be found easily if he or she misses agreed appointments. Also, correct recording allows for calculating the annual incidence and annual risk of infection (ARI), defined as the probability that any person will be infected or reinfected with tuberculosis in 1 year, and TB drug needs on the part of the district and national level. This is a significant figure for developing countries in calculating future cases of TB. For every 1% rise in ARI, there are an estimated 49 new cases of smear-positive TB (Murray, Styblo, Rouillon, 1990). In the past, without a treatment record book, no quarterly report could be given to district health care facilities and therefore, a government had no clue how many cases of TB it had, nor the amount of drugs it would need in the future. (7) Lastly, an NTPs success is dependent on the supervision by district and central health authorities to ensure that the control programme is run properly. This includes regular visits to evaluate the procedures and activities of the health and laboratory staff, assess drug needs and facility capacity and ascertain the total incidence of tuberculosis. Annual and quarterly reports must be collected in order to evaluate case finding and the death, default and cure

rates of the treatment programme. As would be expected, those programmes that are well supervised are far more successful than those that have lax supervision. Chaulet and Zidouni (1993) cite a French study in Algeria (Berkani *et al.*, 1985) which showed that a well supervised area with a caseload of 1 910 identified twice as many smear-positive patients as a poorly supervised area with a caseload of 1 302.

Correctly implemented NTPs have served to improve the level of care for tuberculosis such that many more cases can be treated and the standard of treatment is likewise improved. A commitment on the part many developing countries' governments has increased funding for TB so that drug treatment is often free of charge in government health centres. Also, health workers in these centres have become the most equipped to recognise TB because they often see more TB cases than in private facilities, due to the link between poverty, TB and public sector treatment. TB is often a disease of the poor due to their living conditions and they will seek care in a government health centres where treatment is often free, as they can afford little else.

6-1:3 TB/HIV Co-infection

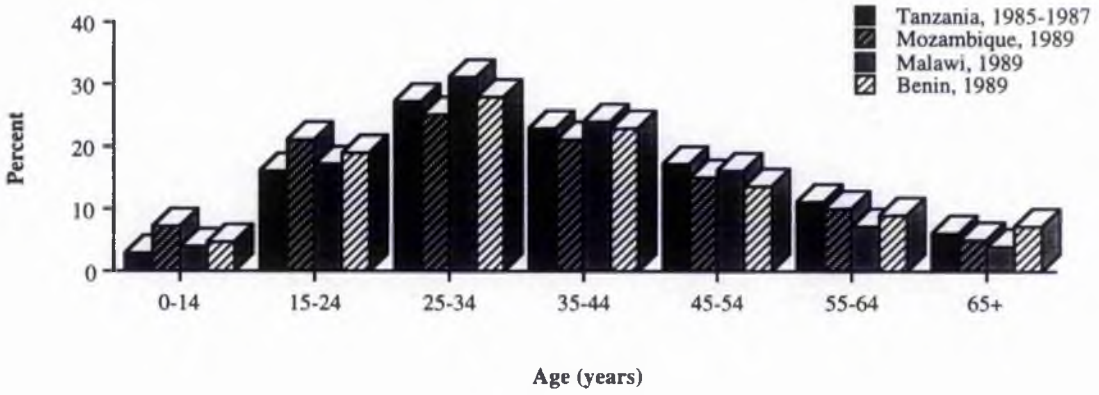
Undoubtedly developing countries suffer from the added challenge of a higher incidence of HIV, which works concurrently with TB infection to increase the incidence of TB. In Africa, for instance, the WHO estimates that there are an estimated 6 million people currently infected with HIV. Because HIV is primarily transmitted through sexual intercourse, those who have several sexual partners such as prostitutes, barmaids, truck drivers, those in the armed forces and those that spend a large proportion of time travelling are those who are most commonly infected with the virus. Likewise, it is in areas such as trucking roads, heavily urbanised areas and those places where there are no family living areas, that the infection is found (Enarson *et al.*, 1993). Initially, most cases of tuberculosis in those with HIV, are likely to arise through endogenous reactivation of those already infected with TB, which can amount to 90% of all TB cases (*FDA Online Documents*, 1995).

6-1:3a The Age Correlation between HIV and TB in Developing Countries

Because of its close relationship with HIV, the spread of TB is quite dependent on the age of the population and whether (1) there is a high annual risk of infection with tuberculosis in the society such that the likelihood of infection at an early age is high and (2)there is a high incidence of HIV. In industrialised countries, 80% of those infected with TB are over the age of 50 whereas in developing countries, 75% of those who are infected are under the age of 50 (Snider, 1994). According to Murray, Styblo and Rouillon (1993), the age distribution in countries changes with the annual risk of infection. In Figure 6-3, where the incidence in Tanzania, Mozambique, Malawi and Benin is between

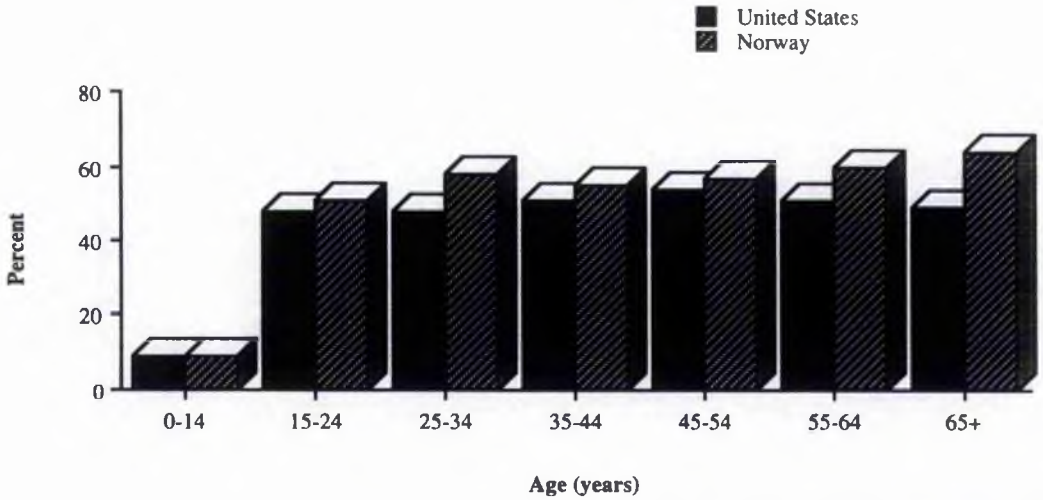
one and two percent, over 80% of TB cases occur in those aged between 15 and 54 and this age distribution peaks between the ages 25 and 34. In contrast, in industrialised countries such as the United States and Norway, shown in Figure 6-4, the age distribution is far more constant after the age of 15. Other forms of tuberculosis, such as smear-negative and extra-pulmonary tuberculosis which are much harder to diagnose, prove to have a similar age distribution according to Murray, Styblo and Rouillon (1993). This estimate also shows a large peak in the age group 25-34 as seen in Figure 6-5.

Figure 6-3: The Age Distribution of Smear-Positive Tuberculosis in Four Sub-Saharan Tuberculosis Programmes



Source: Murray, Styblo and Rouillon, 1993: p. 236

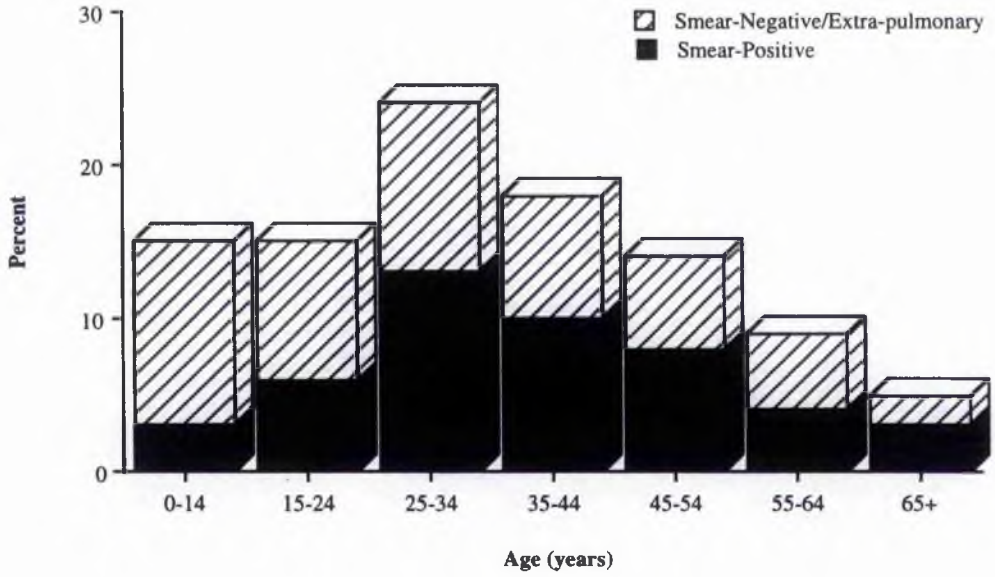
Figure 6-4: Age Distributions of Smear-Positive Tuberculosis as a Proportion of *all* Cases of Tuberculosis in the United States (1985-1987) and Norway (1951-1972)



Source: Murray, Styblo and Rouillon, 1993: p. 236

According to Murray (1989), there is a high probability that almost everyone in an African state will have been infected with TB. This is a reflection of the relative impact of TB on a population and the effect of TB control efforts as cited by Raviglione *et al.* (1992), "Tuberculosis at its full force always claims its highest toll among young adults, while a shift towards the elderly population is epidemiologically a sign of success.". This accentuates a basic difference between developing and developed countries which determines HIV-aided TB infection. Those in industrialised countries who have been infected with TB, primarily were infected before the disease could be controlled. In addition, this population is not likely to have contracted HIV due to their age and the nature of their sexual activity, assuming that most sexual activity, and therefore transference of HIV, occurs primarily between the ages of 15-49 (See Figure 6-5). In contrast, in developing countries, because of the high prevalence of tuberculosis, (between 1.0% and 1.5%, according to Enarson *et al.*, 1993), most have been infected with tuberculosis at a very early age.

Figure 6-5: An Age Distribution Estimation of Tuberculosis in the Developing World, 1990

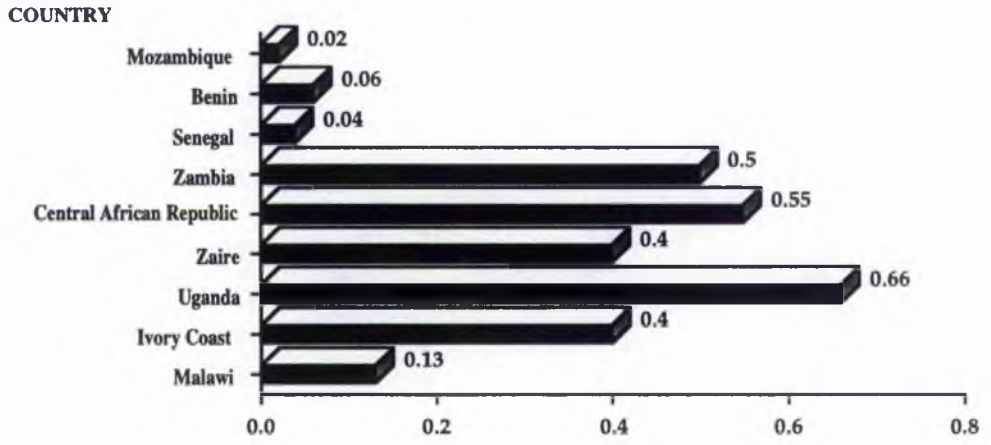


Source: Murray, Styblo and Rouillon, 1993: p. 237

Because of this early exposure, those in the population who develop HIV are far more likely to have been infected with TB and hence, there is the high likelihood of endogenous TB reinfection in developing countries. This seems to be manifest in some data on the percentage of HIV patients in cases of tuberculosis in Africa, illustrated in Figure 6-6 and Table 6-5. In Figure 6-6, varying rates of

HIV-TB co-infected patients possibly suggest either a lower incidence of co-infection or an inconsistent ability to detect and report HIV in tuberculosis patients. Nevertheless, data from Zambia, Central African Republic, Zaire, Uganda and the Ivory Coast would suggest that in these countries, there is a strong link between TB and HIV.

Figure 6-6: Percentage of Observed TB/HIV Co-Infection from Studies of Various African States



DATA SOURCES Malawi: Ponninghaus *et al.*, 1991; Ivory Coast: De Cock *et al.*, 1991; Uganda: Eriki *et al.*, 1991; Zaire: Colebunders *et al.*, 1988; Central African Republic: Mbolidi *et al.*, 1988; Zambia: Meeran, 1989; Senegal: Enarson *et al.*, 1993; Benin: Enarson *et al.*, 1993; Mozambique: Enarson *et al.*, 1993
*Data for Zaire ranges between 22-40% between and 1987, depending on the study (Mbolidi et al, 1988, Colebunders *et al.*, 1988, Mann *et al.*, 1986)

Table 6-5: Estimates of TB/HIV Co-infection in Selected African States

COUNTRIES	% HIV
Medium Prevalence	
Burkina Faso	20-29%
Guinea Bissau	
Kenya	
Swaziland	
Zaire	
Central African Republic	30-49%
Cote d'Ivoire	
Zimbabwe	
High Prevalence	
Burundi	>50%
Malawi	
Uganda	
Zambia	

Source: De Cock, Soro, Coulibaly and Lucas, 1992: 1581-1587

Hence, in sub-Saharan Africa there is also a correlation between the age and the percentage of TB/HIV co-infected patients. It appears that those TB patients who are in the age group of 25-34 have the highest incidence of HIV-seropositivity and similarly, those who are between the ages of 15-24 have an incidence that is only slightly less (Enarson *et al.*, 1993). Unlike in industrial countries, this suggests a strong correlation between HIV and TB infection occurring roughly around the same age. Enarson *et al.* (1993) suggest that although HIV undoubtedly has a strong impact on the growth of tuberculosis in Africa, it is nevertheless, difficult to find conclusive evidence on this. These authors suggest that this is because the TB notification rates in countries with high incidences of HIV such as Malawi and Tanzania are very similar to the TB notification rates in those with low incidences of HIV such as Mozambique and Benin. It is possible that such discrepancies in reporting could very well be due to problems in reporting cases of HIV and tuberculosis, and to problems in detecting cases of HIV in TB patients, but this remains unknown. In addition, TB often appears in asymtomatic AIDS patients, and considering this, those patients that appear with TB are not likely to be tested for HIV-seropositivity due to the fact that (1) HIV testing is expensive and (2) there is a large stigma involved in HIV testing and most health authorities fear that people will link tuberculosis only to AIDS patients if all TB patients are screened for HIV. Such a link would further the stigma already associated with tuberculosis in these countries and those with TB might further delay in seeking treatment. In the current situation, patients are only likely to be tested if they show other signs of HIV or if they experience an adverse drug reaction such as Stevens-Johnson syndrome which is far more common in those with HIV.

6-1:3b The Future Impact of HIV on TB

The future prognosis for TB/HIV co-infection is grim because as HIV infection rises, so will tuberculosis. As can be seen in Table 6-6 by Schulzer, Fitzgerald, Enarson and Grzybowski (1991), in the year 2000 in sub-Saharan Africa, the total rise in smear-positive TB could vary from a 60% increase to an 888% increase depending on the ARI and the percentage of HIV infection.

Table 6-6: The Prevalence of TB in Sub-Saharan Africa in the Year 2000: Four Possible Scenarios

Scenario	% ARI	% Prevalence of TB Infection	% HIV Infection	% Increase in Smear-Positive TB
I	1	45	2	60
II	2	60	2	52
III	2	60	10	280
IV	2	60	20	888

Source: Schulzer, Fitzgerald, Enarson and Grzybowski, 1991: 52-58

6-1:4 TB Resistance to Drugs in Developing Countries

Like other drugs previously discussed, the unregulated availability of tuberculosis drugs for sale in pharmacies and black markets of developing countries has proven to be a problem in controlling TB resistance. Such availability has become so serious a problem that in some countries, governments have prohibited the sale of many anti-TB drugs in pharmacies, limiting them to public health facilities. Extremely poor countries are in such desperate need for tuberculosis drugs, that their use and distribution is often heavily regulated such that only those seeking care in tuberculosis clinics can receive these drugs. These countries where the drug supply is low have lower rates of resistance, as drugs in such short supply are very carefully regulated and any resistance is likely to rise from inappropriate therapy such as monotherapy. However, in those countries such as India, and parts of Africa and Asia where domestic drug production is common and drug regulation is poor, supplies of tuberculosis drugs can be easily procured by almost anyone who can afford them. It is in these countries where the supply of anti-TB drugs is plentiful, that the regulation of these drugs is not so carefully managed and therefore, through inappropriate therapy and inappropriate use, resistance proliferates. In addition, resistance containment efforts are challenged by problems in the quality of tuberculosis drugs in developing countries whereby those that are procured prove to be substandard because of poor local production techniques or poor storage.

6-1:4a Rates of Resistance in Developing Countries as Compared to Industrialised Countries

Indeed, because of the poor management of TB drugs, poor drug supplies and the prevalence of the disease, developing countries appear to suffer more from TB resistance than do industrialised countries. Existing evidence of drug resistance could be attributed to two factors: faulty data collection and incorrect drug use. Data collection measuring resistance in developing countries is very difficult because in these countries, there are priorities that are perceived of greater necessity than the recording of information. Due to a lack of organisation and often a lack of qualified personnel to record information, data are often estimated. Data might be estimated, for instance, from the amount of patients that fail to respond to treatment, when no sensitivity test has been given. Also, sensitivity tests in developing countries are not always that accurate, and so what might be seen as a critical concentration of resistant bacilli in a patient's tuberculosis population might in fact not be this at all. Also, data can be misinterpreted. Bias in resistance data comes from the fact that those samples that are tested for sensitivity are only from those patients who have failed to respond to treatment. Bearing these elements in mind, there is such a great discrepancy between resistance data in industrialised countries and data in developing countries, that it is not entirely accounted for by problems in data collection.

Table 6-7: Drug Resistance by Region

Drug	USA/Canada	Asia, Africa, Caribbean, South America
Isoniazid	7%	39%
Streptomycin	5%	29%
Rifampicin	7%	19%

Source: Hershfield, 1987

Table 6-7: Drug Resistance by Region. In the regions with a large proportion of developing countries, isoniazid can be seen to exhibit the greatest levels of resistance because this is the strongest bactericidal drug and it is relatively cheap to obtain. Streptomycin is ten percent lower than isoniazid and rifampicin is the lowest of the three possibly because the drug is more expensive as compared to isoniazid and streptomycin. In contrast, isoniazid and rifampicin are relatively equal in the percentage of observed resistance in the USA and Canada whereas streptomycin comes in at two percentage points below, probably due to the fact that it is seldom used to treat tuberculosis in these regions.

Of course, it is taken into consideration that resistance data comparisons between countries, are only of a very rough nature due to an inconsistency in data collection techniques and other important techniques in measuring tubercle susceptibility. Nevertheless, data can still be observed in order to get an inexact estimate of resistance in various countries. Bearing in mind dubious data, in Table 6-7, resistance in the United States and Canada is drastically lower than that observed in Asia, Africa the Caribbean and South America. Such resistance is approximately two to five times lower.

Table 6-8: Initial Drug Resistance in the United States

Laboratory	No. of Patients	% of Resistance
Harlingen (Texas)	135	14.1
New Mexico	166	13.9
Massachusetts	188	12.2
Wisconsin	172	10.6
Miami, Florida	58	10.3
Arizona	136	9.7
Los Angeles	105	9.5
Philadelphia	58	6.9
San Francisco	322	6.5
Virginia	48	4.2
Indiana	50	2.0

Source: Gangadharam, 1993: p.316

In addition to this evidence, by Comparing Table 6-8 on initial drug resistance in the United States with Tables 6-9 and 6-10, and 6-11 on initial drug resistance in Africa, Latin America, India and Korea, resistance can be seen to average at approximately 9% in the United States, whereas in regions highly concentrated with developing countries, resistance percentages average at approximately 50% for African states, 25% in Latin American states and an average of 20% in both India and Korea. This

suggests a difference in resistance between the United States and developing countries of between two and six times.

Table 6-9: Tuberculosis Drug Resistance in Selected African States

	% Initial Drug Resistance		
Location	**H**	**S**	**T**
Senegal	18.5	18.8	18.5
Ivory Coast	5.6	6.6	-
Benin	12.8	4.8	22.4
Mauritania	16.9	12.3	45.0
Dori (RHV)	8.7	6.5	47.8
Bobo-Dioulasso	19.5	23.9	25.8

Source: Rey *et. al,* 1979

Table 6-10: Initial Resistance in Latin American States

		% Initial Drug Resistance					
Country	**Location**	**H**	**S**	**R**	**E**	**T**	**Total**
Chile	Santiago	5.9	5.8	0	0	0	14.7
Columbia	Sucra/ Boyace	5.0	10.0	0	0	25.0	35.0
	Meta	4.0	12.0	0	0	12.0	20.0
	Cesar	3.8	7.7	0	0	7.7	15.4
	Antioquia	7.7	7.7	7.7	0	0	15.4
Cuba	-	8.8	8.8	0	2.9	8.8	17.6
Haiti	Port-au-Prince	10.0	5.0	5.0	5.0	0	20.0
Mexico	Guanaj/ Hidalgo	3.1	9.4	0	0	0	15.6
	Oaxaca	2.8	8.3	0	0	0	11.1
Peru	Callao	31.8	54.5	13.6	4.5	4.5	54.5
	Ica	15.0	25.0	5.0	0	10.0	35.0
	Lima	3.0	27.3	6.1	0	6.1	39.4

Source: Gangadharam, 1993: p. 314

Table 6-11: Initial Drug Resistance in Korea and India*

			% Initial Drug Resistance							
Country	**Year**	**No. of Patients**	**H**	**S**	**HS**	**R**	**HR**	**E**	**HE**	**Total**
Korea	1980	108	25.0	4.6	2.8	-	-	5.6	3.8	30.6
	1985	161	13.7	3.7	1.2	2.5	2.5	3.7	3.7	17.4
	1990	115	13.0	6.1	1.8	-	-	0.9	0.9	16.5
India	1990	436	12.2	1.8	3.7	1.8	0.9	0	0.5	21.1

Source: Gangadharam, 1993: p.315

*Of note is the rise in primary resistance to rifampicin, which in parts of India was 0% in the early 1980's (Trevedi *etal.*, 1988) but has risen to 3% in 1989 (Khan *et al.*, 1993). This is significant due to the imperative action of this drug in TB regimens.

In summary, this evidence suggests that there are greater degrees of resistance in developing countries compared to industrialised countries.

6-4:4b The Correlation Between Retreatment, Resistance and Default

Logically, resistance is also related to the number of courses of chemotherapy a patient receives. Several retreatment regimens assume that a patient had either primary resistance at the start of treatment or acquired his or her resistance through treatment default. As the number of courses of chemotherapy a patient receives rises, the more likely it is that the patient is a defaulter and the more likely it is that resistant mutants to various drugs have been selected. An example of this occurred in Algeria in a study of 81 patients, where it was observed that those only having received one course of chemotherapy had resistance two thirds less than those having already received three courses of chemotherapy as observed in Table 6-12 (Mazouni, 1992). As might be expected, the prognosis for those who have received two courses of chemotherapy is extremely poor because of a greater likelihood of resistance to both isoniazid and rifampicin. All of those in Table 6-12 were resistant to at least one drug and 97% were resistant to isoniazid and rifampicin. Such resistance to two of the most significant bactericidal drugs leaves only less effective drugs to fight these patients' tuberculosis, providing that their bacilli are susceptible to these. The prognosis for such cases is estimated to be approximately only a 40-60% survival rate, the same rate that might be experienced with no drug therapy at all (Bloom and Murray, 1992).

Table 6-12: Resistance in Correlation to the Number of Short-Course Chemotherapy Regimens Received by 81 Patients in Algeria.

Number of Chemotherapy Courses Received	Number of Patients	Strains Resistant to Only One Drug	% H + R Resistant
One course	27	33	22
Two Courses	22	64	55
Three Courses	32	100	97

Source: Mazouni, 1992

6-4:4c Reasons for Greater Resistance in Developing Countries

There are several reasons explaining the discrepancy in TB resistance between developing countries. Developing countries have a greater caseload of tuberculosis due to poverty, living conditions, malnutrition and a large proportion of HIV. Hence, this large caseload is more challenging to manage and works concurrently with poor available funding to compound containment efforts. Such difficulties result in many patients not receiving adequate treatment and therefore remaining infectious. Because of the difficulty in following up patients, many for instance, will repeatedly

receive treatment when their tuberculosis become quite serious and then stop treatment when it starts to improve. Intermittent treatment allows for TB resistance to occur in these patients, often resulting in chronic cases. Poor management of tuberculosis is aggravated by the poor management of those drugs used to treat it. Drugs such as rifampicin and streptomycin are available on the black market and used indiscriminately for trivial infection. Rifampicin is a strong antibiotic and there is the temptation to use it for other infections when other antibiotics will suffice. Although rifampicin is used for meningitis and TB it is also sometimes used unwisely for shigellosis, for instance (*Reviews in Microbiology*, 1993). To thwart both its use in other diseases and monotherapy, rifampicin is often prepared in fixed-dose combinations. Unfortunately, there is some question about the bioavailability of rifampicin which can be compromised when it is used in combination preparations with isoniazid. Nevertheless, these combinations can prove more effective than separate administration of these drugs (Geiter, O'Brien, Combs and Snider, 1987), the bioavailabilty of rifampicin is very sensitive and dependent on careful production, which might be jeopardised in local production attempts, especially when combined with another drug. Poor bioavailability of rifampicin is tantamount to monotherapy with the drug it is combined with (most commonly isoniazid), leaving a strong likelihood for resistance to that drug. Isoniazid is another drug that has a high likelihood for resistance because of such heavy reliance on it. Isoniazid, with its strong bactericidal qualities is used in large quantities for prophylaxis, preventative therapy and in some cases, as monotherapy to treat tuberculosis. Isoniazid always appears on every drug regimen, provided that it is not contraindicated in the patient. It is no wonder that there is a growing resistance to this drug under such widespread use. Finally, even with the correct management and administration of effective drugs, the lack of education on the part of the patient causes a lack of compliance to therapy on his or her part furthering the overall percentages of resistance.

6-1:4d Measures to Stop Resistance

As mentioned earlier, to stop the progression of resistance, double or triple therapy is given to tuberculosis patients rather than only one drug. Although ideally, only those drugs to which a patient's tuberculosis is susceptible should be given, this is empirically impractical to achieve as developing countries lack the means or the time to culture each patient's bacteria for susceptibility. A more realistic option would be to culture the organisms from those patients who fail to respond to treatment, exhibiting repeated smear-positive results after treatment. Likewise, no single drug should be added to a failing regimen but a combination should be added (Crofton, 1994) because adding just one drug to a failing regimen is dangerous in that it allows for further selection of resistance. A combination of drugs, however, will serve to destroy any resistant mutants that would otherwise be selected by just

one drug. In addition, those drugs that are administered should be given at regular intervals in order to be effective. If one drug is given infrequently and yet another drug is given daily, this will be impotent in staving off resistance (Gangadharam, 1993). Following this thought, drugs should always be dispensed together so that no preference for one particular drug develops. Fixed dosed combination drugs such as those combining R and H and H and T are advantageous in achieving this. Finally, drugs must be taken for the entire period that they are prescribed. In developing countries, this means that the patient must travel to the health centre every day and have his or her drug consumption monitored during the intensive phase of treatment and checked once a month during the continuous phase of treatment.

6-1:5 Summary of Section 6-1

The ability to eradicate tuberculosis in developing countries has been severely challenged by the correlation between age and TB/HIV co-infection, and greater levels of anti-TB drug resistance. Such problems are unfortunately compounded by ignorance and poor management of these anti-TB drugs. It is only through a systematic standardisation of treatment within each country with resource appropriate NTPs, that developing countries can start on the long road to eradicating TB.

Section 6-2

Relating Cost and Effectiveness to Tuberculosis Treatment

After exploring TB resistance, HIV and NTP's in the previous section, this section will analyse past studies on the cost and cost-effectiveness of tuberculosis treatment. This section will also present the methodology used in this thesis. It further analyses the costs and effectiveness advantages of two main treatments for tuberculosis and the impact of these treatments in containing the disease. Before looking at the impact of tuberculosis drug resistance to treatment costs, past literature on tuberculosis containment costs must first be explored.

In 1991, a startling article appeared in the *Lancet* by Stanford, Grange and Pozniak called "Is Africa lost?" and suggested that a 2 month course of chemotherapy is the current practice for TB in Africa. The authors further suggested treatment of just one week with rifampicin, isoniazid and pyrazinamide using immunotherapy on the seventh day. This type of treatment represents not only a futile attempt to cure tuberculosis, but such a short period of therapy has the potential to lead to higher levels of resistance, affecting not only developing countries, but eventually, industrialised countries (See Murray, Styblo and Roullon, 1993; Gangadharam, 1993; O'Brien, 1993). Such ideas reflect the haphazard character of treatment in developing countries, and the corresponding desperation to find a quick method of eradicating TB. This short treatment, which amounts to little or no treatment at all, will translate to a waste of resources in the majority of cases. Unfortunately, there is no quick method of treating TB and all treatment that is not of the nature and length of either the standard or short-course regimens will prove ineffective for a large proportion of those treated. Treatment in developing countries must vary according to the resources of each country. Determining the correct choice of treatment is an involved process taking into account resources, the quality of health care delivery and priorities. There is no standardised treatment that is appropriate for every country. All too often developing countries are classified as one needy body and although some generalisations about these countries can be made, each developing country must be carefully considered apart from other developing countries. This is indeed true with choosing treatments and control mechanisms for tuberculosis.

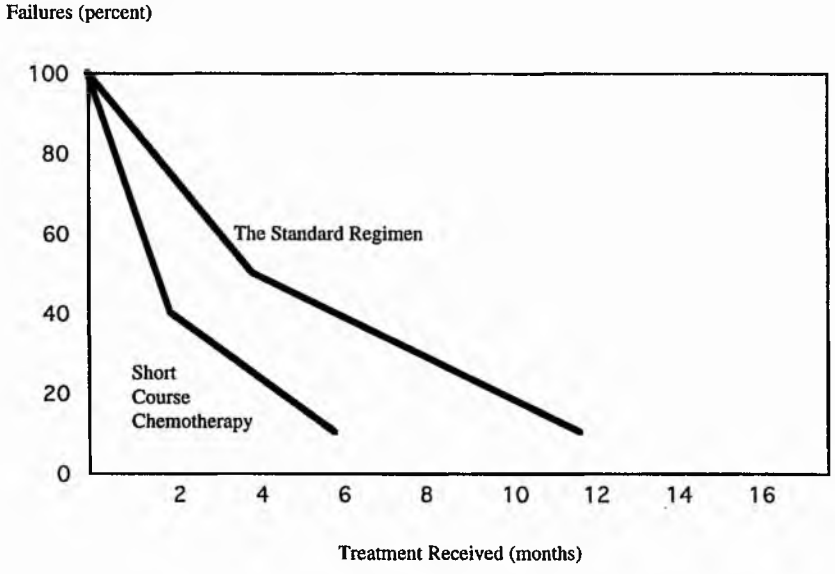
6-1:1 The Superiority of Short-Course Chemotherapy in Terms of Effectiveness

As was previously mentioned, treatment for tuberculosis in developing countries usually consists of a 12 month regimen known as the standard regimen or standard drug regimen (SDR) and a 6 to 10-month variation on 6-month SCC observed in industrialised countries. The standard regimen uses streptomycin injections plus isoniazid and thiacetazone during the intensive phase, and then

thiacetazone and isoniazid during the continuous phase. This regimen consists of older drugs (streptomycin and thiacetazone) whose performance is not necessarily as good as those used in the 6-month and 8-month SCC regimens. In the intensive phase of the short-course regimen, treatment consists of combinations of isoniazid and rifampicin and varying combinations of pyrazinamide, ethambutol, thiacetazone and streptomycin. Isoniazid and thiacetazone is then used in the continuous phase of treatment.

The effectiveness of SCC and SDR is dependent on their respective cure rates, rates of resistance to drugs in each regimen and their impact on the risk of infection in a community. Short-course chemotherapy proves to be more effective due to the fact that it uses more drugs during the intensive phase of treatment. These drugs, such as pyrazinamide, ethambutol and rifampicin, are more effective in stopping resistance and preventing relapses of the disease. Such strong bactericidal and sterilisation effects on these drugs mean that a shorter continuation phase is needed in order to deter a relapse. For initial smear-positive patients, after 2 months of intensive phase treatment, only 50% of those in the standard regimen are likely to be sputum-negative, whereas 80-90% of those receiving short-course chemotherapy will be sputum-negative. In these patients, such fast cure rates for SCC have the added positive externality of decreasing the transmission of tuberculosis. In addition, if a patient stops his or her drug treatment too soon, he or she is more likely to be cured with short-course chemotherapy, a fact supported by data from the World Bank on chemotherapy failure illustrated in Figure 6-7.

Figure 6-7: A Two Year of Follow-up of Patients Failing Chemotherapy as a Function of Months of Treatment



Source: Murray, Styblo and Rouillon, 1993

In this figure, 40% of those who default from SCC treatment at 2 months will remain uncured whereas after 6 months, only 10% of those who default will remain uncured. In contrast, with SDR there is a 65-70% failure rate if default occurs at two months and a 50% failure rate if default occurs at 6 months. The subsequent failure rate for SDR after 12 months equals 10%, the same as SCC at 6 months (Murray, Styblo and Rouillon, 1993). Hence, the rate of default between treatments is a strong determinant of their effectiveness. Assuming patient compliance is partly a function of the length of time of treatment, it is likely to be higher with short-course chemotherapy (Haynes, 1979). Murray, Styblo and Rouillon (1993) cite the East African and British Medical Research Council (1977, 1979) and observe that there is a steady default rate all throughout treatment, suggesting that the longer the treatment, the greater the level of default. The difference between the cure rates of SCC and SDR are also dependent on the actions of the drugs they contain. Relapse rates under incomplete treatment can be lower in short-course chemotherapy than those experienced with the standard regimen. In addition, the standard regimen's effectiveness seems to suffer from higher associated levels of acquired resistance, which is becoming more and more common.

6-2:1a Costs differences between SCC and the Standard Regimen

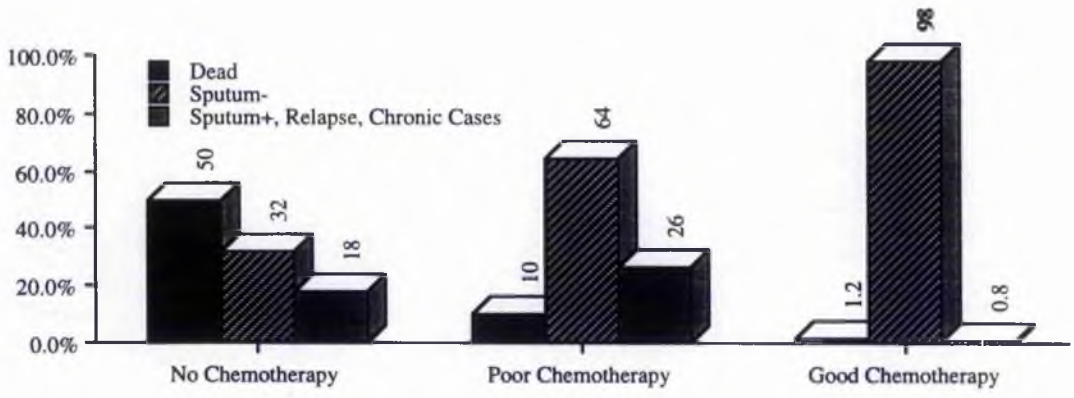
Although SCC is more effective in terms of higher compliance, lower resistance rates and relapse rates than the standard regimen, it must also be noted that it is a more expensive treatment. For this reason, the standard regimen is still used in many developing countries. Indeed, the intensity of short-course chemotherapy usage is surprisingly low in many developing countries when considering its effectiveness. This discrepancy in treatments is largely due to the fact that developing countries perceive short-course chemotherapy as too expensive for them to use.

According to Murray, Styblo and Rouillon (1993), the differences in the costs between short-course chemotherapy and the standard regimen are from drug costs and the levels of hospitalisation required by each regimen. These authors maintain that short-course chemotherapy ranges from US $20-25 per patient treated above the cost of 12-month SDR, which is a significant amount for low income countries. Treatment costs are partially determined by the supplier of the drugs in each regimen. Those suppliers, such as UNICEF or IDA, are characteristically cheaper than European, Chinese or North American suppliers. Additionally, in some developing countries, due to the high cure rate after 2 months for short-course chemotherapy, patients are often hospitalised during this phase. This represents an added cost to this treatment that is sometimes overlooked.

6-2:2 The Current Impact of Different Treatments in Developing Countries

Of course the high incidence of TB in developing countries can by no means be attributed just to drug regimens, but they certainly have a prominent role in containing the disease. In Figure 6-8, a comparison between no chemotherapy, chemotherapy in developing countries and chemotherapy in Norway illustrates that in the case of the developing countries, although chemotherapy is in use, the death rate is still 10% and the rate of case failure is relatively similar to no treatment at all. It seems that from this model, the cases that would have died without chemotherapy are transferred to sputum-negative cases and failures. In the case of Norway, however, cases that would have died are almost completely transferred to sputum negative, or cured cases (Gryzybowski, 1986). In effect, this emphasises the effectiveness that chemotherapy in developing countries has over no chemotherapy, but also illustrates its shortfalls over chemotherapy in industrialised countries. Developing countries, relying primarily on the standard regimen, prove to have a poorer outcome record of treatment than those relying on short-course chemotherapy. In some ways, the situation might even be exacerbated by poor treatment. In effect, treatment of those smear-positive cases who would have naturally died seems to maintain a continuing pool of infection for tuberculosis.

Figure 6-8: The Outcome of Tuberculosis Five Years After Diagnosis: A Comparison Between Good Chemotherapy, Poor Chemotherapy and No Chemotherapy



Adapted from: Grzybowski and Enarson, 1978

Data for each is derived for No Chemotherapy: a longitudinal study in Bangalore, India, 1973; for Poor chemotherapy: Developing Countries in the 1970s; and Good Chemotherapy: the Netherlands, 1975-1976

6-2:2a SCC: Greater Investment in TB Control: Difficult to Justify by Developing Countries

Short-course chemotherapy, although more effective than the standard regimen, suggests a greater investment by a developing country to stop future cases of tuberculosis. Developing countries have very little resources to be making these future investments. Nevertheless, in comparing these two treatments, short-course chemotherapy has the potential to give better overall cures and lower resistance rates. The question then arises as to whether the benefit of greater cures and lower resistance will justify the higher cost of short-course chemotherapy. If the cost per cure of SCC is prohibitive for these countries, then its degree of effectiveness becomes academic.

6-2:3 Methodology Used in Evaluating the Cost and Impact of Drug Treatments for Tuberculosis

In light of the scarce amount of resources that developing countries have for health care delivery, evaluation and planning, it is necessary to find a systematic tool for allocating these resources to maximise their associated utility. The tool that is often best suited to aiding decisions in resource allocation is the economic evaluation of the impact of health care programmes.

Although methods of the economic evaluation of health care programmes are commonly used tools in industrialised countries, they are rarely observed in developing countries. Undoubtedly, the most efficient use of funding is an important priority for developing countries, arguably more so than in industrialised countries because of the former's limited resources. Nevertheless, these countries have few health economists, and few external bodies concentrate on the economic analysis of the impact of the health expenditure in developing countries. Those who would seek to carry out health care evaluations are daunted by the fact that data on the effect of various health interventions as well as the cost of these interventions are very difficult or sometimes impossible to obtain or calculate. Without these data, an economic evaluation is extremely difficult and becomes an exercise in estimates. Hence, most studies that do emerge are often far from complete by the standards of industrialised countries, accentuating health economics as an under-utilised area with great potential in developing countries.

6-2:3a Types of Economic Evaluations

The economic evaluation of health care interventions can be evaluated in several ways, each appropriate to the kind of information that is sought. These include cost-minimisation analysis, cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility (CUA) analysis. Cost-minimisation analysis is used when the outcome of two interventions is assumed to be the same. In this analysis, costs are compared to see which intervention is the least expensive for the desired outcomes. In a cost-benefit analysis, outcomes are not assumed to be the same and costs and benefits

of programmes are compared in terms of the monetary value of costs versus the monetary value of the outcome. CBAs primarily concentrate on the market value of the impact of a health intervention. Placing dollar values on the effects of an intervention is often problematic and dubious. It is, for instance, difficult and controversial to put a dollar value on a life saved. Cost-effectiveness analyses differ from this because these use the monetary value of costs and the value of an outcome in terms of its ability to obtain a particular objective. From this, CEAs express the cost per objective. An example of this might be measuring an intervention in terms of its cost per cure or its cost per death averted. Cost-utility analysis, having grown from cost-effectiveness, is a tool for determining the level of utility or the change in quality of life that an intervention gives a patient as well as that intervention's cost. This is suited to those treatments in which the outcome is not necessarily an immediate cure, but an intervention that improves the patient's ability to cope with a condition. Cost-utility is measured by calculating the willingness to pay for a given effect, the quality of life of a given effect, or from the comparison between the preference of one treatment over another in an intervention (Bootman, Townsend, McGhan, 1991). In summary, all of these methods are used for examining the cost of a particular health programme, and the latter three (in contrast with cost-minimisation which only recognises identical consequences) measure the consequences of various interventions. Cost minimisation, CBA, CEA and CUA are used depending on the kind of available data and the measurement desired. This is captured by Drummond, Stoddart and Torrance (1987) in Table 6-13.

Table 6-13: The Measurement of Costs and Consequences of Economic Evaluations

Type of Study	Measurement/ valuation of costs in both alternatives	Identification of consequences	Measurement/valuation of consequences
Cost-minimisation analysis	Dollars	Identical in all relevant respects	None
Cost-effectiveness analysis	Dollars	Single effect or interest, common to both alternatives but achieved to different degrees	Natural units (e.g., life-years gained, disability days saved, points of blood pressure reduction, etc.)
Cost-benefit analysis	Dollars	Single or multiple effects, not necessarily common to both alternatives, and common effects may be achieved to different degrees by the alternatives	Dollars
Cost-utility analysis	Dollars	Single or multiple effects, not necessarily common to both alternatives, and common effects may be achieved to different degrees by the alternatives	Healthy days or (more often) quality adjusted life-years

Source: Drummond, Stoddart and Torrance, 1987: p. 15

As can be observed, the major differences between these analyses vary according to the identification and measurement of the consequences of all examined health interventions.

6-2:3b Cost -Effectiveness Studies

The most common tool for analysing the cost and the impact of drug treatments for tuberculosis is through the use of cost-effectiveness studies. In almost all cases, tuberculosis treatment relies solely on drugs. As mentioned in Chapter 5, tuberculosis drug treatment consists of either short-course chemotherapy, which is more expensive but cures more patients, or the standard drug regimen, which is less expensive but cures fewer patients. The question arises as to which analysis is appropriate for finding the better treatment in terms of cost and cures. Types of studies such as cost of illness and cost-minimisation, prove too simplistic for seeking such cost comparison information, added to the fact that the outcomes of these treatments are not identical. Cost-benefit studies are considered less suitable because of the complicated and inexact nature of placing a monetary value on the effects of treatment. Likewise, measures looking at the utility a patient gains from TB treatment is inappropriate because the patient is assumed to be either uncured or fully cured by the treatment and therefore, for practical purposes, the utility gained from the cure can be considered to be the same for each patient. Certainly, drug treatments giving a clear and definable cure, such as those using antibiotics, are often more suited to cost-effectiveness studies. In contrast, those interventions where their effects are less obvious, fail to manifest, or result in a combination of more than one effect, are more suited to other analyses, such as cost-utility. Interventions, for example, with more ambiguous effects are NSAIDS for arthritis treatment and loop diuretics for heart failure. With these treatments, the condition is never really cured, but simply attenuated. Equally unsuitable, are situations where one treatment has very high adverse effects but also a very high cure rate when compared to another. Since tuberculosis treatment involves a well defined cure and measure of effectiveness, a cost-effectiveness analysis is the most appropriate to its evaluation.

Cost-effectiveness analyses can be defined as a sequence of mathematical and analytical operations in order to choose an action from various alternative interventions (Rice, 1969). It is a tool for determining the dollar value (cost) per unit of effectiveness (outcome). A cost-effectiveness analysis usually compares at least two interventions and a 'do-nothing' alternative. For each intervention, its costs and effects are calculated so that they can be placed in a ratio that will illustrate cost per outcome. The cost per outcome is then compared over different treatments to see which intervention proves to be the most optimum use of funds. To perform a CEA, the optimum method for achieving a given health outcome must be realistically achieved and more obviously, no less than two methods must be viable (Bootman, Townsend, McGhan, 1991).

There are many important variables to consider when embarking on a cost-effectiveness analysis. Various elements which will affect the study must be defined so that subsequent costs and effects can be evaluated accordingly. The objective of a study must be clearly stated, all alternative treatments

must be considered, the measurement of costs and consequences must appear in the correct units, and all issues relevant to the decision-maker must be presented. A cost-effectiveness study starts with defining the perspective of the study in order to make the study appropriate to its relevant decision maker. The perspective may include, for instance, the individual, the funding body or society: each subsequently affecting those costs considered. A perspective can encompass direct costs or indirect costs. Direct costs are those costs directly related to the operation and administration of a health care intervention while indirect costs are only those costs from lost productivity due to the time a patient lost from treatment (assuming that the patient could have worked normally with his or her condition without this treatment). All of these are classified as tangible costs, whereas those costs such as the mental anguish that a patient experienced because of treatment, of which there is difficulty in assigning a value to, are intangible costs.

Table 6-14: Types of Costs and Benefits

Costs: examples	**Benefits: examples**
capital used	capital released for uses
land, buildings, vehicles	*land, buildings, vehicles*
revenue used	revenue released
labour, supplies, support services	*labour, supplies, support services*
more work for staff	less work for staff
fewer staff training possibilities	more staff training possibilities
patient/relatives/staff costs	patient/relatives/staff benefits
ignorance, dissatisfaction,	*information, satisfaction,*
decision-making burden, time lost,	*relief from decision making,*
inconvenience, expense	*time saved, convenience, less expense*
unhealthier patients	healthier patients
less cure (more pain, disability,	*more cure (less pain, disability,*
worse prognosis, etc.)	*better prognosis, etc.)*
less care (more discomfort, boredom,	*more care (less discomfort, boredom,*
worse environment, etc.)	*better environment, etc.)*
lost output (outside health service)	increased output (outside health service)

Source: McGuire, Henderson and Mooney, 1988: p. 92

Since the perspective determines the costs included, a societal perspective, for example, will include all direct costs such as labour and supplies, and all indirect costs, such as lost productivity and lost economic growth to society because of treatment. Of course, such an emphasis can be problematic. For example, an overemphasis on indirect costs based on lost earnings can slant a study depending on the amount of patients employed. In many countries, for example, those that have tuberculosis are

homeless and unemployed and hence, their costs in terms of lost earnings during the length of various treatments will appear less costly than would those who are fully employed. In contrast, a societal perspective will consider only the costs that the patient incurs, such as the monetary amount that the patient pays for the intervention, transaction costs and costs due to discomfort and lost productivity. Examples of such costs that may be considered from varying perspectives appear in Table 6-14. As is evident, the level of concentration on each of these costs depends on the perspective of the study.

In tuberculosis treatment, the perspective taken is usually the funding body, such as the government, because a societal perspective involves protean patient's costs which are difficult to collect or estimate. In addition, it is the funding body that is usually the most interested in the outcome of such economic evaluations since they are the major decision makers.

Costs fall into several classifications when embarking on a cost-effectiveness analysis (or CBA/CUA). The total cost (TC), represents the cost of producing a given amount of output. Fixed costs (FC) are those that do not change with the amount of output produced in the short run (usually considered 1 year) and these change over time rather than with the quantity produced (i.e. depreciation of machines, housing, equipment). For a given medical intervention, this might for example, include things like ecography equipment, microscopes, x-ray machines and buildings. Variable costs (VC) are those costs that change with each level of output and are in a medical context for example, those items that change with the number of procedures or patients treated: these costs include the costs of drugs, food and consultation fees. The average cost (AC) is equal to the total cost per unit of output (TC/Q: where Q is equal to total quantity). Lastly, the marginal cost (MC) is equal to the extra cost of producing one extra unit of output (TC of n + 1 units) - (TC of *n* units) (Drummond, Stoddart and Torrance, 1987). In a medical context, this for example, represents the cost of treating one more patient over the current caseload.

Another important variable to consider in a cost-effectiveness analysis is the actual measure of effectiveness. This should have some value pertinent to optimum health care delivery. Effectiveness, for example, can be defined by cures, lives saved, years of life saved, or the number of correct diagnoses. Regardless of the measure of effectiveness, it is essential that either the objective of the treatment that is measured is clear in all treatments or if there is more than one measure of effectiveness, all interventions are capable of achieving these (Drummond, Stoddart, Torrance, 1987).

One of the problems of cost-effectiveness analyses arises when there is more than one objective measure of an intervention's effectiveness and relative weights must be placed on these measures (Mooney, 1992). In the case of tuberculosis drug treatment analyses, the measure of effectiveness can be clearly expressed in cures, deaths averted or years of life saved.

There are several approaches to estimating the cost per life year saved. Murray (1994a) highlights the potential years of life lost, the period expected years of life lost, the cohort expected years of life lost, and the standard expected years of life lost methods. These measures do not consider a 'zero mortality assumption'. This is an assumption whereby the years of life lost due to a given illness are derived from a life-table that does not include deaths from that given illness (Haenszel, 1950).

The potential years of life lost (PYLL) are calculated by finding a fixed life expectancy and subtracting the age of death from this life expectancy, as shown in the following formula.

$$\sum_{x=0}^{x=L} d_x(L-x)$$

Where

d_x = the number of deaths at a given age x

L = the life expectancy.

This method suffers in the fact that all deaths occurring after this fixed life expectancy do not count in this measure. Thus, those dying from a given disease after their fixed life expectancy are not considered in the calculation of the amount of life years lost due to the disease. Hence, for instance, if the life expectancy at birth is used in calculating the number of life years lost due to tuberculosis, those that die after this life expectancy are not counted. More than the other measures, this method favours treatments for conditions that affect the very young.

The period expected years of life lost method (PEYLL) estimates total years of life lost from a disease by finding a potential life expectancy at each age of death. The equation for calculating this is

$$\sum_{x=0}^{x=l} d_x e_x$$

Where:

l = the last age group

d_x = the number of deaths at a given age x

This method of calculating risks is a better estimate of the burden of disease in years of life lost than the potential years of life lost method. It also includes the years of life lost by those who are older, and therefore, is a comparatively more utilitarian measure. It is one of the more commonly used methods in cost-effectiveness analyses. Nevertheless, this method can suffer from the fact that there is a bias that develops when considering different life expectancies across countries. Thus, a premature death of an individual from a given disease in a developing country will yield lower life years lost than a death of a individual from the same disease in an industrialised country. Since the life expectancy of

an individual in a developing country proves to be lower than that in an industrialised country, life years lost subsequently prove to also be fewer.

According to Murray (1994a) this method presents a more accurate appraisal of the amount of life lost due to premature mortality, but this premise is based on three assumptions. (1) This method assumes interdependent mortality risks. Once an individual's premature death is averted by an intervention, this individual will not have any higher risk of mortality than any other average member of that population. However, this does not take into account that many of those who were initially threatened by premature mortality might have a chronically disabling condition making the likelihood of their death greater, even after their premature death from one condition is averted. Following this, those that are threatened by a condition like this, might be more vulnerable to another condition. Those that fall into this group include, for instance, those that are elderly, malnourished, alcoholics and drug addicts, who can have far lower immunities to various conditions. This is surely the case of those with tuberculosis who more often than not, have contracted the disease because of weakened immune systems. Indeed, for this reason, when using this method for calculating total life years saved for an intervention, the population concerned must be carefully considered. (2) Age-specific mortality rates currently observed are applied to future populations. What this effectively suggests is that future generations will be equally as likely to have the same age-specific epidemiological patterns that current populations now experience. Future technology improvements which exist in reality in health care delivery, eradicating various diseases, are not taken into account, nor are any other possibilities of new diseases. For instance, the calculation of life years saved in the 1970s for deaths averted in a homosexual population between 20 and 30 are unlikely to have taken into account the future effect of AIDS on this cohort. (3) The life expectancy and years of life lost because of premature mortality are based on current mortality rates, rather than future changes in mortality rates. Similar to the second assumption this does not take into account the effect of technology improvements in calculating an individual's potential life expectancy, nor corresponding changes in life years lost due to premature death from a disease.

There are many similar approaches, using the potential years of life lost method as a basis. Cohort expected years of life lost, and standard expected years of life lost are simply variations on this method. Cohort expected years of life lost (CEYLL) are calculated through

$$\sum_{x=0}^{x=l} d_x e_x^{\,c}$$

Where:

l = the last age group

d_x = the number of deaths at a given age x

As can be observed, this calculation differs from period expected years of life lost because the term e_x^c becomes the life expectancy of a cohort, rather than a blanket life expectancy of each individual in the population. Murray (1994a) maintains that since future morbidity patterns, and correspondingly, the average life expectancy of a cohort cannot be known, these must be estimated. Such estimates, however, still prove to be more accurate than period life expectancies for the whole population. This difference is most highly pronounced in some developing countries where the rate of mortality is expected to decrease greatly in the future. Nevertheless, life expectancies of an age cohort will differ depending on the area. For example, an individual of an age cohort in a very poor area can experience far different morbidity patterns than an individual from the same age cohort in a more affluent environment.

Also similar to PEYLL is the standard expected years of life lost (SEYLL). This is the calculation of years of life lost due to premature mortality through an ideal standard of life expectancy:

$$\sum_{x=0}^{x=l} d_x e_x^*$$

Where:

l = the last age group

d_x = the number of deaths at a given age x

In this calculation, it can be seen that the term e_x^* is based on an ideal standard of life. Murray (1994a) uses this method to calculate DALYs and bases e_x^* on this highest recorded life expectancy at birth for women, of 82.5. This life expectancy is worked into a model life-table called the West Level 26. Here the average life expectancy at birth for men is calculated to be 80, estimated from a 2-3 year observed biological difference in average life expectancy at birth between men and women, rather than behavioural and environmental hazard differences. This model life-table is shown in Table 6-15.

Table 6-15: Standard Life Expectancy due to Premature Death at Each Age According to the West Level 26 Model Life-Table

Age (Years)	Females	Males
0	82.50	80.00
1	81.84	79.36
5	77.95	75.38
10	72.99	70.40
15	68.02	65.41
20	63.08	60.44
25	58.17	55.47
30	53.27	50.51
35	48.38	45.56
40	43.53	40.64
45	38.72	35.77
50	33.99	30.99
55	29.37	26.32
60	24.83	21.81
65	20.44	17.50
70	16.20	13.58
75	12.28	10.17
80	8.90	7.45

Source: Murray, 1994a: p. 435

The data that are to be evaluated is also an important component to a cost-effectiveness study. Data must be unbiased and patients must be randomly chosen for treatment. Additionally, one should use a control group when possible. In practice, this is seldom performed because it is considered inhumane to deny a patient treatment where his or her suffering is concerned. Instead, past studies on the effect of a disease before a treatment was available are sometimes used. Data are obtained from medical literature and where none exists, estimations can be extrapolated from various sources, or a study can be purposely created that will be relevant to the intended analysis. Of course, these data must be checked with a sensitivity analysis which reveals how sensitive conclusions in the study are to changes in the data. In effect, sensitivity analyses illustrate how strong or weak various conclusions are in a cost-effectiveness study and what these conclusions depend on. The upper and lower limits of these data are varied to find out in which area of values the conclusions of an analysis are valid and in which areas they are not. For example, suppose that the cost-effectiveness conclusions of particular treatments for cancer are dependent on the number of patients that experience adverse side-effects to each medicine. From literature and reports of other studies, the parameters that have been used to reach this conclusion are varied from the lowest plausible value limit of fewer adverse reactions to the highest plausible value limit of far more adverse reactions. The results of this are then monitored and in this way, it can be seen how dependent is the study's conclusion on adverse reactions. In particular, data that should be separated for a sensitivity analysis are those based on estimates, those that vary greatly from other studies, and those that are subject to changes due to manipulation during analysis. According to Drummond, Stoddart and Torrance (1987), finding the upper and lower limits in which

to vary data values in sensitivity analyses is dependent on results from other clinical studies, current practice in literature and the opinions of the relevant decision makers.

The calculated costs of an intervention must have limits in what it includes as costs. Suppose that those in a study with TB/HIV co-infection are cured of TB and survive to be treated for AIDS complications. The question arises as whether the cost of the ensuing treatment for these cured patients should be included in the costs of treating tuberculosis. Drummond, Stoddart and Torrance (1987) highlight the fact that this form of applied economics is a partial equilibrium analysis and therefore an artificial boundary is maintained in these analyses. This means that the effects of a health intervention can be better concentrated on while holding all other things constant.

Once costs and benefits of an intervention are established, these can be subject to discounting. This is a tool used to adjust the value of the costs and benefits of an intervention that are experienced in the future. Discounting is a concept derived from the fact that most individuals wish to experience costs in the future and wish to experience benefits immediately, also known as a positive time preference. It is for this reason that credit cards, for instance, are so popular. Credit allows an individual to buy something such as a car and experience the comfort from it, deferring its costs until later when the individual might have saved up more money or when the individual has been able to earn interest by investing this money. Individuals would rather have income today rather than in the future. If they receive it in the future rather than the present, they expect to be remunerated for this. According to Parsonage and Neuburger, the extent of time preference is dependent on (1) the likelihood that real incomes will grow in the future (2) the rate that the marginal utility obtained from each extra pound decreases as real income rises and (3) 'pure' time preference, defined as those preferences for the future unconcerned with changes in real income (Parsonage and Neuberger, 1992: p. 72). This same effect is relevant to economic analyses such as cost-effectiveness.

Discreet discounting of costs and benefits are often calculated with the formula (McGuire, Henderson, Mooney, 1988)

$$\sum_{t=0}^{T} CV_t(1+r)^{-t}$$

Where:

t = time

t=0 = the present period

t=1 = one year in the future

CV_t = the compensating variation at time (year) t.

T = the beginning of the time period

In this formula, the compensating variation is the largest amount that a consumer will pay for a benefit or the smallest amount of compensation that the individual will accept for a loss. This is similarly expressed by Drummond, Stoddart and Torrance (1987) with different variables. The primary difference lies in the fact that these authors use future costs (F_n) in place of compensating variation (CV_t), which, empirically in the formula, have the same function.

$$P = \sum_{n=1}^{n} F_n(1+r)^{-n} = \frac{F_1}{(1+r)} + \frac{F_2}{(1+r)^2} + \frac{F_3}{(1+r)^3} + \ldots + \frac{F_n}{(1+r)^n}$$

Where:

P = the present value

F_n = the future cost at year n

r = the annual discount rate

It is not difficult to see that as the years grow in number, the denominator $(1+r)^n$ also gets larger so that the present value becomes smaller and smaller. If benefits, for instance, are perceived to be experienced over twenty years, then they will be discounted accordingly over this period of time so that $\frac{F_n}{(1+r)^n}$ will be calculated for each of these years.

Although it is more logical to discount costs, there is some question as to when the benefits or effects of a health intervention should be discounted. If the effects of a health intervention are immediately experienced, then there is no need to discount these effects. Drommond, Stoddart and Torrance (1987) present some arguments not to discount benefits. Individuals investing and trading healthy years of life over time is a theoretical rather than an empirical concept. In addition, discounting years of life obtained in the future places a bias for current generations over future generations. This essentially suggests that years of life of those now living are more important than those in the future. This might be significant, for instance, when considering the teratogenic effects of a hypothetical drug on a woman's future unborn children. Such discounting would favour the mother's current years of life over her future children's. Parsonage and Neuberger (1992) claim that discounting benefits lets analysts ignore the possibilities of benefits extending beyond a lifetime to other generations.

In contrast, arguments for discounting benefits include the fact that discounting costs and not benefits is inconsistent and leaves impossible conclusions. Drummond, Stoddart and Torrance (1987) maintain that those health programmes, for example, with a 1 dollar benefit per year for an infinite number of years become worthwhile over time no matter what the initial outlay. In this case,

discounting is shown to take into account the decreasing value of money over time. Also, if costs are discounted but benefits are not, cost-effectiveness will improve the more a project is delayed.

In addition, in calculating cost-effectiveness, an incremental analysis should be performed. An incremental analysis shows the decision maker the extra amount paid for each extra unit of effectiveness achieved by the superior intervention. This value represents the incremental cost between two treatments divided by the incremental effectiveness. Given two interventions, in order to find this value, the difference between the costs of both interventions is calculated separately from the difference between their units of effectiveness. From these two differences of costs and units of effectiveness between treatments, one can find the incremental cost-effectiveness ratio.

6-2:4 Past Studies in the Cost of TB Treatment

6-2:4a Feldstein, Piot, Sundaresan

There are not many studies that have either analysed the cost in the treatment of tuberculosis or the cost-effectiveness between short-course chemotherapy and the standard regimen. One of the first analysing costs was performed by Feldstein, Piot, Sundaresan (1973) who developed a model of resource allocation using tuberculosis in Korea as an example.

$$\sum_i A_{ij} x_j \leq m_i$$

Where:

A_{ij} = the input

x_j = the level of activity

m_i = the total availability of resources that may be utilised for tuberculosis

In this model, the authors tried establish just how much expenditure would be needed for the control of tuberculosis in this state. In what resembles a variation of a production function, total availability of resources (m_i) that may be utilised for tuberculosis is calculated to be greater or equal to the sum of the requirement of the input (A_{ij}) multiplied by the level of activity (x_j) or the intensity to which an input is used.

This formula assumes that i represents any resource ranging from labour and drug supplies to overhead and j represents the given activity in tuberculosis treatment. The input function is then defined as

$$A_{ij} = \sum u_{iT} c_{Tj}$$

Where:

A_{ij} = the sum of the requirement of input u_{iT}

u_{iT} = the requirement of resource i per unit of task T

c_{Tj} = the quantity of task T used in a unit of activity j.

It is through the manipulation of this equation, that these authors calculated the resources that were both available and needed for the treatment of tuberculosis in Korea. Resources (i) were separated into constrained inputs and unconstrained inputs. Constrained inputs were the total costs, cost of expendable supplies, physician-time, nurse-time, technician-time and bed-days. Unconstrained inputs included the cost of the doctor, nurse, auxiliary nurse, technicians, auxiliary technicians, other staff, beds, capitals costs and administrative overheads. These costs were calculated from a long list of activities performed by health care staff. These encompassed all areas of time spent by staff in TB screening, treatment, drug distribution, drug administration, default control, hospital admission, BCG vaccination, and chemoprophylaxis. From these costs, a total cost is calculated per task for each activity.

It is through this calculation and by considering the incidence of TB in Korea at the time, that the authors estimated the impact of expenditure on the country's TB programme. Korea's budget for TB control in 1964 was estimated to be US $515 000 and effective use of this was estimated to save 55 289 disability years (not DALYs) or 10.7 years per US dollar. Feldstein, Piot and Sundaresan estimated that for every US dollar spent in this programme, there was an average return of US $150 dollars assuming a per capita annual income of US $140. This article offers an interesting method into calculating the costs of tuberculosis. It is one of the first articles of its kind relating cost and TB. Nevertheless, its immediate relevance is weak due to the fact that it is based on data that are over 30 years old and methods for health care evaluations have changed since 1973. Furthermore, this is a pre-HIV study.

6-2:4b Fryatt, Bhattarai and Niroula

In addition to this study, a more modern and practical analysis of TB costs was undertaken in an unpublished study by Fryatt, Bhattarai and Niroula of the Britain Nepal Medical Trust. The design of this study was to ascertain the cost of SCC in the Terai region of east Nepal in the spring of 1991. In this study, 4 hill districts were analysed in order to ascertain if the programme could be run by the local District Public Health Office's (DPHO) budget.

Figure 6-9: Short-Course Chemotherapy Programme Costs in Nepal

- Admin: Other 3%
- Admin: Nepali Staff 3%
- Admin: Expatriate Staff 9%
- Publicity 1%
- Trainings 3%
- Transport: Porter 2%
- Transport: Air 2%
- Transport: Road 4%
- Field: Running Costs 6%
- Field: Non-TB Drugs 2%
- Field: TB Drugs 17%
- Field: Nepali Staff 28%
- Field: Expatriate Staff 19%

Source: Fryatt, Bhattarai and Niroula, 1992

The authors subsequently found that SCC was 3.6 times the cost of standard chemotherapy. However, because patients receiving SCC did not require a two-month stay, clinics and hostels were 40% cheaper to run in SCC areas. In addition, there was less use of non-TB drugs in SCC areas, attributed to the regimen's greater effectiveness.

Table 6-16: Annual Costs by Activity for Standard and Short-Course Programmes in Nepal (Nepalese Rupees: 1991, US $1=29.3)

Activity % Total	Sub-Group	Standard Costs	SCC Costs	Ratio of Standard: SCC
ADMINISTRATION & SUPPORT	Personnel			
	i. expatriate	335 950	352 500	1:1.05
	ii. Nepali	128 464	110 161	1:0.86
SDR				
590 537 (17%)	Buildings	81 715	75 961	1:0.93
SCC	Equipment and Running	44 408	40 044	1:0.90
578 666 (15%)	costs			
FIELD WORK	Personnel			
(4 districts)	i. expatriate	740 560	740 560	1:1.00
	ii. Nepali	1 050 440	1 106 284	1:1.05
SDR				
2 513 417 (71%)	Drugs			
	i. anti-TB	187 864	672 096	1:3.58
SCC	ii. other	115 018	65 291	1:0.57
2 837 545 (72%)				
	Running costs (clinic & hostel)	419 535	253 314	1:0.60
TRANSPORT	Road	158 460	149 121	1:0.94
SDR	Air (National & International)	95 419	96 045	1:1.00
285 993 (8%)				
SCC	Porter	32 114	90 184	1:2.80
335 350 (9%)				
TRAINING OF GOVERNMENT STAFF				
SDR				
97 061 (3%)				
SCC				
126 683 (3%)		97 061	126 683	1:1.31
PUBLICITY	Setting up	18 080	18 080	
SDR				
38 530 (1%)	Other	20 450	20 450	1:1.00
SCC				
38 530 (1%)				
TOTAL		3 525 538	3 916 774	1:1.11

Source: Fryatt, Bhattarai and Niroula, 1992

Considering these three differences in costs, the authors concluded that in these areas, SCC utilisation incurred an 11% increase in programme costs and cost per patient was 4% higher. The percentage of SCC costs can be seen in Figure 6-9. The greater costs of SCC mainly reflected the costs accompanying training for the implementation of a new drug programme and the inaccessibility of the SCC districts chosen. It is for this reason that transport costs and training costs appeared to be high. A comparison of these costs with the standard regimen can be seen in Table 6-16 where all costs are broken down into their various components. This offers a rare opportunity to ascertain the actual costs

of a SCC programme in a developing country. By many accounts, the ability to access costs of these programmes is rare, due to problems in cost accounting in developing countries.

6-2:5 Past Studies in the Cost-Effectiveness of TB Treatments

6-2:5a Barnum

In 1986, Barnum performed a cost-effectiveness analysis of short-course chemotherapy regimes containing rifampicin and ethambutol (2[months]SHRZ/6[months]HE, 2[months]SHRZ/ 4[months]HR) and compared these to standard regimens implementing isoniazid and thiacetazone (2[months]STH/16[months]TH) in Botswana. In this analysis, Barnum found that despite the high cost of rifampicin and ethambutol per case of TB, when considering the number of people effectively treated, the RE regimen was half the cost of the TH regimen. The author highlighted the fact that the difference in these costs was primarily due to greater patient compliance to the short-course regimen due to its implicit shorter duration. Additionally, he credited this difference to the ability to substitute ambulatory care for inpatient care under RE and the fact that RE is more bacteriologically effective than TH.

Similarly to the Feldstein, Piot and Sundaresan study (1973), total cost was calculated by simply adding all the costs of each activity in tuberculosis treatment. Barnum calculated the costs for treatment with the standard regimen through the equation

$$C_1 = 60(c_I + c_S + c_{TH}) + c_L + \sum_{3}^{18} B_{It}$$

Where:

c_I = Cost per inpatient day

c_S = Cost/day of streptomycin

c_{TH} = Cost/day of thiacetazone and isoniazid

c_L = Cost of sputum tests

ΣB_{It} = The sum of the costs of the continuous phase of treatment (between the 3rd and the 18th month of treatment assuming that the patient receives ambulatory care requiring one visit per month).

It can be seen from this equation that the first term $60(c_I + c_S + c_{TH})$ was used to calculate the drug and inpatient costs of the first two months of intensive treatment. The second term (c_L) was used to calculate the cost of the second month's sputum test which is independent of the intensive and continuous phase. The third term (ΣB_{It}) was used to calculate all costs for each month associated with

the remaining 16 months of treatment in the continuous phase. The cost for each month of continuous phase treatment (B_{lt}) was calculated from the following formula.

$$B_{lt} = (c_A + 30c_{TH})N_t + c_L N_{t_{ont=4,8,12,18}} + c_x N_{t_{ont=12,18}}$$

Where:

c_L = Cost per Sputum Test

c_A = Cost per monthly ambulatory visit

c_{TH} = Cost/day of thiacetazone and isoniazid

N_t = The proportion of patients still complying with treatment after t months

Thus, the first term, $(c_A + 30_{CTH})\, N_t$, represents the cost per month of one outpatient visit and a 30-day supply of drugs. The second term, $c_L N_{t\ ont=4,8,12,18}$ represents all costs from 4 sputum smears done in the 4th, 8th, 12th and 18th month of treatment. Lastly the third term, $c_x N_{t\ ont=12,18}$, represents all costs that were incurred from the two chest x-rays that were taken in the 12th and the 18th month of treatment. It can be seen in this equation that each of these three groups of costs was multiplied by N_t to compensate for the fluctuation in the number of patients due to falling rates of compliance.

It follows that with extrapolation the equations for the other two treatments would be for 2SHRZ/6HE,

$$C_1 = 60(c_I + c_S + c_H + c_R + c_z) + \sum_3^8 B_{lt}$$

and for 2SHRZ/4HR,

$$C_1 = 60(c_I + c_S + c_H + c_R + c_Z) + c_L + \sum_3^6 B_{lt}$$

From these equations it can be seen that B_{lt} varies both according to the number of x-rays and the number of sputum smears taken for these two treatments. It must be noted that these equations do not take into account either the cost of initial sputum smears for patients during diagnosis or the fact that patients can default on treatment during the intensive phase.

In calculating cost-effectiveness of these regimens, the author divided the cost of the regimen by the cure rate and the compliance rate over the entire treatment period with the equation

$$CE_i = \frac{C_i}{r_i N_T}$$

Where given regime i :

CE_i = cost-effectiveness of each regime
C_i =cost per patient of regime i not taking into account the rate of default
r_i = cure rate of regime i
N_T = total compliance at the end of the treatment period for regime i

It can be seen from this equation that a fall in $r_i N_T$, which represents the measure of effectiveness, causes a smaller and smaller denominator such that the cost per percentage effectiveness becomes higher and higher. In this case, the cure rates (r_i) for the standard regimens was a low ≈0.70 over 18 months. Resistance to T and H and the corresponding rate of compliance (N_T) was ≈0.50, producing an effectiveness of ≈35%. The cure rate (r_i) for the short-course regimens were much higher at ≈0.90 and the rate of compliance (N_T) was ≈0.85.

Table 6-17: The Cost-Effectiveness of Various TB Treatment Regimens in Botswana as Calculated by Barnum (1986)

Regime no. *i*	Description*	Cost per person treated (in Botswanian pula) *Ci*	Cost per person effectively treated (in Botwanian pula) *CEi*
1	**$3_{inpatient}$STH/15TH**	1 374	3 437
2	**$2_{inpatient}$STH/16TH**	938	2 441
3	$2_{inpatient}$SHRZ/6HE	957	1 301
4	$2_{inpatient}$SHRZ/4HR	968	1 213
5	**$2_{outpatient}$STH/16TH**	306	863
6	$2_{outpatient}$SHRZ/6HE	323	475
7	$2_{outpatient}$SHRZ/4HR	337	457

Source: Barnum, 1986: p. 849
*in all regimens, the continuous phase is assumed to be outpatient care

This rendered a SCC effectiveness of ≈77%. Hence, as viewed in Table 6-17, the outpatient treatment of, for example, number 5 costs 306 Botswanian pula per person. In this example, with a cure rate of

0.7 and a compliance rate of 0.5, CE_i is equal to approximately 874 Botswanian pula, or as calculated by Barnum, 863 pula. In this way Barnum derived C_i and CE_i for each TB regimen in Botswana. From these findings, Barnum concluded that regimen no. 7 was the most cost-effective, followed by regimen no. 6 and no. 5. Barnum also found that the outpatient standard regimen number 5 was 47% greater in terms of the final cost per patient than the outpatient short-course regimen no. 7. Unfortunately, the author did not perform an incremental analysis on these data. In addition, when calculating cure rates, Barnum assumed that all defaulters remained uncured when this is not necessarily the case.

There are some other difficulties with this study. For his comparison, Barnum used only 18-month standard regimens instead of 12-month standard regimens which is now the normal practice. This is significant because cure rates might be higher when only considering a 12-month intensive phase standard regimen instead of the extra 6 months from an 18-month phase. Because of the link between time and default, the rate of default used in calculating the cure rate for a 18-month treatment will be abnormally high compared to a more commonly used 12-month period. The author also failed to mention that the high 30% resistance rate responsible for the low cure rate of the standard regimen could be raised if it could be determined which patients had already received treatment. This amount cannot be entirely attributed to primary resistance. Indeed, not much information about the patients was given such as smear-status, HIV-status or location, all of which can be very important determinants in the outcome of treatments. To highlight the difference between the two forms of drug treatment, Barnum compared the cost-effectiveness of inpatient care in the standard regimen to the most cost-effective form of ambulatory care in the short-course regimen. It is academic to compare these two because they are under two completely different constraints. Additionally, Barnum failed to highlight the fact that much of the improvement in this programme was not due to a change in drugs regimens, but to major changes in the government's approach to TB care. Such government efforts improved the training of field workers to ensure patient compliance and reduce inpatient care to only 20% of cases. In fact, this is an analysis of revised treatment methods, not strictly an analysis of drug regimens.

In summary, as would be common in most analyses, Barnum's results were primarily dependent on the fact that there was lower resistance and higher compliance to the short-course regimens that was not experienced by the standard regimens. Once the variables for the standard regimen approach an effectiveness of the short-course regimen (0.77) then the results of this cost-effectiveness are no longer as strong. They then become completely reliant on the action of the drugs themselves. Nevertheless, the author concluded that raising cure rates and compliance to the standard regimens is much more difficult in Botswana than raising them for short-course regimens. It is possible that because the short-

course regimens involved newer, more expensive drugs, extra effort went in to making sure that patients complied with their treatment.

6-2:5b Joesoef, Remington, and Jiptoherijanto

Another model of cost-effectiveness was performed by Joesoef, Remington, and Jiptoherijanto (1989). Cost-effectiveness was based on a regimen's ability to achieve the objective of preventing cases of TB in the future. In this study, the authors developed an epidemiological model of tuberculosis from which they were able to project costs. From this they calculated cases of smear-positive TB prevented in the future by three drug regimens. These regimens consisted of a 100% standard course chemotherapy regimen, a 100% SCC regimen and an existing combination of 35% SCC and 65% standard regimen. In order to calculate the probabilities of a regimen preventing future cases of TB, they used a rate equation model. This rate equation model describes the probabilities that individuals will be infected and develop tuberculosis.

$$\Delta S_1 = SB - S_1(T_{12} + T_{13} + D - \Delta S_7/S)$$
$$\Delta S_2 = S_1 T_{12} - S_2(T_{24} + D - \Delta S_7/S)$$
$$\Delta S_3 = S_1 T_{13} - S_3(T_{34} + D - \Delta S_7/S)$$
$$\Delta S_4 = S_2 T_{24} + S_3 T_{34} + S_5 T_{54} + S_6 T_{64} - S_4(T_{45} + T_{46} + T_{47} + D - \Delta S_7/S)$$
$$\Delta S_5 = S_4 T_{45} + S_6 T_{65} - S_5(T_{54} + T_{56} + T_{57} + D - \Delta S_7/S)$$
$$\Delta S_6 = S_4 T_{46} + S_5 T_{56} - S_6(T_{64} + T_{65} + D - \Delta S_7/S)$$
$$\Delta S_7 = S_4 T_{47} + S_5 T_{57}$$
$$S = S_1 + S_2 + S_3 + S_4 + S_5 + S_6$$

Where

B = the crude birth rate
D = the crude death rate
S_1 = the non-infected population
S_2 = the infected population
S_3 = the BCG vaccination population
S_4 = the population with active radiological lesions
S_5 = the tubercle bacillary positive population
S_6 = the healed population
S_7 = population that has died from tuberculosis
S = the total population

All T terms refer to the yearly transition probability of those in one group moving into another group. For example, when individuals of those in the tubercle bacillary positive group (S_5) move into the cured group (S_6) or individuals in the non-infected population (S_1) move to the infected population

(S_2). As is evident, terms in this equation are governed by the movement of one group of individuals to another group. Hence, for example, in the first equation, ΔS_1, the uninfected population increases with the growth of the crude birth rate B and decreases when individuals move into the BCG vaccinated population, the infected population, or the population of those who have died from causes other than tuberculosis. From this model, using 1980 data in Indonesia, Joesoef, Remington, and Jiptoherijanto calculated that S_1= 13.70% (20 282), S_2 = 33.20% (49 149), S_3= 44.50% (65 878), S_4 = 2.675% (3 960) S_5 = 0.255% (378), and S_6 = 5.669% (8 393), D = 1.19% and B= 3.37%. It is from these equations that the authors have estimated the influence of three approaches to drug treatments on the transition probabilities of this model. Using this, they projected each approach's influence on future costs and levels of tuberculosis as illustrated in Table 6-18.

Table 6-18: Projected Prevalence Rates, Costs and Prevented Cases Under Three Treatment Strategies

Treatment Strategy (1)	Projected Prevalence in the year 2000 (2)	Cumulative Costs, 1980-2000 (in thousands of $US) (3)	Cumulative Prevented Cases, 1980-2000 (4)	Cost/Prevented Case (in $US) (3)/(4)
Existing	0.123%	188 355	2 784 387	67.7
Standard	0.139%	215 540	1 816 756	118.6
Short	0.090%	127 413	4 635 932	27.5

Source: Joesoef, Remington, and Jiptoherijanto, 1989

Table 6-19: Compliance, Success, Relapse and Coverage Rates in 1980 Under Three Different Programme Strategies in Indonesia

Rates	Existing Regimen	Standard	Short-course
Active Radiological Lesion Group (S_4)			
Compliance	60.0%	50.0%	80.0%
Success	70.0%	60.0%	80.0%
Relapse	3.6%	4.8%	2.4%
Coverage	5.0%	5.0%	5.0%
Smear-positive (S_5)			
Compliance	60.0%	50.0%	80.0%
Success	60.0%	50.0%	70.0%
Relapse	3.5%	4.5%	1.8%
Coverage	10.0%	10.0%	10.0%

Source: Joesoef, Remington, and Jiptoherijanto, 1989

The associated costs of each treatment were calculated from drug costs alone which equalled US $24.26 for the standard regimen and $35.93 for the short-course regimen, discounted at a rate of 10%. The corresponding effectiveness of these regimens can be observed in Table 6-19. From this

projection, the authors concluded that short-course chemotherapy is the most cost-effective in preventing cases of tuberculosis in the future in Indonesia. The authors estimated that the rate of TB will be reduced by only 52% and 45% with the existing and the standard regimen respectively, but will decrease by 65% with the short-course regimen. Such cost-effectiveness estimates were based on the fact that the short-course regimen had fewer retreatment cases, and therefore, had a higher level of initial effectiveness.

There are fundamental methodological problems with this study. The study was from the point of view of the Indonesian government whose policy was only to treat smear-positive cases of tuberculosis. Hence, the authors only took into consideration smear-positive cases ignoring smear-negative and extra-pulmonary cases in their calculation of the number of cases of tuberculosis prevented. In addition, this study used a 10% discount rate per year instead of a 3% or 5% discount rate per year, which suggests that costs in the future will be calculated so that they will be deceptively low. This study also did not define what drugs were used in each treatment, which is significant since there are so many variations of short and standard regimens. In addition, the authors gave little detail on how cost-effectiveness projections were derived. Finally, this study was only based on drug costs, whereas other costs, such as labour inputs, were not included. The authors defended their omission of these costs because they felt they were not necessary since the perspective was from the Indonesian government. Nevertheless, it is grossly inaccurate to assume that the only costs that the government will occur are drug costs when other inputs for treatment must also be calculated.

6-2:5c Murray , DeJonghe, Chum, Nyangulu, Salamao and Styblo

One of the finest works performed in the cost-effectiveness of tuberculosis treatment in developing countries was performed by Murray, DeJonghe, Chum, Nyangulu, Salamao and Styblo (herein referred to as Murray *et al.*) (1991). In this study, data from the Mutual Assisted Programme of the International Union Against Tuberculosis and Lung Disease in Malawi, Mozambique and Tanzania were collected in order to calculate the cost-effectiveness of short-course chemotherapy and the standard regimen. It calculated the cost of each programme from the perspective of those funding tuberculosis treatment. Costs for the tuberculosis treatments were broken into three components: fixed costs not associated with the TB programme, fixed costs associated with the TB programme and variable costs. From these costs, other variables were calculated. Average unit costs were calculated by diving the total fixed and variable costs by the amount of patients treated. The average incremental unit was calculated by dividing the sum of variable costs and fixed costs attributed to the TB programme by the number of patients. Lastly, marginal cost per patient was calculated from dividing variable costs by the total number of TB patients in the programmes. This is fundamentally flawed to

call these the marginal costs when they are in fact the average variable costs (VC/Q). The costs of various treatments in the three countries are illustrated in Table 6-20. Variations in costs were primarily due to differences in civil service salaries and the cost per day of inpatient feeding.

Table 6-20: Costs per Case Treated in Malawi, Mozambique and Tanzania ($US)

	Malawi	Mozambique	Tanzania
Short-course chemotherapy with hospital admission			
Average	160	217	174
Average Incremental	99	155	127
Marginal	69	140	101
Standard chemotherapy with hospital admission			
Average	91	73	72
Average Incremental	71	54	63
Marginal	42	40	37
Ambulatory short-course chemotherapy			
Average	139	196	152
Average Incremental	75	132	103
Marginal	46	117	77
Ambulatory standard chemotherapy			
Average	66	55	50
Average Incremental	45	36	41
Marginal	19	18	15
Retreatment chemotherapy with hospital admission			
Average	209	323	252
Average Incremental	141	232	182
Marginal	97	206	146

Source: Murray *et al.*, 1991: p. 1306; Murray, Styblo and Rouillon, 1993, p. 251

The effectiveness of each treatment was measured in two ways: through direct benefits and indirect benefits. Direct benefits represented those positive effects of treatment that were directly experienced by the patients treated, for instance, cures and deaths averted. In contrast, indirect benefits were calculated as those positive effects of treatment that did not directly affect the patient treated, but in fact affected the population around the patient. Indirect benefits are essentially the positive externality of treatment which others experience after a patient is successfully treated, such as less transmission of TB, more productivity or a greater social contribution by the cured patient. Murray *et al.* primarily measured these indirect benefits through less TB transmission, and referred to these as transmission benefits. These indirect benefits were calculated on the basis that a case of tuberculosis would have four cycles of transmission taking 18.5 years. During these 18.5 years, each untreated smear-positive case of tuberculosis would cause 5.2 deaths and 3.8 deaths when discounted

at 3% per year. From this measure of those deaths attributed to smear-positive tuberculosis, the authors calculated that direct mortality would account for 18% and indirect mortality, due to subsequent transmission, would account for 82%.

In order to calculate the benefits in terms of the differences between cure rates, transmission rates and death rates of the treatments and compare them to those that remain untreated, an expected spontaneous cure rate of 20-35% of all smear-positive cases was not included as a benefit.

Table 6-21: Results of Chemotherapy Programmes in Malawi, Mozambique and Tanzania (Given as a Percentage of Patients)

	Malawi		Mozambique		Tanzania
Treatment Results	**Short-Course 1984-1988**	**Standard 1985-1988**	**Short-course 1984-1988**	**Standard 1980-1982**	**Short-Course 1982-1988**
Cured	87.2	43.7	70.8	38.3	76.9
Treatment complete	0.0	10.4	7.3	15.0	0.0
Failed	1.3	4.3	1.5	11.0	2.4
Died	6.5	4.7	1.5	6.7	6.5
Absconded	2.2	24.2	11.3	15.7	9.9
Transferred out	2.7	12.5	7.8	13.3	4.2
Excreting (still infectious)	3.1	29.2	8.3	33.2	7.4
Effective cure rate	90.4	66.2	90.3	60.2	86.1

Source: Murray *et al.*, 1991: p. 1306

Therefore, the effective cure rate was calculated from the sum of those cured, plus 35% of those who defaulted and transferred out for standard chemotherapy and 65% of those who defaulted and transferred out for short-course chemotherapy. Effective cure rates are shown in Table 6-21. This difference was assumed to be due to the stronger bactericidal and bacteriostatic action of short-course chemotherapy. In addition, results were recalculated to account for a 5% false positive diagnosis. This figure was derived from Tanzania where false positives were shown to range from 2.6-5.3%. Overall cure rates for the standard regimen averaged at 60-65% whereas for short-course chemotherapy, they averaged at 85-90%.

Murray *et al.* calculated the cost-effectiveness of these treatments in terms of cost per cure, cost per direct death averted, cost of total death averted and cost per year of life saved, as shown in Table 6-22. Total death averted referred to the amount of lives saved over a 18.5 year period due to the decreased transmission of TB. The authors concluded that short-course chemotherapy was the least expensive drug treatment for smear-positive patients. SCC was found to be more cost-effective compared to the standard regimen because it had a higher cure rate, a lower selection of resistant mutants, lower failure rates and lower associated retreatment costs. The authors pointed out how cost-

effective this is compared to other interventions. They estimated that the cost per year of life saved in ambulatory short-course chemotherapy for smear-positive patients is US $1-4.

Table 6-22: Average Incremental Unit Costs ($US)

	Malawi	Mozambique	Tanzania
Short-course chemotherapy with hospital admission			
Per cure	165	232	202
Per direct death averted	200	267	236
Per total death averted	38	57	47
Per year of life saved	1.7	2.6	2.1
Standard chemotherapy with hospital admission			
Per cure	215	301	270
Per direct death averted	187	272	227
Per total death averted	54	76	68
Per year of life saved	2.4	3.4	3.1
Ambulatory short-course chemotherapy			
Per cure	107	81	101
Per direct death averted	130	94	117
Per total death averted	25	20	23
Per year of life saved	1.1	0.9	1.1
Ambulatory standard chemotherapy			
Per cure	111	82	107
Per direct death averted	96	74	90
Per total death averted	28	21	27
Per year of life saved	1.3	0.9	1.2

Source: Murray *et al.*, 1991: p. 1307

In contrast, other cost-effective interventions, such as measles and neonatal tetanus immunisation, O.R.S. and blood-bank screening for HIV, cost US $5-10 per year of life saved. Murray *et al.* also concluded that short-course chemotherapy is more cost-effective than the standard regimen in both ambulatory and hospital environments except when considering the marginal cost of ambulatory care.

This study gives a very accurate and interesting description the optimisation of TB treatment in Africa, nevertheless, some elements must be critically considered. Data for this comparison spanned over different time periods and were based on three countries, excluding data on the standard regimen in Malawi. Also, in relation to the data, there was no sensitivity analysis performed to test the strength of the authors' conclusions. This study also does not perform an incremental analysis. Lastly, the results of this study were heavily dependent on transmission benefits in calculating cost per total death averted. These transmission benefits were based on many assumptions and estimations. Following this, such benefits could not be used for smear-negative tuberculosis.

Indeed, this analysis highlighted smear-positive tuberculosis as the most cost-effective form of tuberculosis to treat, however, it also considered the far less cost-effective treatment of smear-negative patients. The authors suggested that 15% of smear-negative cases would convert to smear-positive.

They considered this and the large amount of averted transmission from these 15%, concluding that the cost per death averted of treating smear-negative tuberculosis is US $185. This is 3.5-8 times the cost of treating smear-positive patients (although it is not stated, it is assumed that this cost is with short-course chemotherapy). The authors also approached the problem of cost-effectiveness in treatment for TB/HIV co-infected patients. They concluded that treating TB/HIV co-infected patients is ten times more expensive because these patients have such a poor survival rate during and after treatment. However, these authors highlighted the fact that when indirect benefits are considered, such as decreased transmission, the treatment of smear-positive HIV-seropositive patients falls to only 25% more than the TB treatment of smear-positive HIV-seronegative patients. Murray *et al.* also found that screening for HIV in those with TB would be expensive and would cause a TB programme to lose much of its credibility if it excluded some individuals from treatment on this basis.

6-2:5d Kamolratanakul, Chunhaswasdikul, Jittinandana, Tancharoensathien, Udomrati, Akksilp

Kamolratanakul, Chunhaswasdikul, Jittinandana, Tancharoensathien, Udomrati, Akksilp (1993) (herein referred to as Kamolratanakul *et al.*) performed a cost-effectiveness analysis between SDR and three SCC regimens in Thailand of 1642 smear-positive patients in five zonal TB centres between 1987-1989. The study shows the cost-effectiveness of treatment with SDR to be much lower than for those using SCC. The SDR regimen was lower in effectiveness, mainly because of a higher number of drug reactions and patient default. The SDR regimen also had slightly more patients whose sputum did not convert (probably because of acquired resistance from previous treatment). Hence, the SDR regimen had an effectiveness of 47.7% whereas the SCC regimens had effectiveness ranging from 83.7% to 93.7%, as depicted in Table 6-23.

Table 6-23: Cure Rates of Three SCC and an SDR Treatment in Thailand

Results of Treatment	2SHT/16TH (N=153)	2HRZ/4HR (N=142)	2SHRZ/6TH (N=576)	2HRZ/4H_2R_2* (N=771)
Drug Side Effects	44 (28.8%)	9 (6.3%)	147 (25.5%)	45 (5.8%)
No. Drop Outs	68 (44.4%)	8 (5.6%)	60 (10.4%)	114 (14.8%)
No. Complete Treatment	83 (54.2%)	132 (93.0%)	506 (87.8%)	653 (84.7%)
No. Sputum conversion	82 (53.6%)	130 (91.5%)	525 (91.1%)	645 (83.7%)
No. Sputum Non-conversion	12 (7.8%)	1 (0.7%)	9 (1.6%)	8 (1.0%)
No. Sputum Relapse	0	0	12 (2.1%)	4 (0.5%)
Efficacy**	85.5%	99.2%	95.8%	98.2%
Effectiveness	47.7%	93.7%	85.9%	83.7%

Source: Kamolratanakul et al., 1993: p. 634
*Subscript 2's refer to 600mg. isoniazid and rifampicin taken *twice* weekly
**Efficacy refers to the treatment's performance in an ideal setting (i.e. the action of only the drugs)

Table 6-24: Provider and Patient Costs for TB treatment in Thailand

Regimens	Provider Costs			Consumer Costs		
	Routine Service Costs	Medical Care Costs	Total Costs	Direct Costs	Indirect Costs	Total Costs
2SHT/16TH (18 visits)	81.04	18.63	99.67	123.07	60.95	184.02
2HRZ/4HR (6 visits)	27.01	43.29	70.30	81.60	36.22	117.82
2SHRZ/6HT (8 visits)	36.02	37.14	73.16	60.96	49.38	110.34
$2HRZ/4H_2R_2$ (6 visits)	27.01	31.78	58.79	62.31	24.16	86.47

Source: Kamolratanakul *et al.*, 1993: p. 635
Routine Service Costs refer to overhead costs of running TB centres.
Medical Care Costs refer to material costs of radiology, laboratory and pharmacy departments.

Table 6-25: The Cost Effectiveness of SDR and Three Forms of SCC in Thailand

Drug Regimen	Cost-Effectiveness Ratio ($US)	
	Provider Perspective	Patient Perspective
2SHT/16HT	208.96	385.78
2HRZ/4HR	75.03	125.74
2SHRZ/6HT	85.16	128.46
$2HRZ/4H_2R_2$	70.24	103.31

Source: Kamolratanakul *et al.*, 1993: p. 635

The authors of this study calculated cost-effectiveness from two perspectives, the provider and the patient. Provider costs and cost-effectiveness were much lower than patient costs, as shown in Table 6-24. From these costs, the cost-effectiveness ratio per patient cured was calculated so that $2HRZ/4H_2R_2$ was the most cost-effective regimen followed by 2HRZ/4HR and 2SHRZ/6HT. The SDR regimen of 2SHT/16TH proved to be the least cost-effective regimen according to this study, as observed in Table 6-25.

This a well performed study with a large sample group and a large selection of drugs. It included the impact of adverse drug reactions on cure rates, which few studies have considered. It also used a wide selection of SCC treatments to explore the cost-effectiveness of each. Nevertheless, it is difficult to ascertain the driving forces behind the costs. Costs for the standard regimen were estimated to be higher because they required a chest x-ray and more service costs. The question as to why chest x-rays were more expensive for the standard regimen was not addressed. Service costs were defined as overhead costs in all sections of the TB centres during the 21 months of this study. When calculating

this, each visit is an estimated US $4.50. This is interesting because the cost of patient visits during the initial phase and follow-up during the continuation phase were not separated. This is important because patient visits during the initial phase involve a more intense level of activity than those visits during the continuation phase.

Kamolratanakul *et al.* did perform a kind of sensitivity analysis, but only chose to test the impact of the substitution of the median for the mean in calculating the treatment results. Relevant factors such as the default rate and elements of the cost were not explored in the sensitivity analysis. Another criticism of this study is that Kamolratanakul *et al.* did not consider death rates in calculating cure rates for their samples, as shown in Figure 6-22. Obviously, death can signify a failure on the part of a treatment in curing a patient.

In addition, this study used a standard regimen that lasts for 18 months, which is no longer relevant (IUATLD, 1994) because 12 month regimens are now used. If the provider costs are limited to only 12 months, then the routine service cost will equal US $54.00 and medical care costs will equal US $12.42, making total provider costs US $66.42. This adjustment lowers the total provider costs below all but one SCC drug treatment and subsequently, lowers the cost-effectiveness of SDR to US $139.24 instead of US $208.96 (from the provider's perspective). This, in conjunction with the potential ensuing lower default rate of only twelve months of treatment, might have a significant impact on the results of this study.

6-2:5e Saunderson

Another cost-effectiveness study on tuberculosis treatments was performed by Saunderson (1995) in 1992 in Uganda. This study compared a currently operating regimen that used hospital care with a hypothetical alternative regimen that was completely ambulatory. The 'current regimen' was a treatment with hospitalisation during the intensive phase followed by an ambulatory continuation phase for 4-10 months (depending on the drug regimen). In the 'alternate design' that Saunderson suggested, ambulatory treatment was to be used for the entire course of treatment, and the costs of this were extrapolated from the current programme's costs. These costs had to be estimated because the alternative design was not in use, and therefore, there were no existing costs to obtain total costs from. Also, since there were no existing patients to obtain cure rates from, cure rates had to be estimated. The most interesting characteristic of this study is that it addresses the costs to the patient for TB treatment, which has been done in few other studies. Nevertheless, Saunderson's sample size was very small, equalling 34 patients, with 32 recordable replies. Patients were randomly selected smear-positive cases approaching the end of their stay in hospital. Monetary costs that patients experienced

included transportation, hotel costs, private and traditional medical care costs before TB diagnosis, food (both in and out of the hospital) and the costs incurred by relatives caring for the patient.

Table 6-26: Total Costs of TB Treatment Between the Current Practise and Alternate Design

Cost	Current Practise	Alternative Design
Sputum Examination	5.60	8.32
Drugs	20.40	26.33
Stationary	0.20	0.20
Health Education	1.55	4.19
Supervision	3.79	7.58
In-patient Care	12.85	-
Out-patients-initial	3.04	3.04
Out-patients-follow-up	8.16	16.32
Total cost to health service	55.59	65.98
Costs to Patient		
Before diagnosis	18.50	9.25
During hospital Stay	21.00	-
Due to loss of Work	95.00	40.00
Social Cost	?	?
Total Costs to the Patient	134.50	49.25
Summary		
Total Cost	190.09	115.23
Cost to Health Services	55.59	65.98
Cost to Patient	134.50	49.25

Source: Saunderson, 1995: p. 1209

Saunderson also measured the cost of time away from normal activities. The average time away from work was calculated from the average salary of a nursing aid, making the average loss for each patient equal to £95.00. This cost had no bearing on the sex of the patient. 24 of the patients were subsistence farmers and 8 were in paid employment. All patients interviewed, except one, said that they experienced lost productivity and had either produced less, as in the case of subsistence farmers, or stopped working, as in the case of those in paid employment. The total cost, estimated from costs before diagnosis, during hospital stay and due to lost work time, is shown in Table 6-26.

The cure rates for this study were estimated from various districts, but variations were commonly observed. Saunderson shows the cure rate for a south-west zone in Uganda to be approximately 51.2%. This is only estimated from those who died and defaulted and transferred (1/3 of those who transferred were assumed to have completed treatment), as shown in Table 6-26. Failures and drug reactions were not considered in the cure rates. Cure rates were finally arbitrarily estimated at 50-60%, and this was used along with a cure rate of 70%, for calculating the cost-effectiveness of each treatment. As observed in Table 6-28, Saunderson calculated the total cost per cure, the health service cost per cure and the patient cost per cure.

Table 6-27: The Estimated Cure Rates for Treatment in Uganda used by Saunderson (1995)

Result	Percent in South-west Zone
Completed Treatment	51.2%
Died	11.4%
Defaulted	37.4%

Source: Saunderson, 1995: p. 1209

Table 6-28: The Cost-Effectiveness Between the Current Practice and the Alternative Design for TB Treatment in Uganda

	Current Practice		Alternative Design		
Cure Rate	**50%**	**60%**	**50%**	**60%**	**70%**
Total Costs	190.09	190.09	115.23	115.23	115.23
Cost per Cure	380.18	316.82	230.46	192.05	164.61
Health Service	55.59	55.59	65.98	65.98	65.98
Cost per Cure	111.18	92.65	131.96	109.97	94.26
Patient Costs	134.50	134.50	49.25	49.25	49.25
Cost per Cure	269.00	224.17	98.50	82.08	70.36

Source: Saunderson, 1995: p. 1209

The weaknesses in this study is that it uses cure rates that have been estimated and compares them to a hypothetical treatment that has not been implemented. It is a reflection on the data rather than the study itself. Both the cure rate estimation and the cost estimation are weak: the results are hypothetical and it is not until the programme is implemented that true cost-effectiveness ratios can be compared. Caution should be taken when making decisions based on this study. However, it should be noted that Saunderson, constrained by poor available data, was forced to perform this study with hypothetical data.

The cost-effectiveness results are primarily dependent on patient costs, and especially patient costs due to lost work. When only considering the health service cost per cure, the current practice still proves to be more cost-effective by a small margin. Looking at costs for the alternative design, the drug costs, sputum examination costs health education costs, supervision costs and follow-up costs all prove to be higher than those in the current practise. The drug costs are different because the drug regimens compared are not the same. Those used for the current practice are 2SHRZ/6TH, which is the commonly used SCC regimen in developing countries. The regimen for the alternative design is 2EHRZ/4RH, which, although the commonly used SCC regimen in industrialised countries, is a virtually unheard of regimen in developing countries. Saunderson does not justify this inconsistency and the choice of drug regimens for each treatment design appears arbitrary. It is possible that the drug regimen for the alternative design was chosen because it has a shorter treatment period and would

therefore have lower time-dependent patient costs. In order to have made the results of this study more consistent, the drug regimens should have been the same, because indeed, the design of this study does not appear to compare these.

Although it is not stated, the perspective of this study is estimated to be from society because of the inclusion of indirect costs. From an economic perspective, one motivation for a study that measured costs in lost days of work, would be to discover what effect particular treatments have on productivity. Unfortunately, only 25% of the sample interviewed were actually wage earners. The other 75% were subsistence farmers whose work could be argued to have had an insignificant impact on productivity. Nevertheless, Saunderson calculates a productivity loss in wages of £95.00 for each patient. Certainly, those studies that measure patient costs are far better suited to a health care system where the patient has some role in decision making in the treatment that he or she receives. In many developing countries, TB is perceived as such a strong health threat, that treatment is provided by public health facilities, often free of charge. If the decision maker is far more likely to be the body funding the TB treatment, and not the patient, only the direct costs per cure of the TB intervention are relevant to this perspective. In the case of Saunderson's study, even in the absence of a two month hospital care period, his alternative design is still less cost-effective.

Much to Saunderson's credit, he performed a sensitivity analysis on his hypothetical estimates of costs and cure rates. He did not, however, present an incremental analysis for this study. Essentially, Saunderson highlighted his study as an HIV-era study, a study that takes into account those costs of a running programme, and a study that considers the costs incurred by the patient. He compared his study to two SCC-SDR cost-effectiveness studies (Barnum (1986) and Murray *et al.* (1991)), when in fact his study by no means involved a comparison of SCC and SDR. In addition, although Barnum (1986) is a pre-HIV study, and although Saunderson discussed HIV and health counselling, he did not integrate or discuss the impact of HIV on the estimated cure rates over those cure rates in the past. In fact, it is difficult to explicitly observe the difference between his study and a pre-HIV study.

In summary, the results of this cost-effectiveness study are primarily dependent on the impact of a shorter treatment period and the elimination of time spent in hospital on a patient's earnings. Patient costs may have an indirect effect on the rate of default, but this effect is unknown as cure rates were not available for the alternative regimen. In addition, the regimen that Saunderson used in calculating drug costs for the alternative regimen is so very modern and expensive, that it is unlikely that it will be used in developing countries on a wide scale before the year 2020 (optimistically). If the perspective were changed to the funding body, cost per cure in terms of health care costs still finds the current practice more cost-effective. In addition, the validity of these results are threatened because they are based on hypothetical results. This study is nevertheless, interesting in its estimation of patient costs

which are seldom calculated, however, there is an implicit reason for this: it is determined by the decision maker.

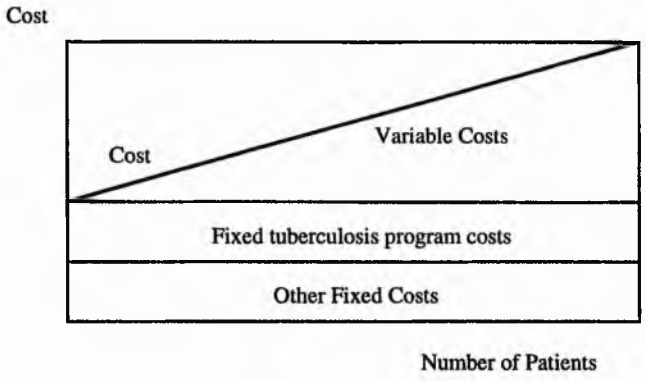
6-2:6 Murray, Styblo and Rouillon and World Bank Research on the Cost of Tuberculosis Treatment

Some results of this cost-effectiveness analysis between short-course chemotherapy and the standard regimen in Malawi, Tanzania and Mozambique by Murray *et al.* (1991) were shown in more detail in Murray, Styblo and Rouillon (1993). In addition, other cost considerations in SCC and SDR TB treatment are considered.

6-2:6a The Costs and Impact of SCC and SDR

In a way that is identical to Murray *et al.* (1991), Murray, Styblo and Rouillon (1993) separated a TB programme's costs according to variable costs, fixed costs associated with the TB program and fixed costs associated with the primary health care infrastructure. Variable costs included those costs which were associated with the amount of patients and the amount of drugs, food and reagents for diagnosis that each consumes. Fixed costs associated with the TB programme included administration costs and vehicles. In contrast, fixed costs outside of the programme were composed of those costs that primarily arose from utilisation of those structures and utilities shared with other health programmes. This is illustrated in Figure 6-10 which shows the costs in their TB measure as a function of the number of patients.

Figure 6-10: Tuberculosis Program Costs



Adapted From: Murray, Styblo and Rouillon, 1993: p. 250

From these cost measures, the authors also broke costs into three unit costs. These consisted of marginal costs, derived from the average variable costs per case; average incremental costs which were

derived from variable costs plus fixed tuberculosis program costs per case; and average costs which were equal to the total costs per case.

These costs did not include retreatment costs for failure. This seems inconsistent because the study went into such depth by including the indirect transmission benefits of the programme over 18.5 years. These incremental cost calculations and cure rates are illustrated in Table 6-29.

Table 6-29: Costs and Benefits of Short-Course Chemotherapy and the Standard Drug Regimen Based on National Tuberculosis Programs of Malawi, Mozambique and Tanzania According to Murray, Styblo and Rouillon (1993)

Parameter	Standard Drug Regimen	Short-course Chemotherapy
Average incremental cost per year of life saved with hospitalisation ($US)	3.00	2.00
Cure rate	60	85
Percent of cases requiring retreatment (percent)	30	10

Source: Murray, Styblo and Rouillon, 1993, p. 253

Cure rates for these different regimens were 60% for the standard regimen and 85% for short-course chemotherapy. Although the costs of retreatment were not considered, the authors still showed the percentage of cases that will require retreatment. 30% of those treated with standard chemotherapy would require retreatment, whereas this only amounted to 10% of those receiving short-course chemotherapy.

Murray, Styblo and Rouillon also discussed the cost-effectiveness in comparing treatments for smear-negative tuberculosis cases. They maintained that the cost-effectiveness of chemotherapy for smear-negative pulmonary tuberculosis was dependent on the predictive value of chest radiographs (estimated at 50%), case-fatality rates of untreated smear-negative cases (estimated at 40% from previous studies), the cure rate of the chemotherapy used (estimated at 50%), and the percentage of untreated cases that would progress into smear-positive cases. From the first three variables, the authors estimate a US $450 cost per death averted in treating smear-negative tuberculosis. This is ten times the cost per death averted for SCC in hospitalised smear-positive patients and twenty times the cost of that for SCC treatment of smear-positive ambulatory patients. The cost of this is mitigated when considering those smear-negative cases that become smear-positive, because such treatment stops pre-diagnosis transmission that would occur once a smear-negative case turned into a smear-positive case. This reduced cost per death averted to US $185 assuming 15% will become infectious. Nevertheless, this estimate is quite conservative. In some studies, progression to a smear-positive state

has been as much as 56% (Hong Kong Chest Service/Tuberculosis Research Centre, Madreas/British Medical Research Council, 1984).

Table 6-30: Estimated Average Incremental Costs in $US per Patient Treated in Low- and Middle-Income Countries

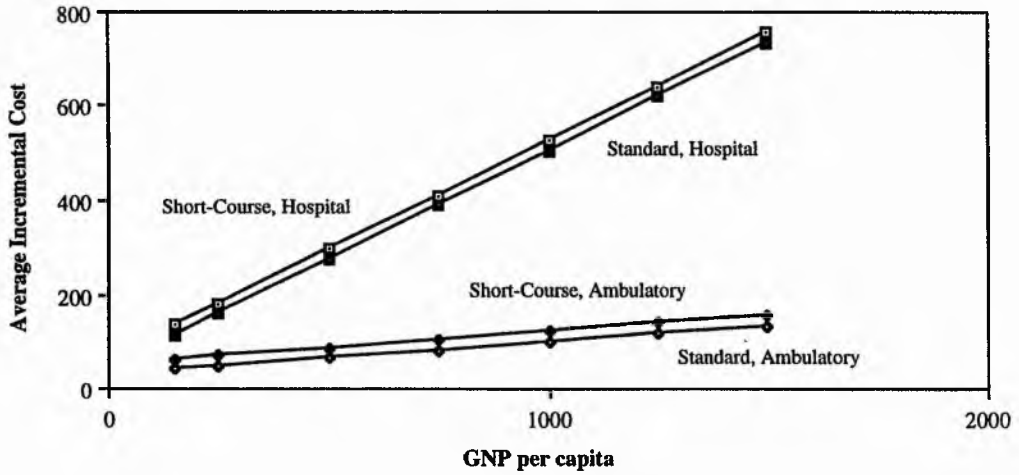
GDP per capita	Short-course hospitalisation	Short-course ambulatory	Standard hospitalisation	Standard ambulatory
150	136	63	113	41
250	181	70	159	48
500	296	87	274	64
750	411	104	389	82
1 000	526	122	504	100
1 250	641	139	619	117
1 500	756	156	734	134

Source: Murray, Styblo and Rouillon, 1993: p. 251

6-2:6b TB Treatment Costs in Countries with Varying GNPs

Murray, Styblo and Rouillon also observed that the cost of therapy varies with a country's GNP. In essence, as GNP rises the cost of inputs, such as labour, becomes more expensive, as shown in Table 6-30. Likewise, there is a greater expenditure on more expensive inputs, for instance, disposable syringes are used instead of reusable syringes. There is also an interesting trend between hospital care and ambulatory care costs as GNP changes. As can be seen from Figure 6-11, where GNP per capita rises, the cost difference between hospital and ambulatory care grows wider and wider, reflecting the much quicker increase of hospital care costs over ambulatory care costs.

Figure 6-11: Estimated Average Incremental Cost ($US) per Patient Treated in Low- and Middle-Income Countries



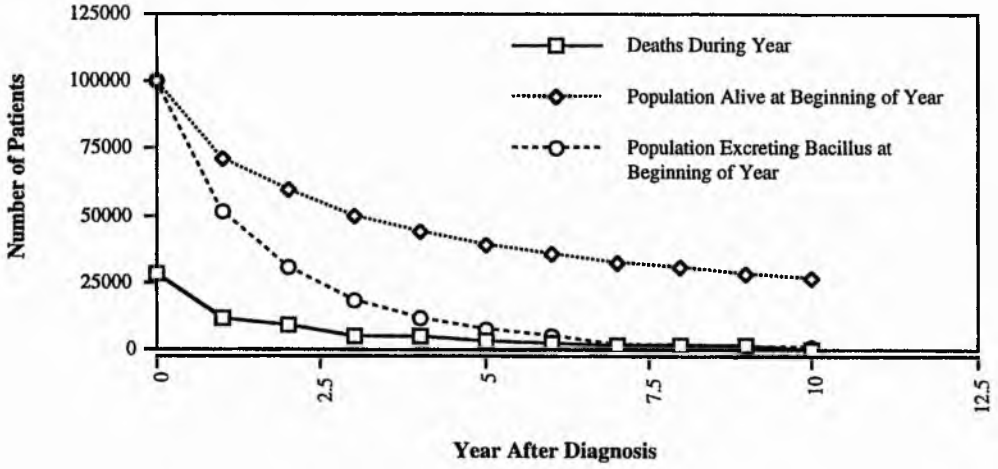
Adapted from: Murray, Styblo and Rouillon, 1993

This is possibly attributed to the cost of labour and expenditure on expensive supplies and overhead, which seem to rise with GNP. It should also be noted that hospital care in low income countries looks comparatively cheaper according to the authors, but this does not take into account the quality of treatment in these hospitals. A hospital in a lesser developing country often has a poor isolation system for patients and food for patients is often left up to the patient's family. Another interesting pattern that develops with rises in GNP points to the gap between standard and short-course ambulatory care costs and the gap between standard and short-course hospital care costs, which both remain relatively the same with rises in GNP. This is primarily because costs differentiating the two are based on drug costs with are unlikely to change with rises in a country's GNP. It must be noted that this relatively constant difference makes short-course chemotherapy more feasible with rises in GNP. To those countries with low GNPs per capita, the value of foreign currency needed for purchasing medical supplies proves to be much more than local currency. This makes short-course chemotherapy less obtainable. However, as GNP per capital rises, and the relative value of foreign currency to a country's local currency falls, there proves to be a smaller relative difference between the two treatments. This probably reflects why countries with higher GNPs per capita have adopted SCC because such differences in the cost between these two regimens are no longer so significant.

6-2:6c The Spread of Tuberculosis and Transmission Benefits from Treatment

Very little work has been performed concerning the average number of new cases of TB that is caused by each smear-positive TB case. In calculating indirect transmission benefits, Murray, Styblo and Rouillon (1993) have produced some interesting work in charting the process and impact of TB transmission. Benefits of treatment are derived from an extrapolation of Berg's (1939) study of 6 162 cases of tuberculosis. As can be seen in Figure 6-12, starting with a population of 100 000, death and survival from untreated TB are charted next to the number of patients still infectious at the beginning of each year over a period of ten years. One can observe a curvilinear trend whereby there is initially a sharp rise in deaths, a fall in total population and population excreting tubercle bacillus after which they start to become more constant. It is from these data that Murray, Styblo and Rouillon estimated that for every one smear-positive TB case, there will arise one more case in the future. This transmission cycle is estimated to be slightly over 4 years. According to these authors, transmission of tuberculosis of one smear-positive case of tuberculosis occurs at a rate of between ten and fourteen persons per year. Those who are smear positive will transmit tuberculosis for an average of two years which is why prevalence is calculated as twice the incidence (Styblo, 1984). This means that each smear-positive case is responsible for an average negative externality of twenty to twenty-eight new cases of tuberculosis.

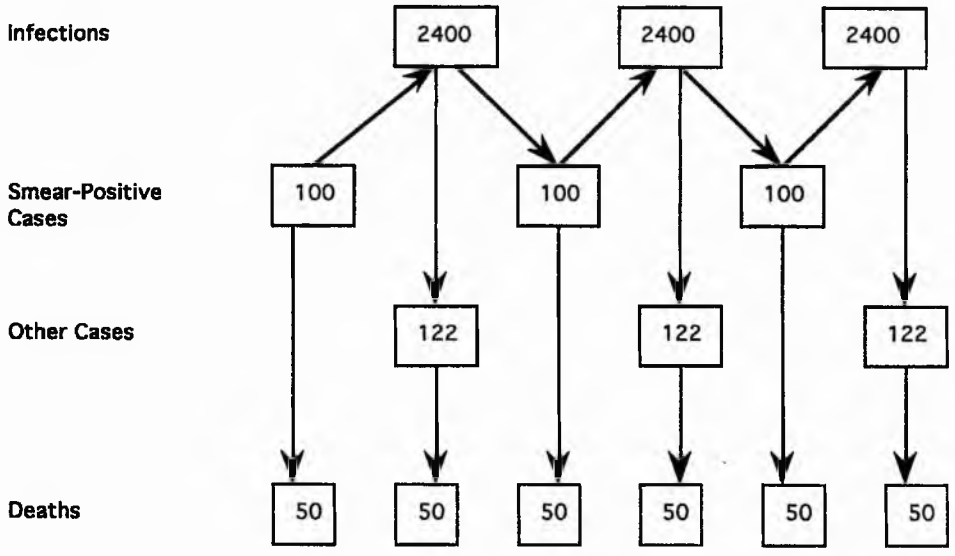
Figure 6-12: Life Table for Untreated, Smear-Positive Pulmonary Tuberculosis



Adapted from: Murray, Styblo and Rouillon, 1993

Such effects are illustrated in Figure 6-13. Given 100 smear-positive cases, they will in turn cause 2 400 more infections. From this amount, a proportion will become smear-positive (100) and a proportion will contract other types of tuberculosis (122). Without interference by treatment, this process will continue to repeat itself, and from each group of TB cases, there will result an average of 50 deaths.

Figure 6-13: The Pattern of Tuberculosis Transmission



Source: Murray, Styblo and Rouillon, 1993: p. 244

6-2:7 Drug Reactions and Complications to Drug Treatments

Another, less highlighted, problem in using the standard regimen instead of short-course chemotherapy, involves drug reactions and complications primarily from SDR's intensive use of thiacetazone and streptomycin. In developing countries, thiacetazone, whose use is banned in the US, is a common drug appearing in TB treatment regimens. This drug, often given in combination tablets with isoniazid, is a dangerous drug for those with HIV. In these co-infected patients, it is strongly correlated with the development of Stevens-Johnson syndrome, an adverse reaction characterised by haemorrhaging and a blue or purple cast to the skin. In France, Grosset (1992) found adverse reactions to thiacetazone in 18-20% of those HIV-seropositive cases treated with it. In Malawi where the incidence of HIV is high, rates of Stevens-Johnson syndrome associated with thiacetazone use rose to 1% in 1990. In Zimbabwe, the probability of adverse drug reactions to thiacetazone was estimated to be five times as likely (Houston, Pozniak, Ray, 1991). Subsequent substitution of this drug for ethambutol has lead to a drastic decrease in this adverse effects to less than 0.2% or 1 in 500 (Enarson, *et al.*, 1993). An additional problem with the use of thiacetazone is the fact that a strain of tuberculosis specific to West Africa, *Mycobacterium africanum*, has a high level of natural resistance to thiacetazone (Crofton, Horne & Miller, 1992). The high number of reactions and possible resistance to this drug make it far more costly than just the monetary value of obtaining it. However, this is one of the main drugs used in the standard regimen, because it is so much more inexpensive than other drugs.

Because as much as 33-50% of those seeking treatment for tuberculosis are HIV-positive, the standard regimen can prove deadly. Furthermore, HIV screening of all those seeking treatment in itself would prove more costly than short-course chemotherapy. With greater patient compliance and fewer side effects for AIDS patients, cure rates are likely to be higher and resistance lower for SCC.

Another complication of therapy is the use of streptomycin injections in HIV or potential HIV patients. Syringes for injections are often re-used so that there is the possibility of a transference of the virus on a needle that has not been adequately sterilised. Enarson *et al.* (1993) emphasise the potential for HIV transmission through streptomycin injections by suggesting that in a country with 15 000 cases of tuberculosis, 1 million injections will be given per year. If there is a 33% HIV incidence, with so many injections, the transmission risk is high, especially with an overloaded health staff. Nevertheless, the awareness in health personnel of the need to sterilise needles to prevent nosocomial HIV infection is high. Added to this, the virus is weak outside of the body and can survive on a needle for a maximum of only seven hours (*personal communication:* David Matthews, 1995). Hence, if needles are used only once a day, the likelihood of the survival of the virus on a needle the next day is minimal.

6-2:8 Summary of Section 6-2

The superiority of short-course chemotherapy in treating tuberculosis is undoubtedly established when compared to the standard regimen. Nevertheless, the problem arises in the fact that the cost of SCC is much higher in relative terms for a developing country. SCC remains higher because it contains those drugs such as rifampicin and pyrazinamide that are newer and have more expensive production processes. Although most of these drugs are no longer covered by a patent, they still remain comparatively expensive to produce.

Ascertaining the optimum choice of regimens for treatment is a difficult task and must rely on cost-effectiveness analyses, a form of applied economics. Attempts at this have been carried out by a small number of authors, but such studies have not irrefutably established the superiority or inferiority of SCC in cost-effectiveness terms. Although, due to it's higher effectiveness, SCC is the obvious choice for industrialised countries, more research is still needed to ascertain if this is the optimum choice for developing countries in their attempt to both contain tuberculosis while working within their financial limits. With greater research in this area, external aid agencies, funding bodies and the health ministries of developing countries can be better aided in making the best treatment choice for the management tuberculosis containment . When developing countries are more influenced by the initial price of interventions, this kind of operational research is a way to maintain the benefits of more expensive, but far more effective treatments.

Section 6-3

CONCLUSION TO CHAPTER SIX

In developing countries, tuberculosis remains as the number one cause of death in those aged between fifteen and fifty-nine. This disease has a devastating effect on the population, taking its individuals at the peak of their potential economic and social contribution to society. This is surprising considering that there is an effective cure for this disease. Tuberculosis could potentially be eradicated for several reasons: (1) the origin or the disease resides in individuals who can be identified; (2) the spread rate of the disease is reduced if those with the disease are treated; (3) the transmission of the disease is inefficient meaning that a small reduction in the incidence has a large impact in decreasing the overall spread; and (4) those materials needed to treat the disease such as drugs and laboratory equipment can be used even in low income areas. Even in the presence of the problem of HIV, TB could be greatly reduced. With TB/HIV co-infection, case identification remains unchanged if sputum smear microscopy is used, and it is still possible to cure TB/HIV co-infection.

The use of NTPs in standardising tuberculosis treatment on a national level in each country is a necessary element to managing tuberculosis. In addition, greater gain could be made by implementing more effective drug treatments where their costs prove to be justified. Indeed, the use of SCC is still uncommon in many areas of developing countries, who are more inclined to depend on the standard regimen. Nevertheless, although expenditure on SCC is greater than the standard regimen, it's associated costs are lower because it achieves greater cure rates through less acquired resistance, fewer drug reactions and shorter treatment times. This allows for greater compliance and higher cure rates In essence, although SCC is more expensive, its cost in terms of less transmission of the disease, greater productivity of cured workers, less relapse and greater patient utility from the treatment can prove to be far lower than the standard regimen's. It is possible that associated resistance will have some impact on the cost of TB treatments and therefore change this relationship between SCC and SDR. This relationshiop is also dependent on the area in which TB is treated. The organisation and management of drug supplies, influence of HIV and context of resistance of TB in Ethiopia is hence, presented in the next chapter.

CHAPTER SEVEN

TUBERCULOSIS CONTROL EFFORTS IN ETHIOPIA

PART ONE: HEALTH CARE DELIVERY AND DETERMINANTS OF HEALTH

This chapter, 'Part One of 'Tuberculosis Control Efforts in Ethiopia', presents the first part of the case studies presented in order to analyse the impact of TB drug resistance on the cost of TB treatment in Ethiopia. It illustrates the difficult challenge of a low income developing country in fighting infectious bacterial disease, and will especially focus on the containment of tuberculosis in Ethiopia. Before looking at the impact of TB resistance on the cost of TB treatment, it is important to look at other factors that also have an impact on TB, and therefore, the incidence of TB and the cost of TB treatment. This includes the general determinants of health status in Ethiopia, drug management, tuberculosis control efforts and HIV. Therefore, section 7-1 describes the country's demographics determining health and influencing tuberculosis. After the discussion in Chapter 3 of drug management and the discussion in Chapter 4 examining antibiotic utilisation, Section 7-2 of this chapter analyses the management of tuberculosis antibiotics in Ethiopia. The recommendations in Chapter 5 and Chapter 6, on the management of tuberculosis are further illustrated in Section 7-3, which will discuss the current state of tuberculosis control efforts in Ethiopia. Also, the analyses in Chapter 5 and Chapter 6 of the link between TB and AIDS are further expanded in Section 7-4 which explores the nature and victims of HIV in Ethiopia in preparation for a discussion of the interaction between the two diseases in Section 8-1 in Chapter 8.

Introduction

In 1984 Ethiopia shook the world because of a famine that thereafter made it synonymous with most modern literary references to intense starvation. It was not surprising that famine occurred on such a wide scale in this country where over 80% of its people still rely on agriculture for their livelihood and even in the best of times, its cultivable land consists of cracking clays, which prove

difficult to farm. Such fragile circumstances mean that crops are destroyed and families must sell what little they own in order to buy food when virtually any drought or flood occurs. This however, has not been enough in the past as proven during the drought of 1984, when over $2 billion dollars in emergency relief aid flowed into Ethiopia. This vast sum, if spent on long-term aid, could have potentially halted the high proportion of famine-caused morbidity and mortality (Cross, 1994).

Since 1984, much in Ethiopia has changed. In 1991 a revolution deposed the military dictator, Mengistu Haile Mariam, responsible for spending famine aid funds on military hardware. Two years later, the province of Eritrea separated from Ethiopia after 30 years of struggle. The result of this was a new democracy under Meles Zenawi with economic and political freedom which has instigated a transition to more intensive farming methods and industry. Nevertheless, a good wage for a day labourer is still only 3 birr (30 pence) and the average life expectancy is approximately 50 years for both men and women. Ethiopia is still ranked among the poorest countries with a per capita income of just $110 US dollars per year (Transitional Government of Ethiopia, Office of the Council of Ministers, 1993). In addition, levels of education are low. 74.4% of children are enrolled in primary education, 22.8% are enrolled in secondary education and 0.5% are enrolled in tertiary education. Although literacy rates are a high 76%, superstition and ignorance are still common. Further complicating this is the fact that 70 different languages and dialects are spoken, hindering communication.

Reasons for the low life expectancy in Ethiopia reflect large problems in nutrition, sanitation and housing, all having their relative impact on health. However, studying this impact is difficult for three distinct reasons. Dependable and complete data on rates of health are difficult to obtain if these exist at all, as is the case in many parts of Africa and least developed countries. In addition, Ethiopia is a deceivingly large country with several different altitudes over which disease patterns drastically differ, and therefore data generalisations cannot be readily made. Lastly, continuous environmental disasters, civil war in the north and political objectives incongruous with health needs, have all added unnatural disease etiologies whose understanding cannot be studied in a limited epidemiological context (Kloos and Zein, 1993).

Currently only 6% of the national budget from the Ethiopian Ministry of Finance goes to health, representing less than US $1 per capita per year. Of this, 35-40% is spent on hospital care (*Personal communication*: Dr. Barbiero, USAID). The WHO is currently pressuring the government to spend more on TB. In contrast, US AID is focusing on primary health care utilisation given the low rates of health service coverage. Unfortunately, TB is discounted as an AIDS-related disease and therefore there is a push to place funds in other areas, for instance, "well baby" and immunisation programmes.

One of the effects of such changing dynamics and low per capita expenditure on health has been the relatively constant morbidity and mortality from tuberculosis. The high existing incidence of TB paired with malnutrition and HIV have caused the disease to flourish. Subsequent efforts to reduce the incidence of the disease have been all but complete failures until recently when a national tuberculosisprogramme was initiated.

Section 7-1

DEMOGRAPHIC, SOCIO-ECONOMIC AND ORGANISATIONAL DETERMINANTS OF HEALTH

This section looks at the health service coverage in Ethiopia and the organisation of government health services. These are factors that influence the correct implementation of TB treatment and therefore, are influences on the development of drug resistance. This section also discusses the morbidity patterns of infectious diseases experienced in Ethiopia, and highlights tuberculosis as a significant health threat.

Ethiopia lies on the Eastern part of the African continent, an area also known as the "Horn of Africa". Its area encompasses 1.25 million square kilometres which are divided into three zones: the Dega (cold), defined as land that is at an altitude of 2 400 meters and above, the Weyna-dega (temperate) zone defined as land from 1 500-2 400 meters in altitude, and the Kolla (hot) zone defined as land 1 500 meters and below. The altitudes of these zones are significant because their environments predict the types of morbidity that affect their inhabitants. In the colder Dega and Weyna-dega zones, there is more tuberculosis, louse-borne typhus and relapsing fever, whereas those in areas below 1800 meters there is malaria, and below 2000 meters there is human and animal trypanosomiasis.

From the 1984 national census, the population in 1992 was estimated to be approximately 53 844 700 which gives an average population density of 44.1 people per square kilometre. (including Eritrea which has since separated). The population growth rate is 2.98% per year, and by this estimate, the population in 1993 was approximately 55 449 272, and by the end of 1995, it will be approximately 58 803 289 (including Eritrea as statistics on Eritrea's population are not yet available). The 1992 male to female ratio proved to be 49.9 to 50.1 with 11.3% of the population living in urban areas and 88.7% living in rural areas. During this year, the population age structure was 18.6% aged 0-4 years, 29.6% aged 5-14 years, 36.0% aged 15-44 years, 11.1% aged 45-64 years, and only 4.37% over 65 years. The average life expectancy at birth is estimated between 49 and 53.4 years. From these statistics, it can be seen that a large proportion of the population (48.2%) lies under the age of 15 and does not work but still needs clothing, shelter, food, education and health care. A further amount are over 65 (4.37%) such that, 47.1% must economically support 52.9% of the population. Corresponding to this, 80% of the population relies on subsistence farming and animal livestock and 90% must rely on agricultural production, leaving the remaining 10% to work in industry (Transitional Government of Ethiopia, Office of the Council of Ministers, 1993). The effect of this is such that the current economic growth rate is unable to support the population growth, and the majority of the population live below the United Nations defined absolute poverty level.

The young age and economic structure point to the strain of the society in maintaining acceptable levels of health. Only 18.5% of the population have access to clean drinking water. Malnutrition is rampant, proven by a 2-6% population incidence of wasting, 18-24% of population stunting and 30-40% of the population underweight. Infant mortality numbers 141 per 1000, and child mortality is 99 per 1000. Total fertility amounts to 7.5 children per woman and maternal mortality is 5.7 per 1000. With such a large proportion living under the absolute poverty level, malnutrition, poor sanitation and poor housing all contribute to the development of poor immune systems and widespread disease. The spread of HIV is a further contribution to poor immunity, and therefore, greater disease prevalence. Hence, diseases dependent on the severely immunocompromised state of the individual proliferate. The paradigm case is indeed, tuberculosis.

7-1:1 Health Service Coverage

Exacerbating the problem of a poor living environment and a fragile economy, health service coverage only amounts to 45-47% of the population. Antenatal coverage equals 16% and assisted baby deliveries equals 5%. Utilisation is affected by the distance that has to be travelled from a patient's home to a health facility. Kloos *et al.* (1987) observe that between 35-94% of all individuals who seek care from a health facility live within a 2 km radius of it. In Addis Ababa, 30-36% of those seeking care travelled by foot and the amount of those making journeys by foot seemed to increase the more rural the location.

Table 7-1: Distribution of Health Care Facilities According to Year of Establishment

Year	Hospitals	Health Centres	H. Stations
1891-1901	2	0	1
1902-1911	1	0	0
1912-1921	5	0	2
1922-1931	8	0	3
1932-1941	9	0	24
1942-1951	15	6	42
1952-1961	24	61	159
1962-1971	11	48	648
1972-1981	4	23	616
1981-1991	0	1	2
Other	7	18	628
Total	88	157	2125

Source: Transitional Government of Ethiopia, Office of the Council of Ministers, 1993: p. 31

Access to care is also influenced by the available facilities and the number of health care workers. From Table 7-1, there are 648 882 people for every hospital (defined as large buildings with several wards and over 150 beds), 363 704 people for each health centre (defined as meeting primarily outpatient care with 10-20 treatment rooms) and 26 871 people for each health station (1-4 roomed

facilities with limited and basic health care delivery services). For every hospital bed, there is an estimated 4200 people. It is no wonder that these health facilities are overwhelmed.

The majority health facilities were established before 1971 and considering the construction capabilities during this time, have proven to be quite outdated. Also, existing health facilities have become dilapidated. This is illustrated in Table 7-2 which shows that 42% of all hospitals, and close to 20% of health centres and health stations are in need of major repair. Similarly, approximately 10% of all health station buildings are in need of complete replacement.

Table 7-2: Health Institutions According to Building Condition

Health Institution	Good Condition	Building Seeking Minor Repair	Building Seeking Major Repair	Building Seeking Replacement	Unknown
Hospital	29.0%	19.3%	42.0%	6.8%	6.8%
Health Centre	28.7%	42.0%	19.7%	4.5%	5.1%
Health Station	36.0%	20.8%	18.5%	9.9%	14.7%

Source: Transitional Government of Ethiopia, Office of the Council of Ministers, 1993: p. 33

Table 7-3: Distribution and Population Ratio per Health Worker Between Addis Ababa and the Rest of the Country, 1990

Area	Medical Officer	Health Officer	Nurse	Health Assist.
Addis Ababa	1 020	79	1 646	3 460
Rest of the Country	638	15	1 929	6 585
Addis Ababa %	62	84	46	35
Population Ratio to Health Personnel	30 600:1	540200:1	14 200:1	5 100:1

Area	Pharmacist	Pharm. Tech.	Lab. Tech.	X-Ray Tech.	Sanitarian
Addis Ababa	276	152	323	127	196
Rest of the Country	101	131	270	111	193
Addis Ababa %	73	54	55	53	50
Population Ratio to Health Personnel	134 700:1	179 400:1	85 600:1	213 300:1	130 500:1

Source: Transitional Government of Ethiopia, Office of the Council of Ministers, 1993: p. 60

7-1:1a Urban Bias

Like many developing countries, Ethiopia suffers from an urban bias where a large proportion of health facilities and health personnel are located in heavily populated areas. As observed in Table 7-3, Addis Ababa, the capital of Ethiopia, has 42% of all health personnel in the country.

Table 7-3 also shows that the population per doctor ratio is extremely high at 30,600:1, the population per nurse is approximately half this at 14,200:1 and the population to pharmacist is even higher at 134,700:1. This high population to pharmacist ratio might reflect the strong dependence of individuals on the government to supply drugs because the low income of the country offers only a

small market for commercial pharmacies. (Such an effect is likely to decrease as a country becomes more affluent allowing for a more effective demand for drugs)

7-1:2 Morbidity Patterns and Infectious Disease

Morbidity patterns in Ethiopia are dominated by infectious diseases. Of the top twelve diseases observed in hospitals, all but gastritis were infectious (although there is some connection to this in industrialised countries to *H. Pylori*). The ranks of these diseases has not changed significantly over ten years, as shown in Table 7-4. The rank of 12 for tuberculosis in both 1981 and 1991 suggests that efforts to decrease its incidence have been relatively impotent and evidence from health centres and hospitals suggest that the incidence of this disease is, in fact, rising.

Table 7-4: Rank of the Top Twelve Diseases in Hospitals and Health Centres in 1981 and 1991*

Rank	Disease	Rank in 1981	Rank in 1991
1	Helminthiasis	1	1
2	Dysentery and Gastro-enteritis	2	2
3	Eye disease including trachoma	3	3
4	Pneumonia	4	4
5	Infection of skin and subcutaneous tissue	5	5
6	Acute upper respiratory infections	6	6
7	Gastritis and duodenitis	7	9
8	Malaria	8	7
9	Sexually transmitted diseases	9	8
10	Otitis media and other conditions of the ear	10	11
11	Bronchitis (all forms)	11	10
12	Tuberculosis (all types)	12	12

Source: Transitional Government of Ethiopia, Office of the Council of Ministers, 1993: p. 63

* Data is limited to only those cases that received care in health care facilities. However, central statistical authorities conclude through a "Rural Household Sample" that there is no significant difference between these statistics and the morbidity experienced by those that do not seek care in health facilities.

To obtain a more extensive view of morbidity patterns, one can look at the estimates of the number of patients in each morbidity category per health station, per year by the Emergency Recovery and Reconstruction Project of 1991 (ERRP). As can be seen from Table 7-5, each health station should be equipped to treat almost 10 000 patients per year. From past morbidity data, it is estimated that malaria, tuberculosis, gonorrhoea, ear infections, rheumatic pain and accidents represent the highest proportions of patients seeking health care at health stations.

Table 7-5: Estimated Number of Patients Treated According to Morbidity Category per Year per Health Station

Disease	Estimate of those treated per health station per year
Malaria	815.50
Unknown Fever	340.70
Skin Infection	574.70
Diarrhoea	567.66
Gastritis	567.66
Other Gastrointestinal Disease	333.42
Common cold	540.43
Tonsilitis	514.65
All TB	1033.26
Gonorrhoea	708.11
Other Sexually Transmitted Diseases	268.04
Eye Infection	157.58
Ear Infection	673.52
Tooth Diseases	247.80
Malnutrition	213.26
Intestinal Parasite	379.72
Rheumatic Pain	1003.65
Other Accidents	763.73
Anaemia	226.52

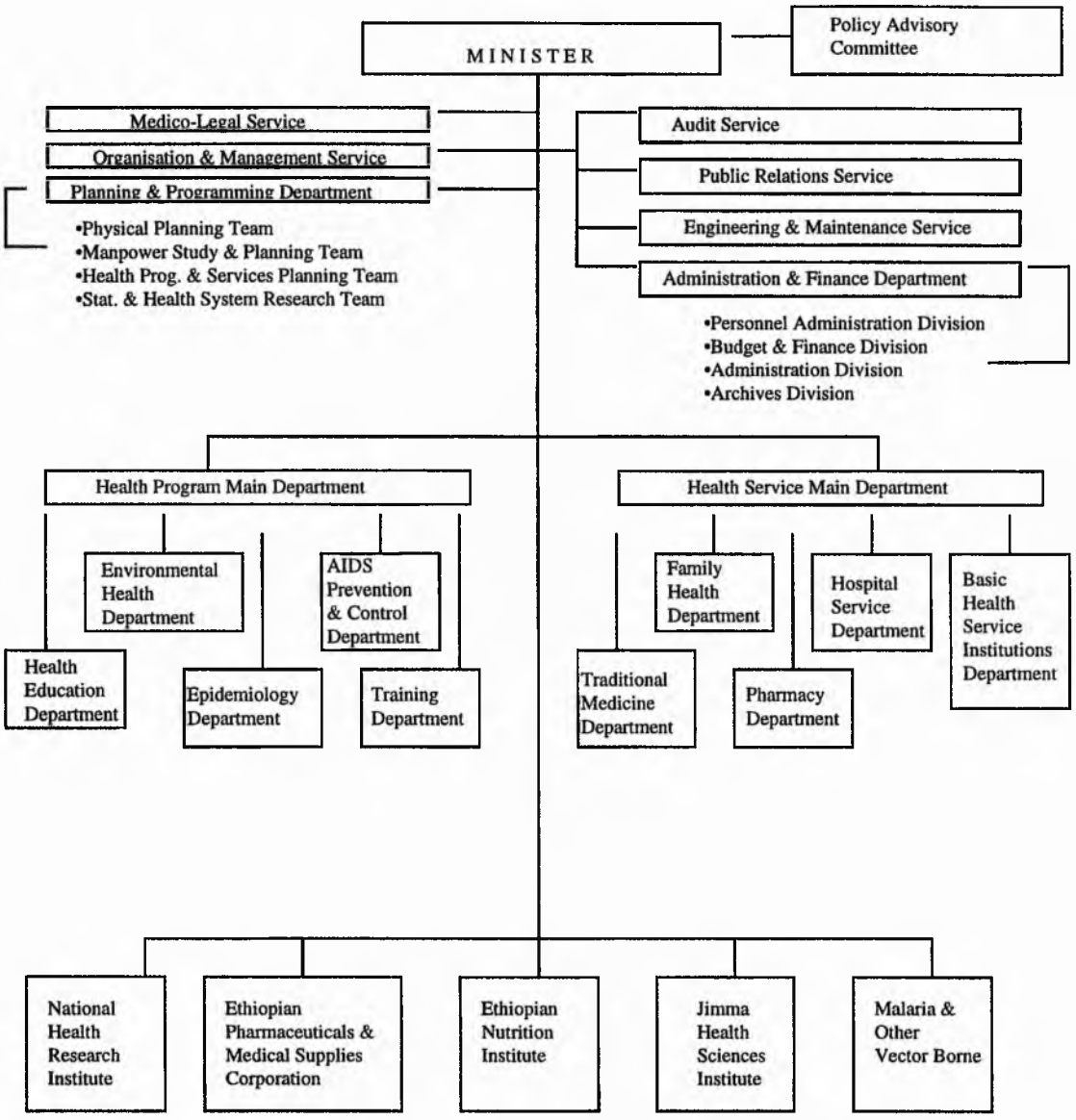
Courtesy of: Transitional Government of Ethiopia, Department of Pharmacy (unpublished)

7-1:3 Organisation of Government Health Services

Health expenditure funded by the Ministry of Health (MOH) accounted for 3.1% of the national budget in 1990 and 2.67 (US $0.44 in 1994) birr per capita (6 birr ≈ US $1 in 1994). 89.9% of all hospitals, all health centres and 94% of health stations are owned by the Ministry of Health and other government agencies. Health services are primarily the responsibility of the Ministry of Health which is supervised by the Minister of health and two vice ministers. Each vice minister heads 5 departments and other institutions. These include the Ethiopian Pharmaceutical and Medical Supplies Corporation (EPHARMECOR), Ethiopian Nutrition Institute (ENI), the Jimma Health Science Institute (JHSI), Control of Malaria and Other Vector Disease division, and the National Research Institute of Health (NRIH). The organisational hierarchy of the Ministry of Health is depicted in Figure 7-1.

The health services within various districts are supervised by the regional and district health departments which supervise an infrastructure of hospitals, health centres, health stations, central referral and specialised hospitals. Health centres give preventive and curative ambulatory care to both referral patients and non-referral patients. These usually have 10-15 rooms, a rudimentary clinical laboratory, a small number of beds for mothers in labour and critical patients. Health stations are the most basic manifestation of health care facilities, mainly functioning in rural conditions to increase health service access. These contain 1-3 health care workers, have 2-3 rooms and use simple diagnostic tools and function for essential curative services.

Figure 7-1: Hierarchy of the Ministry of Health in Ethiopia



Source: Transitional Government of Ethiopia, Office of the Council of Ministers, 1993: p. 90

Rural hospitals give 24 hour curative care and also give preventive care to inpatients. These facilities contain most types of health care personnel except for specialist doctors. They also have some simple operating theatres for less serious and emergency procedures. Regional hospitals are located in large towns with regional administrative bodies and these hospitals employ specialist doctors along with all the services offered by rural hospitals. These hospitals usually specialise in at least four areas, commonly surgical procedure, paediatric, obstetrics and gynaecology. Lastly, central referral and specialised hospitals, primarily centred in Addis Ababa, function to train health care workers and offer all types of specialised care and additionally act as referral centres for regional and rural hospitals.

7-1:4 Summary of Section 7-1

In Ethiopia, a poor economic structure, poor living conditions and a poor environment has challenged the health care delivery system. Morbidity is driven by infectious diseases, many of which can be cured by antibiotics. Existing health care delivery has been pathetic in the past with poor health service coverage where in many rural areas it highly inaccessible. In an effort to improve the management of health care, the Ministry of Health has developed several specialised bodies to concentrate on areas where health care delivery is weak.

Section 7-2

THE DISTRIBUTION AND MANAGEMENT OF DRUGS AND MEDICAL SUPPLIES

This section shows the management and distribution system of medical supplies and drugs, tracing new developments that have occurred since the revolution. It also analyses tuberculosis drug distribution showing unpublished data from the Ethiopian Department of Pharmacy on the tuberculosis drug supply to public health facilities. A description of the distribution of TB drugs is an integral component to understanding the driving forces behind the cost of TB treatment.

During the revolution in 1991, in the north of Ethiopia, 345 health stations, 34 health centres and 11 rural hospitals were destroyed, compounded by the large-scale theft of medical equipment, leaving the area and the country even less able to cope with meeting the health problems of its inhabitants. Facing the challenge of rebuilding these facilities and purchasing drugs and medical supplies, the country found itself intensely overburdened, unable to treat even small proportions of its population. As depicted in Table 7-6, the existing budget for drugs and medical supplies was far insufficient to meet the health demands of the country, especially considering the recent destruction of what little health facilities the country had in the north.

Table 7-6: 1992 Budget Allocations of Drugs and Medical Supplies in Ethiopia

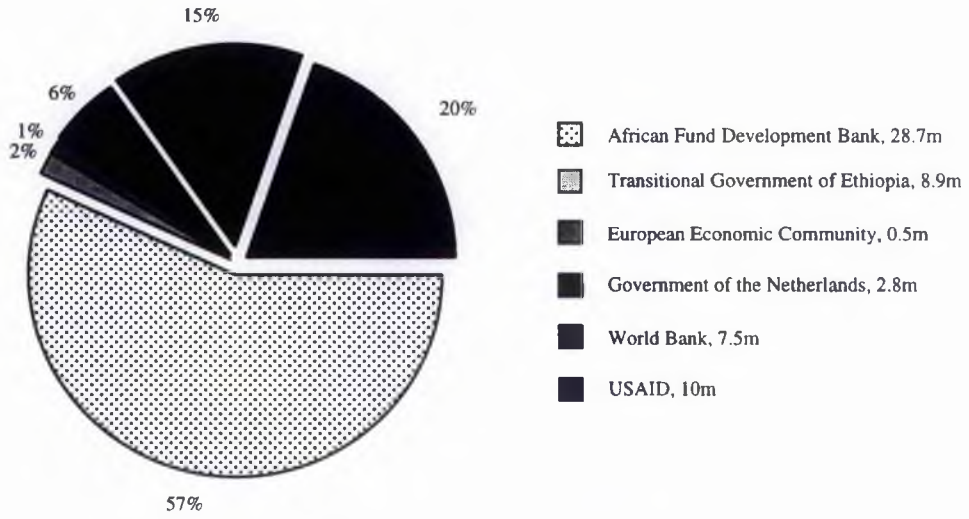
Area and/or Type of Health Facility	Allocation
a. Addis Ababa	5 580 600 birr ($858 553.85, in US 1994 dollars)
b. Hospitals in the remainder of the country	4 182 800 birr ($643 507.69, in US 1994 dollars)
c. Health Centres + Health Stations	9 552 400 birr ($1 469 600.00, in US 1994 dollars)
TOTAL	19 330 400 birr ($3 221 733, in US 1994 dollars)

Source: Transitional Government of Ethiopia, Office of the Council of Ministers, 1993

7-2:1 The ERRP

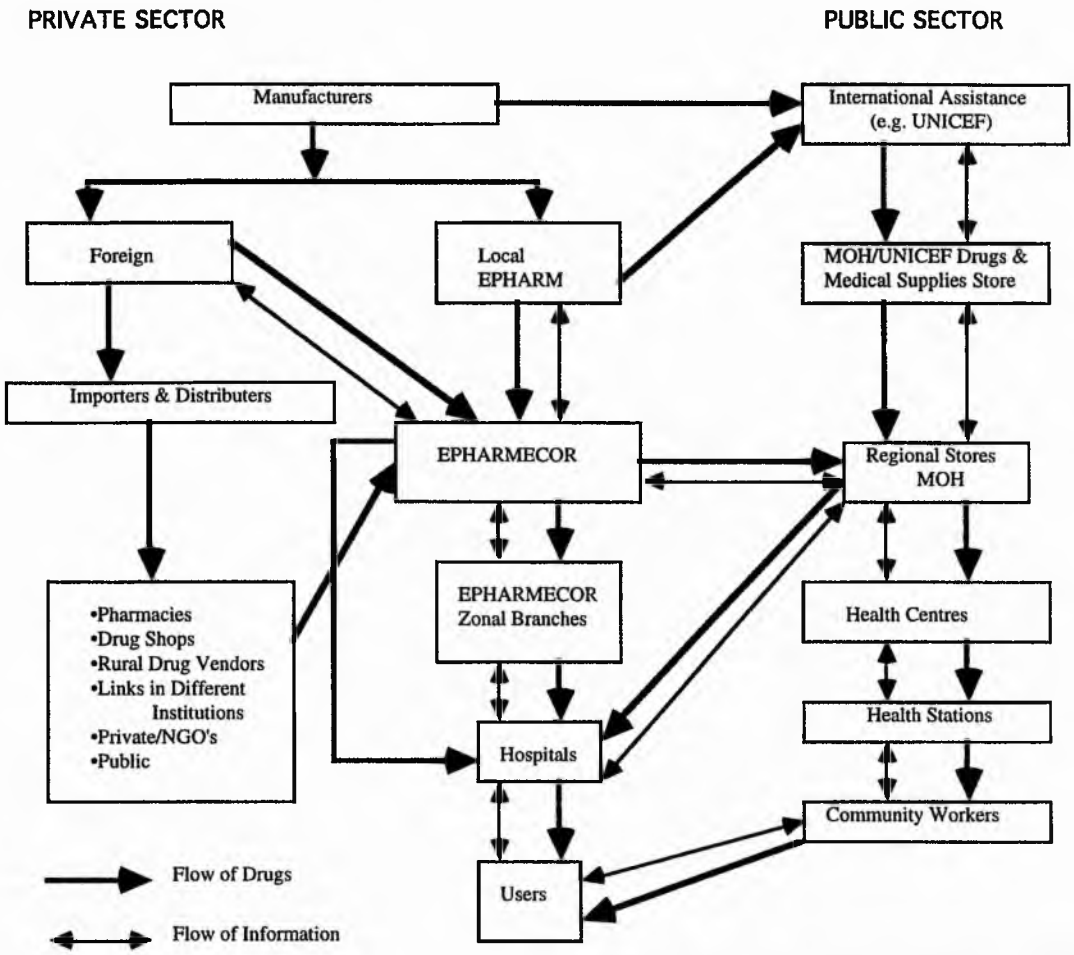
Because of the wide-scale destruction of health facilities and medical equipment during the revolution in 1991, the WHO, the Netherlands, USAID, the World Bank, and the African Fund Development Bank joined the Transitional Government of Ethiopia for an emergency aid project: the Emergency Recovery and Reconstruction Project (ERRP). Subsequently, the ERRP has proven the major supplier of most drugs and medical supplies during the past three years. Together, these six groups initially contributed US $26.2 million which has risen to 50.4 million US dollars in aid for recovery (see Figure 7-2).

Figure 7-2: Allocated Contributions of the ERRP From January 1992 to March 1995 (in US Millions of Dollars)



Courtesy of: Transitional Government of Ethiopia, Department of Pharmacy (unpublished)

Figure 7-3: The Distribution System for Medical Supplies and Pharmaceuticals



Courtesy of: The Transnational Government of Ethiopia, Department of Pharmacy (unpublished)

7-2:2 Drug Supply

Drugs primarily originate from local producers, foreign manufacturers or UNICEF as is illustrated in Figure 7-3. These drugs in turn move to EPHARMECOR or private importers and distributors, often determined by whether their use will be in the private or public sector. Public sector drugs going to EPHARMECOR will be transported directly to hospitals or to regional stores of the MOH or EPHARMECOR zonal regions for distribution to hospitals, health centres and ultimately health stations and health workers. In contrast, the private sector moves drugs from private importers and distributors to pharmacies, drug shops, rural drug vendors, NGO's, other institutions and sometimes the public sector. Looking at Figure 7-3, it is evident that this infrastructure depends on an information flow to determine the future demand of drugs in order to avoid surpluses and shortages. The distribution and importation of drugs can come from all sources. The ERRP, for example, uses UNICEF and international private distributors as illustrated in Table 7-7.

Table 7-7: Pharmaceutical Importers Used by the ERRP

Importer	Drugs Registered	Drugs to be Registered in the Future
Azeca	17	8
Arabian	8	0
Hoechst	5	8
Makris	3	4
Paul Ries	11	10
Pharma	14	-
Regassa Gurumen	-	-
Samual Deressa	-	-

Courtesy of: Transitional Government of Ethiopia, Department of Pharmacy, MOH, Addis Ababa (unpublished)

7-2:3 Anti-TB Drugs

Anti-TB drugs in Ethiopia have been extremely difficult to secure, especially those used in short-course regimens. Tuberculosis drugs, in comparison to other drugs, are far more expensive because of the cost of drugs themselves, and because of the quantities required as a result of the long treament periods. For instance, it was estimated in 1994 that at a 50% detection rate, 154 000 cases of TB would be detected, and of these, 69 300 would be eligible for SCC whereas the remaining 84 700 would be placed on the standard regimen. The calculation of drug needs for both regimens are described in detail in Table 7-8 and Table 7-9.

Table 7-8: 1994 Estimates of SCC Drug Needs in Ethiopia by the Department of Pharmacy, MOH (N= 69 300 patients)

Drug	Amount	Requirement/Patient	Total Amount Required	Number of Tins
S	1 g	60 g	4 158 000	41 580
R + S	150mg./100mg.	180 tab.	12 474 000	124 740
Z	500mg.	240 tab.	16 632 000	16 632
Water for Injection	5 ml./pt.	300 ml./pt	20 790 000	20 790
Syringes	5 ml./pt.	300 ml./pt	20 790 000	20 790
Needle	1/pt.	60	5 0820 00	5 082

Courtesy of: Mohammed Abadir Mussie, Department of Pharmacy (unpublished)

It is through these estimations that future drug needs for TB are calculated. The prevalence of TB is estimated and from this, groups are identified according to the regimen for which they are eligible. From these estimates, future demand for each TB drug is calculated accordingly. To allow for drug reactions and those with a low tolerance for Thiacetazone with Isoniazid (TB450), 10% of the total (154 000) is estimated to need ethambutol. This, for example, means an extra 12 894 120 ethambutol tablets will be required. In addition, from these estimates 42 296 600 of 100 mg isoniazid will be

necessary to treat children (5%), and a further 4 714 320 extra isoniazid tablets will be needed for those unable to tolerate TB450.

Table 7-9: 1994 Estimates of the Standard Regimen Drug Needs in Ethiopia by the Department of Pharmacy, MOH (N=84 700 patients)

Drug	Amount	Requirement/Patient	Total Amount Required	Number of Tins
S	1 g.	60 g.	5 082 000	50 820
T + H (TB450)	450mg.	360 tab.	30 492 000	30 492
Water for Injection	5 ml.	300 ml.	25 410 000	25 410
Syringes	5 ml.	300 ml.	20 790 000	207 900
Needle	1	60	5 0820 00	50 820

Courtesy of: Mohammed Abadir Mussie, Department of Pharmacy, MOH, Addis Ababa (unpublished)

Table 7-10: Anti-Tuberculosis Drug Provisions Under the ERRP Pharmaceutical Sector for Public Health Institutions, 1992-1993

Drug Type	unit	Theoretical Annual Requirement	Actual Procured	Deficit	Percent not Procured
E (400mg.)	tab.	12 245 310	11 435 000	-810 310	6.6%
H (50mg.)	tab.				
H (100mg.)	tab.	15 932 070	10 507 000	-5 425 070	34.1%
H (300mg.)	tab.	4 081 770	600 000	-3 481 770	85.3%
Z (500 mg.)	tab.	15 997 905	2 044 000	-13 953 905	87.2%
R (150mg.)	cap.	12 047 805	5 993 200	-6 054 605	50.3%
R (300mg.)	cap.				
S (1gm injection)	vial	9 216 900	2 794 000	-6 422 900	69.7%
TB450	tab.	40 817 700	15 395 000	-25 422 700	62.3%
Syringe 5ml + needle	each	9 216 900	1 121 400	-8 095 500	87.8%
Water for injection	vial	9 216 900	3 216 000	-6 000 900	65.1%
Vitamin B6 (100mg.)	tab.	-	15 001 000		

Courtesy of: Mohammed Abadir Mussie, Department of Pharmacy, MOH, Addis Ababa (unpublished)

This technique proves relatively effective in calculating drug needs, but it is primarily dependent on the accuracy of the calculation of the prevalence of tuberculosis and detection rates. After these calculations, there arises the challenge of procuring the demanded TB drugs, which has proven problematic for Ethiopia in the past. Although ERRP provides them now, this has only been established as a temporary programme. The most striking characteristic of Table 7-10 is the vast difference between the amount of drugs needed and those actually procured. This difference is significant, representing as much as a 60-80% deficit. Although the deficit is the lowest for isoniazid (100mg), possibly accounting for the ability to make this drug locally, this still does not account for the 85.3% deficit for the 300mg form of this drug. Another interesting observation from this table is the 87.8% deficit in syringes and needles for injecting streptomycin. This is indeed, reflected in various health centres and hospitals having to sterilise and re-use syringes. Overall, no drug has been

completely procured, except perhaps, ethambutol. It seems that in the case of every TB drug, there has been difficulty in obtaining the quantity needed for treatment.

Procuring these drugs primarily comes from the ERRP, WHO, Emergency donor aid and local production. As can be observed in Table 7-11, a large percentage (39.5% and 35.6% respectively) of drugs are obtained from ERRP and local production, followed by 19.1% by the WHO. Interestingly, all rifampicin containing combinations essential for the short course regimen are donated by the WHO. This brings to light the current imperative dependence on the WHO for the delivery of short course chemotherapy.

Table 7-11: Anti-TB Drugs Supply in Ethiopia According to Donor, 1993-1994

Drug Name	Unit	ERRP	Local Production	WHO	Emergency
E (400mg.)	1 000	2 490			500
H (100mg.)	1 000	2 420	12 000		3 000
H (300mg)	1 000		5 333		
Z (500mg.)	1 000	420			
R (300 mg.)	100	7 600			500
S (1gm. injection)	-	16 600		13 000	
TB450	1 000	5 300	14 000		1 000
R + H (300mg./100mg)	100			800	
R + H (300mg./150mg.)	100			3 000	
TOTAL %		39.5% (34830)	35.6% (31333)	19.1% (16800)	5.7% (5000)

Courtesy of: Mohammed Abadir Mussie, Department of Pharmacy, MOH, Addis Ababa

7-2:4 Summary of Section 7-2

In 1991 Ethiopia found itself torn by a revolution that had significant repercussions for the country as a whole. Health care facilities in the north had been destroyed and many supplies had been stolen. These facilities had to be rebuilt and medical supplies for the country as a whole needed to be improved. Such improvements were made by the ERRP which has played a major part in suppying emergency aid for better health care delivery. A large proportion of drugs including those for TB are obtained through the ERRP and other organisations, nevertheless, there is still a deficit in drug needs. Although local production is strong even in TB drugs, there are drugs that cannot be produced locally. As much as 40% of TB drugs come from the ERRP. This is worrying because the ERRP was established as a temporary organisation, and the Ministry of Health may have to find some other way of procuring drugs in the future.

Section 7-3

CURRENT EFFORTS TO CONTROL TUBERCULOSIS IN ETHIOPIA

In this section, those actions on the part of the Ethiopian Ministry of Health to control tuberculosis are presented. Changes in the control of TB that have occurred under the Transitional Government of Ethiopia, such as the establishment of an effective national tuberculosis programme, are discussed. Competent management of tuberculosis treatment and tuberculosis drugs are an important factor in decreasing treatment default, and therefore, resistance.

Tuberculosis is thought to be a disease that primarily affects the poor because poverty allows for malnourishment and poor living conditions where tuberculosis infection will more easily progress into disease. In Ethiopia, one of the poorest countries in the world, tuberculosis reaches one of its highest incidences. This is a disease that strikes the most impoverished in countries, it flourishes when living conditions or life styles of individuals are poor. For example, at the Tekur Anbessa Hospital in Addis Ababa, tuberculosis patients were found to be far poorer than other patients and 53% could not pay their bills as compared to 38% of non-TB patients reflecting the association between poverty, poor living standards and the development of tuberculosis (Hodes and Seyoum, 1989).

Efforts to control TB in Ethiopia have been feeble due to the lack of funds, organisation and a standardised system for treatment. TB centres were established in the 1950s and the 1960s and continued to function under archaic systems, excelling in disorganisation and providing little follow-up of patients. There was a general lack of laboratory equipment to diagnose TB, a lack of expertise in treating the disease, and sporadic, unpredictable drug regimens for patients. Furthermore, the centres remained separate from regular health centres, making service less integrated with other health care measures and far less accessible to patients. The national tuberculosis control programme offices opened in 1976 but were given no budget allocation and relied solely on the financial support of UNICEF and WHO which was not substantial enough to meet the needs of a nation-wide programme (*Guideline for the National Tuberculosis Control Programme in Ethiopia*, 1992). The resources needed to treat TB simply were not available. This was compounded by the incidence of HIV and AIDS, famine, drought and years of civil war. Hence, TB centres and efforts to control TB did little, if anything, to lessen its incidence.

In 1992, after the fall of the Dergue regime, efforts to change the treatment of TB were made with the establishment of a more effective national tuberculosis programme. Its efforts included the distribution of a national guideline book for TB control, yet even in 1994, this programme is still struggling. For the programme to be successful, there has to be a standardisation of treatment, enough support from the Ministry of Finance and other aid organisations, adequate training in TB treatment,

adequate tools to diagnose TB, and a plentiful supply of TB drugs that can be assured for years to come (Guideline for the National Tuberculosis Control Programme in Ethiopia, 1992).

7-3:1 The High Incidence and Prevalence of Tuberculosis and Control Strategies

In 1980, it was estimated that as much as 3% of the population had active tuberculosis (Hodes and Azbite, 1993). In the past, tuberculosis has accounted for a large proportion of hospital admissions. Between the 1960s and 1970s, tuberculosis accounted for 5-7% of all hospital admissions (Hodes and Seyoum, 1989). In 1970-71 approximately 3.3% of all hospital admissions were for tuberculosis at the Ethiop-Swedish Paediatric Hospital (Ghidey, Yohannes and Habte, 1983). Later, between 1983-1985, 11.2% of Tekur Anbessa Hospital admissions were for tuberculosis (Hodes and Seyoum, 1989). Tuberculosis in 1982 was the most frequent reason for hospitalisation after child delivery, and was attributed to 5.8% of 161 692 admissions. In the 1980s it also accounted for the highest cause of death in hospital, forming 12.2% of 6256 hospital deaths (MOH, 1986). Some efforts have been made to prevent tuberculosis with the BCG vaccination. BCG coverage of 1-year-olds in Ethiopia became more intensive in the 1980s and although its effect in the country on decreasing TB in children is unknown, in Addis Ababa, TB incidence decreased by 14% in vaccinated children compared to unvaccinated children.

WHO has set up the goal of a 65% case detection and an 85% cure rate of TB by the year 2000, leaving only an impossible 6 years to accomplish this. Epidemiological data, although scanty at best, present quite a challenge to the WHO's edict. Between 1986-1987, TB was the 12th leading cause of outpatient morbidity, the 3rd reason for hospitalisation, and was and undoubtedly still is the leading cause for hospital death. The reporting of tuberculosis is chronically unreliable. Hodes and Azbite (1993) cite that 84 142 cases of tuberculosis were reported in 1986-1987, 149 444 were reported in 1987-1988, and only 73 365 were reported in 1989-1990. This increase in 1987-1988 represented a dubious 78% total increase in Ethiopia and a 103% increase in Addis Ababa. The last reliable survey of the annual risk of infection was in 1978 and placed it at 3%. Now, the national tuberculosis programme estimates that there is a 2.5% annual risk of infection, representing 41 000 to 70 000 new cases of smear-positive tuberculosis per year assuming that 1% annual risk of infection represents 55 smear-positive cases per 100 000. Likewise, it estimates between 90 000 and 154 000 cases per year of smear-negative cases and extra-pulmonary cases together, using the assumption that these cases represent 1.2 times the incidence of smear-positive cases. The prevalence, at twice the incidence, is thought to be approximately 180 000 to 308 000, and the rate of mortality, calculated as 50% of the infectious cases is estimated to be approximately 20 000-35 000 deaths per year. The annual risk of

infection in children is an estimated 1.4% (Azbite, 1992), this suggests a possible drop in the risk of infection which was observed to be 3% in a 1953-1955 survey.

Contrasting data on the incidence of tuberculosis come from the IUATLD. The IUATLD estimates an annual risk of infection of 1.5%, and also estimates a total of 165 cases of all types of TB per 100 000 population. Between the 23rd of May and the 6th of June, 1993, the IUATLD visited the All Africa Leprosy Research and Training Centre (ALERT) to review efforts in combing treatment of both TB and leprosy (both *Mycobacterium* caused diseases). The results of this research were reported by Arandottir (1993) in an unpublished report. This reports estimates 55 000-95 000 cases of TB reported per year. Case detection varies in different regions, for instance, Butajira has a case detection of 83/100 000, Hosanna Hospital: 60/100 000, Shinshicho: 212/100 000, Shashamane hospital: 692/100 000, and the Regional Health Department in Zeway: 133/100 000. This report suggests a case detection rate of approximately 50%. The default rate in many areas was as much as 70%, which was primarily attributed to a lack of drugs.

Most case finding for tuberculosis is passive whereby the facility waits for the patient to seek treatment. The time it takes a patient to seek treatment varies. The manifestation of TB symptoms can determine the length of time it takes for a smear-positive patient to seek treatment. At the TB centre in Addis Ababa, a survey of 163 smear-positive patients revealed that patients were far more inclined to report to health centres within two weeks if their TB symptoms include hemoptysis (blood stained spit or sputum), chest pain or dyspnea (difficulty breathing). Those only experiencing a cough were observed to delay in seeking treatment (Teklu, 1993).

7-3:2 Current Treatment Regimens

Currently TB is treated using the standard regimen, although some use of short course chemotherapy is starting to grow due to increased grants for the needed medicines. Indeed, some of the first experimentation with SCC in Ethiopia was at the TB Centre in Addis Ababa and St. Peter's Sanatorium. In a study by Wolde *et al.* (1992), smear-positive patients were hospitalised during the intensive phase of their treatment and received the standard regimen, Rifater (a combination of H, R and Z) and another combination preparation of H, R and Z. After two months of treatment, average smear conversion and culture conversion was 82% and 80% for those patients on Rifater. Those receiving the other combination preparation of H, R and Z had sputum conversion rates of 86-88% and culture conversion rates of 86%. Those receiving the standard drug regimen had an average sputum conversion rate of 60% and a culture conversion rate of 30% (culture conversion, as mentioned earlier, is more sensitive in detecting TB bacillus). This study concluded that SCC is clinically more effective

in treating TB than SDR. The authors also noted that combination tablets can help avoid monotherapy, and therefore, resistance.

7-3:3 Drug Resistance

Resistance of bacteria to many drugs in Ethiopia is higher than that observed in tuberculosis. (Trunch, 1991; Geyid and Lemeneh, 1992; Gedebou and Tasew, 1983). Indeed, resistant TB, in comparison to other African countries, has been low in Ethiopia. In a report by Patty *et al.*, (1978) 46% of 184 TB strains tested proved resistant to isoniazid or streptomycin. However, there was no observed resistance to rifampicin in those strains tested, but rifampicin had not been used in treatment. Correspondingly, default rates of patients were 50-60%, but primary or acquired resistance was impossible to determine. In another study by Wolde *et al.* (1986), of 276 samples tested from TB centres in Addis Ababa, Harar and Asmara, 15.2% had some manifestation of resistant tuberculosis. Isoniazid resistance was found to be a high 12%, rifampicin resistance was at 1% and combination resistance to H, S and T was 1.4%. Resistance to pyrazinamide and ethambutol was not observed. This study does not reveal whether isolates came from the same patients over a period of time, or if each isolate came from separate patients. In a study by Lemma *et al.* (1987) at the Sidamo Regional Hospital in 1987, of 104 samples, resistance to isoniazid and streptomycin was observed whereas no resistance was observed to thiacetazone, rifampicin or ethambutol. Total resistance in the 104 strains was 7.6%, and this was all supposed to be primary resistance. However, these studies only tested those strains that were not responding to treatment such as relapse and treatment failures, and for this reason, resistance rates are unrealistically high and biased, acting only as a measure of levels of resistance in treatment failures rather than the entire population. Most resistance is attributed to default, but there is some speculation as to resistance arising in those infected with both TB and leprosy. There is the potential that those treated for leprosy with rifampicin could find themselves with rifampicin-resistant TB (Gunderson, 1987), but it is doubtful that this would be clinically significant. Indeed, the joint efforts of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) to control leprosy and tuberculosis would likely be able to contain this.

7-3:4 Summary of Section 7-3

In Ethiopia, tuberculosis has had a devestating impact on the country. As an opportunistic disease, TB has grown with few impediments in Ethiopia, where the environment fosters poor immune systems in individuals. Efforts to control TB in the past have been poorly formulated, poorly funded, and therefore, impotent against this disease. Recent changes, however, have started to have some success in curing, and hence, containing this disease. Still, short course chemotherapy is relatively

new in this country and is only used on a small scale. Past drug treatment has had little impact because it has not been used to its potential, which is proven by low resistance rates to drugs. More resistance is likely to occur with more use which will undoubtedly increase the costs of treatment.

Section 7-4

HIV IN ETHIOPIA

When considering the containment of tuberculosis, one cannot ignore the powerful impact of HIV on this opportunistic disease. It is undoubtedly important to know the incidence of HIV in order to calculate the growth, nature and appropriate treatment for TB. This section shows the reported incidence of HIV in Ethiopia using unpublished data from the Ethiopian Ministry of Health. HIV has had a tremendous impact on the spread of TB, and therefore, its incidence which is related to TB treatment, must be considered.

Those with HIV are more likely to die during TB treatment, and they have much lower tolerance to drugs, especially thiacetazone. In addition, AIDS cases will commonly need to be hospitalised during treatment. Unfortunately, it is extremely difficult to obtain accurate statistics on the reporting of HIV. As health service coverage is so low, many cases of HIV will go unreported. Also, because of inherent factors in the disease, HIV-seropositive individuals will remain asymptomatic. This is important because TB can often strike during the late asymptomatic stages of HIV.

7-4:1 HIV Growth

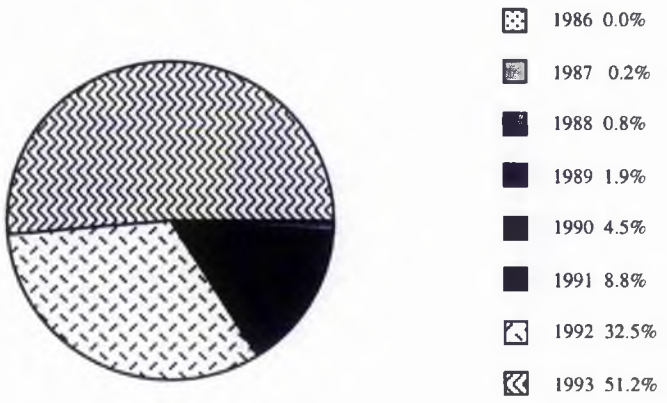
HIV has not penetrated Ethiopia like it has in many African countries, but the disease is still on the rise. The low incidence of reported cases, as compared to other African countries, could probably be explained by the fact that until only recently, the country was relatively isolated by the Dergue regime. Nevertheless, cases are starting to rise exponentially posing a frightening health threat on an already overburdened country.

Between 1986-1987 some of the first cases of HIV were reported at the Tekur Anbessa Hospital in Addis Ababa, Ethiopia. From over 100 HIV-seropositive patients, the average age for these patients was 33.2. 76% of these patients were under forty and there were 70 males and 30 females in this group with ages ranging between 16-58. (Tsega, E., 1990). Up until this point, HIV was a relatively rare disease. The current situation is that it is unknown how many people are infected with HIV, but the National AIDS Control Programme of the MOH in Addis Ababa takes quarterly statistics on reported cases. According to AIDS case surveillance in Ethiopia, from the 31st of March 1994, 11 927 cases of AIDS had been reported from 48 hospitals. The average age of patients was 30 and there was an average delay of 2 months before these cases were reported. 1.6% represented paediatric cases, 34.7% were married, and the male to female ratio was calculated to be 1.6:1.

As can be seen in Figure 7-4, AIDS can be seen to steadily increase in growth from 0.2% in 1987 to 51.2% in 1993. Hence, in 1993, more than half of the growth of AIDS occurred. Data on AIDS

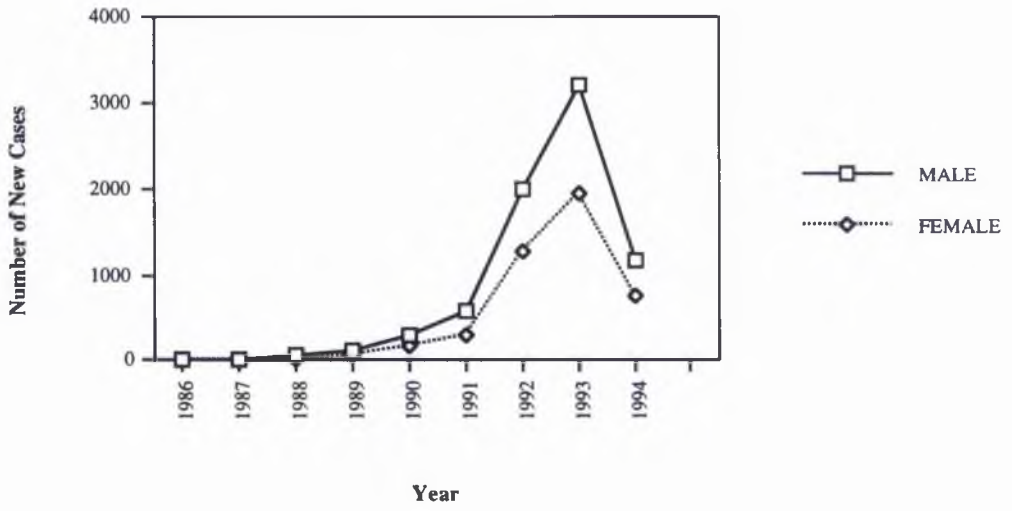
growth for 1994 are incomplete as the report only stretches to the middle of this year, which explains the deceiving fall in new cases in Figure 7-5.

Figure 7-4: Percentage of Growth of AIDS in Ethiopia Between 1986-1993.



National AIDS Control Programme of the MOH in Addis Ababa:
AIDS case surveillance in Ethiopia, March 31, 1994 (unpublished)

Figure 7-5: Growth in Cases of AIDS per Year in Ethiopia Between 1986 and 1994*



*Data for 1994 is not yet complete, explaining the fall in new cases in this year
National AIDS Control Programme of the MOH in Addis Ababa:
AIDS case surveillance in Ethiopia, March 31, 1994 (unpublished)

7-4:2 Risk Factors for HIV

In addition to recent vast growth in AIDS, from looking at Figure 7-6, most growth in cases of AIDS initially occurred in males and then started to appear in females. This trend has maintained

itself, proven by the fact that growth in males with AIDS has remained one third higher than in females. Reasons explaining this could possibly be due to the fact that males in Ethiopia have a greater opportunity to travel because of various kinds of employment. This would allow for greater exposure to urban areas where HIV is far more likely to be transmitted. Likewise, a greater proportion of young males are likely to be more promiscuous than young females. For instance, a large amount of males might patronise a small core of prostitutes with HIV, but fewer women will be prostitutes or have as great a number of sexual partners. This highlights the fact the most AIDS cases were transmitted sexually, with a total of 86.5% heterosexual transmission leaving only 1% homosexual transmission. Only 2.9% of cases were attributed to blood transfusions, maternal HIV, illegal injections and drug abuse. Unfortunately another 9.6% of cases could not be determined. Hence, as seen in Figure 7-6, the highest risk for HIV transmission in Ethiopia is from heterosexual intercourse.

Figure 7-6: Risk Factors for Reported Cases of AIDS in Ethiopia (1986-1993)

National AIDS Control Programme of the MOH in Addis Ababa: AIDS case surveillance in Ethiopia, March 31, 1994 (unpublished)

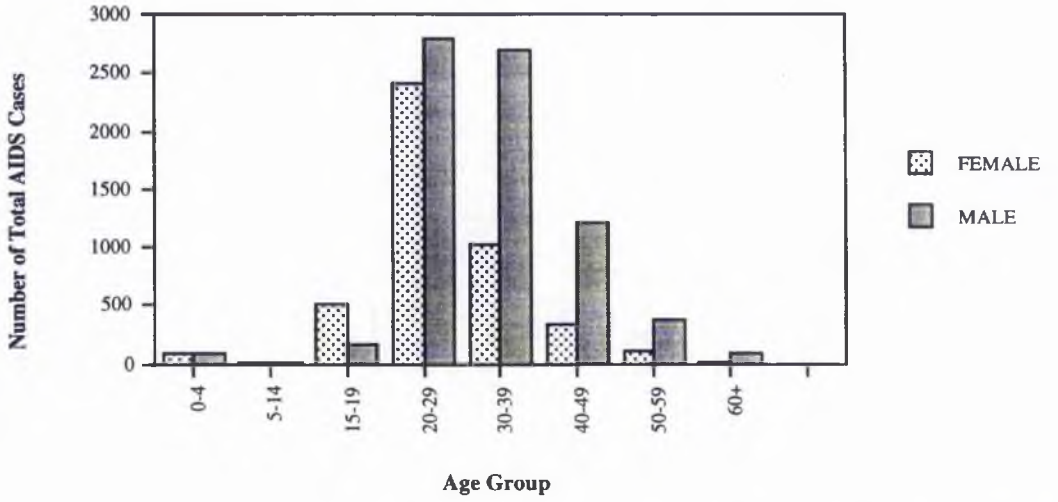
7-4:3 Age and Sex of AIDS Patients

Most AIDS patients were in the age-group of 20-39, probably the most sexually active ages for adults. If an individual feasibly became sexually active and was infected with HIV in his or her teens, it is highly likely that the impact of this infection in the form of AIDS would manifest itself in the ages from 20-39. This is indeed, supported by Figure 7-7. Also, it should be noted that HIV incidence is greater in females than males in the age group 15-19 and it is comparatively higher in the 20-29 age group than the 30-39 age group. This suggests a shift in cases, whereby future cases of AIDS will be more common in young females between 15-25, perhaps as much or moreso than in young males.

Such a shift might reflect greater sexual activity of younger females in the age group 15-19 than, for instance, those over thirty.

Like the age-group where TB strikes in developing countries, it is in this group of those aged 20-39 where the greatest economic and social contributors lie. Hence, diseases that strike so hard at this age range represent some of the greatest loss for society as compared to those diseases that primarily strike the elderly or the very young.

Figure 7-7: Growth in HIV According to Sex and Age in Ethiopia



National AIDS Control Programme of the MOH in Addis Ababa: AIDS case surveillance in Ethiopia, March 31, 1994 (unpublished)

Table 7-12: Clinical Symptoms Experienced by Reported AIDS Patients in Ethiopia (1986-1993)

Clinical Symptom	Males	Females	Total (%)
weight loss	6546	4051	88.85%
fever > 1 month	6221	3878	84.67%
persistent cough > 1 month	**5076**	**3023**	**67.90%**
diarrhoea > 1 month	4538	2798	61.51%
generalised lymphadenopathy	1968	1002	24.90%
oropharyngeal candidiasis	1497	886	19.98%
generalised pruritic dermatitis	1215	814	17.01%
TB (P/EP)	**1241**	**719**	**16.43%**
recurrent herpes zoster	1106	587	14.90%
pneumonia (inc. PCP)	395	217	5.13%
skin rash	116	63	1.50%
CNS derangement	123	48	1.43%
night sweats/body weakness	**111**	**58**	**1.42%**
chronic herpes simplex	77	58	1.13%
Kaposi's Sarcoma	30	8	0.32%
loss of appetite	**19**	**6**	**0.21%**

National AIDS Control Programme of the MOH in Addis Ababa: AIDS case surveillance in Ethiopia, March 31, 1994 (unpublished)

7-4:4 Symptoms

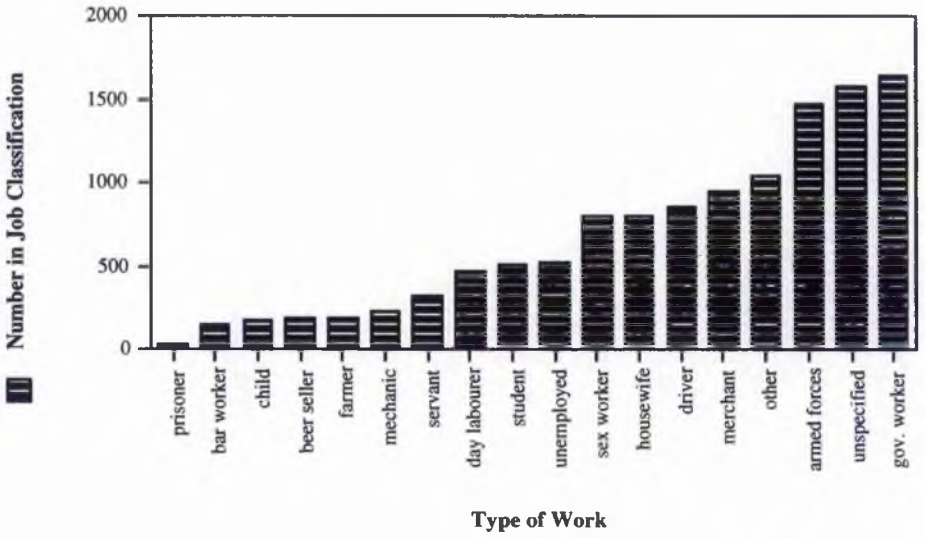
A list of the percentage of patients that suffered from various clinical symptoms of AIDS is given in Table 7-12. This table shows that weight loss is the most common symptom, followed by fever and persistent cough. Few of these in this group experienced AIDS-related derangement or Kaposi's Sarcoma. This is possibly due to the fact that in Ethiopia, without such high technology in fighting infectious disease as well as a much higher prevalence of infectious disease, diseases such as diarrhoea and TB attack the system before diseases associated with more advanced stages of AIDS can attack.

7-4:5 Employment, HIV and its Urban Concentration

From observing data on the employment of reported AIDS cases, HIV appears to be a disease associated with the middle classes in Ethiopia, rather than the poorer classes (See Figure 7-8). In addition, 41% of all reported cases were residents of Addis Ababa, suggesting a further urban concentration of the disease. Those with the highest rates of AIDS are government workers, armed forces, merchants and drivers. This is followed by housewives, prostitutes and the unemployed. Although a large proportion of employment is unknown, all of those cases where employment is known except the housewife, child and farmer, have well defined jobs that are either centred in urban areas or involve a large amount of travel. Jobs such as government workers, merchants, sex workers, unemployed, servants, mechanics, beer sellers, bar workers, students and prisoners are those positions which require the individual to work in a highly urbanised area. Employment, for instance, in the armed forces or as car and truck drivers are jobs that can require a significant amount of travelling for the individual from urban area to urban area. It is only the classifications, such as unspecified, other, day labourer, child and housewife, who are in positions that could be in either rural or urban areas. What is surprising is that reported cases of farmers is very low, the only well defined rural job. Although 80% or more of the total population make their livelihood from farming, their incidence of AIDS is not even remotely proportionately represented. This could be partially because of an under-representation in reporting. It could also be explained by a possible urban concentration of the disease. The distribution of workers with AIDS mostly from the city or in positions that require travel is that, like TB, HIV could be said to be a disease that thrives in urban conditions. In these areas, there is the increased opportunity for more sexual exchange between different people. HIV is also known to move between those who travel extensively. For example, in the early eighties during the Dergue military regime, many soldiers with new authority and weapons were not unknown to abuse this power and rape local women. Many of these soldiers were also thought to be quite promiscuous. This, combined with the large amount of continuous travel throughout the country, meant that they were an initial major mechanism for the transmission of AIDS in Ethiopia during the Dergue regime. Sexual

promiscuity in drivers could also be another mechanism for transmission. HIV is known to move along major highways, especially in Africa. Many drivers' jobs involve extensive travel and a lonely lifestyle such that they are more likely to seek sexual company with a large number of strangers along their driving route. Another component contributing to the urban concentration of this disease is prostitutes. Prostitutes, which are undoubtedly a strong pool of HIV infection, are available at many bars, and for instance, in bars in Addis Ababa, their services can be procured for approximately 100-200 birr or 10-20 pounds. Although this represents a month's or more wages for a farmer, servant, driver, day labourer, beer seller or bar worker. It can represent as little as 25-10% of the month's wages of a merchant, soldier or government worker. Hence, this group can take advantage of more effective demand for prostitutes. In essence, all these variables explain why HIV is associated with those holding jobs in urban areas and jobs where the wages are relatively high.

Figure 7-8: Reported AIDS Patients According to Type of Employment



National AIDS Control Programme of the MOH in Addis Ababa: AIDS case surveillance in Ethiopia, March 31, 1994 (unpublished)

7-4:6 Education

These high statistics reflecting heterosexual transmission suggest the need for greater education on the transmission of HIV. Ignorance of HIV in Ethiopia is a difficult challenge to containing the spread of AIDS. Patient ignorance of AIDS was revealed in an informal interview with several staff members at Kefetegne 13 Health Centre in Addis Ababa. This health centre, which until only recently

specialised in sexually transmitted diseases, still had a very strong case load of patients in this area. Patients with AIDS were unclear as to the kind of birth control they should be using. Where abstinence would have been ideal, some HIV patients even refused to use recommended condoms during intercourse. Amazingly, HIV patients would ask for the pill, diaphragm or IUD, all which have little proven ability to stop HIV transmission. Indeed, education on the transmission and severity of HIV is not widespread and HIV is likely to continue its high rate of growth without such education.

7-4:7 Summary of Section 7-4

HIV in Ethiopia will continue to grow, especially considering recent political changes encouraging outside investment and travel from other African countries. Already, new reported cases of AIDS are on the rise. There appears to be an urban concentration of this disease making the risk factors highest for male, middle-class individuals living in urban areas aged between 20-39, with multiple sexual partners. Women represent approximately two-thirds the amount of males affected with HIV, but this proportion is likely to change with increased transmission. The growth in new cases of AIDS and HIV are expected to be dependent on education and awareness of the disease coupled with a concerted effort on the part of those aged between 15-55 to use appropriate precautions.

SECTION 7-5

CONCLUSION

Ethiopia is undoubtedly one of the very poorest countries in the world. It is hampered by poor living conditions, a changing political climate and environmental disasters. Recent changes in the political system after the revolution of 1991 have fomented several significant changes in Ethiopia which have had an impact on health and the economy. Still, over 80% of Ethiopians survive by farming and 48% of the population are under the age of 15. Health service coverage is a mere 47% with an urban concentration of health facilities. Infectious disease still proves to be one of the greatest health threats in this country. To facilitate health care delivery after the destruction from the revolution, the MOH of Ethiopia, the WHO and other aid organisations instigated the ERRP. The ERRP has been instrumental in rebuilding health facilities, providing equipment and drugs. The supply of drugs for Ethiopia is increasing, but in the case of TB there is still a large deficit, even with the ERRP. A major health threat on the rise is HIV in Ethiopia. Unlike other African countries, this disease has just recently started to rise due to prior isolation of the country before 1991.

Health service coverage, tuberculosis drug management, HIV and tuberculosis control programmes are all likely to have some impact on the cost of treatment. Poor health service coverage for TB contributes to the spread of TB and the implementation of better TB programmes is designed to improve this situation. Likewise, correctly calculating TB drug needs from past information on disease incidence can bypass problems arising from a surplus or deficit of drugs. As reported from other studies described in earlier parts of this thesis, a surplus of drugs can lead to a waste of resources and drug expiration with the possibility that expired drugs, which might not be as effective, will be used. These expired drugs can cause resistance. Likewise, a deficit of drugs may mean that TB treatment becomes intermittent, also allowing for TB drug resistance to develop. In the case of HIV, there are likely to be more complications such as drug reactions which add to the cost of TB treatments. Therefore, the incidence of HIV as it relates to TB/HIV co-infection becomes important. From this information, some signs of the incidence of TB/HIV co-infection in Ethiopia will be explored in the next chapter.

CHAPTER EIGHT
TUBERCULOSIS CONTROL EFFORTS IN ETHIOPIA
PART TWO: CASE STUDIES IN ADDIS ABABA

Introduction

After exploring some of the health problems, health care management and organisation of health care delivery in Chapter Seven, Part One of 'Tuberculosis efforts in Ethiopia', this chapter, 'Part Two of Tuberculosis Control Efforts in Ethiopia' will show the impact of TB resistance on the cost of TB treatment, focusing on specific case studies that analyse data collected in August and September of 1994 in Addis Ababa. Following Section 7-4 in Chapter Seven on Aids in Ethiopia, Section 8-1 further shows the interaction between HIV and TB at St. Peter's Sanatorium in Addis Ababa. When looking at the impact of resistance on the cost of TB, it is also important to look at the dynamics of the treatment group, including the incidence of HIV. As shown in Chapter 5, antibiotic resistance in those who are HIV-seropositive can have more complications than those who are HIV-seronegative. Those who are HIV-seropositive are likely to need more and longer hospitalisation. They have less tolerance to some drugs, and therefore, some drugs cannot be used in these patients because of their life-threatening effects. These patients are likewise, more likely to die from resistance, and the time from diagnosis to death is much quicker. Tying into the examination in Chapter 2 of technology concentration, Section 8-2 of this chapter discusses the inappropriate concentration of technology at the National Tuberculosis Centre in Addis Ababa and cost considerations in its diagnostic procedures. When looking at the total cost of TB treatment, the cost of diagnosis can be significant. Choices in the type of screening are fundamental aspects determining TB treatment cost. Lastly, Section 8-3 presents a cost-effectiveness analysis between SCC and SDR in the public sector of Addis Ababa. It is specifically in this study that the impact of resistance on the cost of TB treatment is explored. This section also discusses the impact that TB drug resistance will have on the cost-effectiveness of treatments. In addition to this, it further builds on the description in Chapter 6 of the optimisation of

TB treatments in developing countries, showing that through the use of cost-effectiveness analysis, the most appropriate treatment can be identified. It is hoped that through these case studies, the reader will obtain a greater understanding of the dynamics and challenges to cost-containment and management of a health condition, such as TB, in a low income developing country in sub-Saharan Africa, especially considering the challenges of HIV and anti-TB drug resistance.

Section 8-1

ST. PETER'S SANATORIUM IN ADDIS ABABA

This section will show the treatment results of over 1500 critical patients that received treatment at St. Peter's Sanatorium in Addis Ababa. It also includes the results of over 762 patients screened for HIV, including those with TB/HIV co-infection that died. The distribution of types of TB in these patients is presented with a discussion on the changes in patient response to treatment in the HIV era. In those screened for HIV, a total of 31% were HIV-seropositive. Resistance in the sanatorium is further discussed from observations and an interview with the medical director. A resistance rate of approximately 10-20% is observed by the medical director. The incidence of TB/HIV co-infection and the incidence of resistance will be considered in discussions in the last section of this chapter.

It is difficult to ascertain the amount of HIV/TB co-infection in patients in Ethiopia because TB patients are seldom screened and a large proportion of data either comes from severe AIDS cases or informal estimates by doctors. Nevertheless, the amount of TB in HIV patients is thought to be quite high, possibly one of the commonest infections in those with HIV in some areas. Tsenga (1990) reports that of the clinical presentations of 100 HIV patients at the Tekur Anbessa Hospital in Addis Ababa, tuberculosis was the most observed infection and it aggressively manifested itself in uncommon forms.

This section will show tuberculosis at its most critical manifestation at St. Peter's Sanatorium in Addis Ababa. These are data that were collected in Addis Ababa by visiting the sanatorium in September 1994 and recording data records from 1992-1994, kept by the current medical director on all clinical test and outcomes of treatment for patients. This analysis will include smear status, patient origin, treatment results and a report on HIV/TB co-infection. Information on the incidence of TB/HIV co-infection is difficult to obtain if it exists at all. An interesting characteristic about the patients at St. Peter's Sanatorium is that many have been screened for HIV, and therefore, some representation of TB/HIV co-infection can be derived.

8-1:1 Patient TB Distribution

The St. Peter's Sanatorium is a hospital in Addis Ababa that only treats tuberculosis and only accepts those patients that have been referred from the TB Centre in Addis Ababa. TB patients arrive at the sanatorium twice weekly and all patients at this hospital have extremely critical TB necessitating hospitalisation. The hospital contains 200 beds occupied by patients for approximately two months after which these patients are referred back to the TB Centre for ambulatory treatment. Tuberculosis

patients include both males and females in separate wards. All patients at this hospital receive SCC due to the higher death rate associated with SDR.

In 1993 a total of 928 patients were treated at St. Peter's Sanatorium and from these, there was an average of one third more males than females. The male to female ratio was a low 0.75 males to every 1 female between the ages of 0-14 years and then continued to grow so that the male to female ratio was 1.2:1 for the ages of 15-24 years and peaked at the ages of 35-44 years with a 2.58:1 male to female ratio. As seen in Figure 8-1, after the ages of 0-14, the number of males hospitalised is consistently higher than females. The predominance of patients hospitalised proved to be smear-positive, with the remainder of patients smear-negative including extra-pulmonary patients. A total of 381 (50%) patients in 1993 proved smear-positive and 346 (45%) patients were smear-negative with a remaining 35 (5%) classified as unknown, as illustrated in Figure 8-2. The disproportionate level of smear-positive cases in this group reflects the severity of this most infectious form of TB.

Figure 8-1: Total Caseload in 1993 at St. Peter's Sanatorium

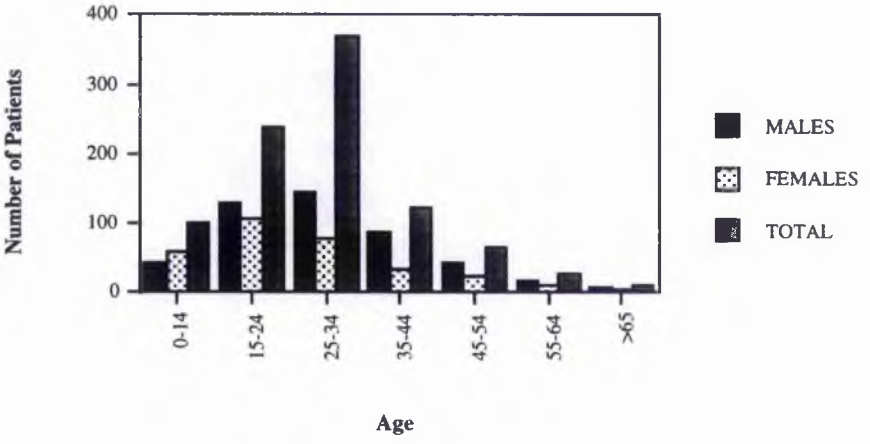
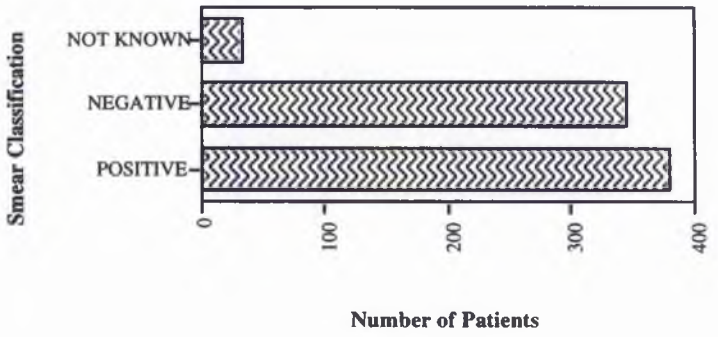


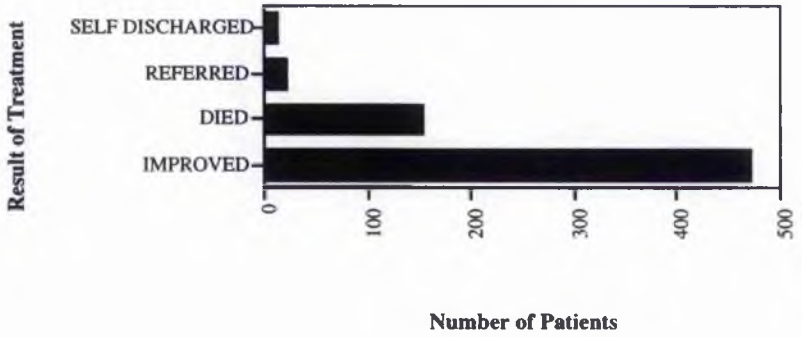
Figure 8-2: Smear Classification of Patients at St. Peter's Sanatorium



8-1:2 Results of Treatment

In 1994, a total of 472 (71%) patients treated for TB at the sanatorium improved, but 154 (23%) died, 13 (2%) insisted on discharging themselves and 22 (3%) were referred to other areas as illustrated in Figure 8-3. The high death rate of 23% reflects the extremely critical state of patient's TB and the fact that many of these patients were HIV-positive.

Figure 8-3: Results of Treatment for Patients at St. Peter's Sanatorium, 1994



8-1:3 Changes in Patient Response to Treatment in the HIV Era

It is interesting to look at St. Peter's Sanatorium in a pre-HIV context to compare current figures to those over ten years ago. In the early eighties at the St. Peter's Sanatorium in Addis Ababa, Feleke and Teklu (1983) reported that of 861 patients treated over one year, 63% were young males from Addis Ababa with TB in its advanced stages. In 1993 this dropped to 51% males and 34% of these were under the age of 35. This change in the male to female ratio reflects a trend where more females were being treated at the St. Peter's Sanatorium.

Table 8-1: Age and Sex Distribution of TB Patients at St. Peter's Sanatorium from 1978-1979

Age	Male		Female		Total		Retreatment	
	number	%	number	%	number	%	number	%
16-30	347	69.00	219	69.00	593	69.00	94	57.30
31-45	129	23.80	71	22.30	200	23.10	57	34.80
46-60	31	5.50	23	7.20	54	6.30	9	5.50
Over 60	7	1.30	4	1.20	11	1.30	3	1.80
No Record	2	0.04	1	0.30	3	0.30	1	0.60
Total	543	100.00	318	100.00	861	100.00	164	100.00

Source: Feleke and Teklu, 1983: p. 445

In the Feleke and Teklu study, 70% of all patients were under the age of 31 and 92% were under the age of 45. In 1993, 76% of all patients were under the age of 35 and 89% were under the age of 45. The average time for hospitalisation was three months or less in 90% of all cases, which is very similar to the amount of time spent now. One of the most interesting changes in the HIV era is that Teklu and Feleke report a mortality rate of 9.2% in contrast to the 23% mortality rate in 1994 (See Table 8-1). This suggests that the rate of death has more than doubled in over ten years at this health facility. Treatment, however has improved to the clinically more effective SCC treatment. Such an increases in the death rate could reflect the impact of HIV on tuberculosis treatment.

8-1:4 Patients with TB/HIV Co-infection

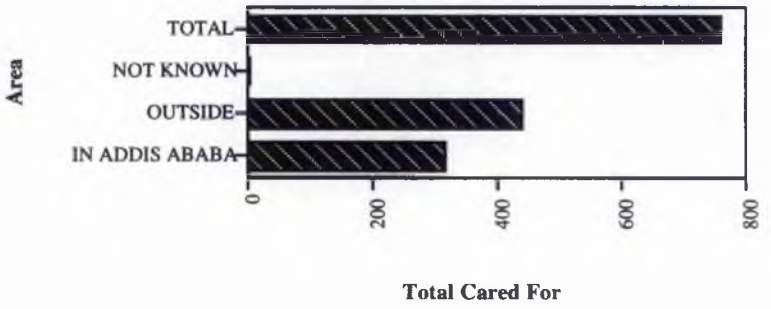
In this hospital, many patients have been screened for HIV because of the serious nature of their symptoms. Cases of HIV range from asymptomatic HIV to very severe AIDS. Many patients were given other antibiotics because of chronic diarrhoea and other AIDS related infections. Some patients also experienced severe drug reactions to TB medicine, which is another common HIV-related phenomenon. It was not uncommon for these patients to experience usually rare isoniazid-related hepatitis. More common was exfoliative dermatitis, also known as Stevens Johnson's syndrome, consisting of a severe blue discoloration of their skin with severe peeling from adverse drug reactions to thiacetazone.

8-1:5 The Source of Patients

A large proportion of patients screened for HIV have come from outside of Addis Ababa. As shown in Figure 8-4, 41.7% came from within Addis Ababa, 0.26% were from unknown areas and a high 58% came from other areas. This suggests a great cost in travel to 58% of these patients, illustrating the serious nature of their TB since they travelled from outside of the city to seek treatment.

In addition, this reflects the popularity of the TB Centre in Addis Ababa which is virtually always overloaded in treating cases of tuberculosis both from outside of Addis Ababa and within.

Figure 8-4: Area of Origin of Those Patients Screened for HIV at St. Peter's Sanatorium



8-1:5 The Results of HIV Screened TB Patients

A total of 235 out of 762 (31%) screened patients were HIV positive in 1993 at St. Peter's Sanatorium according to the National AIDS Control Programme of the MOH in Addis Ababa. Nevertheless, the sanatorium later reports up to 260 (74%). The concentration of these cases proved to be much higher in the age group of 15-49 than a normal age/sex distribution for TB as depicted in Figure 8-5. The largest number of cases of TB/HIV co-infection occur in the age group of 20-29 years, and this was only slightly less in the 30-39 age group. The age group of 20-39 seems to be where the highest proportion of TB/HIV co-infection lies, representing a total of 72% of all cases. Hence, those in this age range are most at risk for TB/HIV co-infection and this should be considered when screening TB patients for the HIV.

Figure 8-5: Total TB/HIV Co-infected Patients at St. Peter's Sanatorium According to Age and Sex, 1993

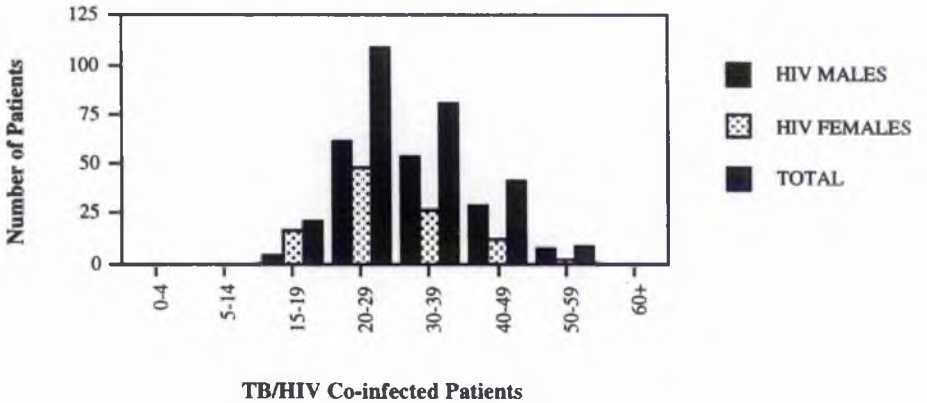


Figure 8-6: Male Ward for Patients at St. Peter's Sanatorium

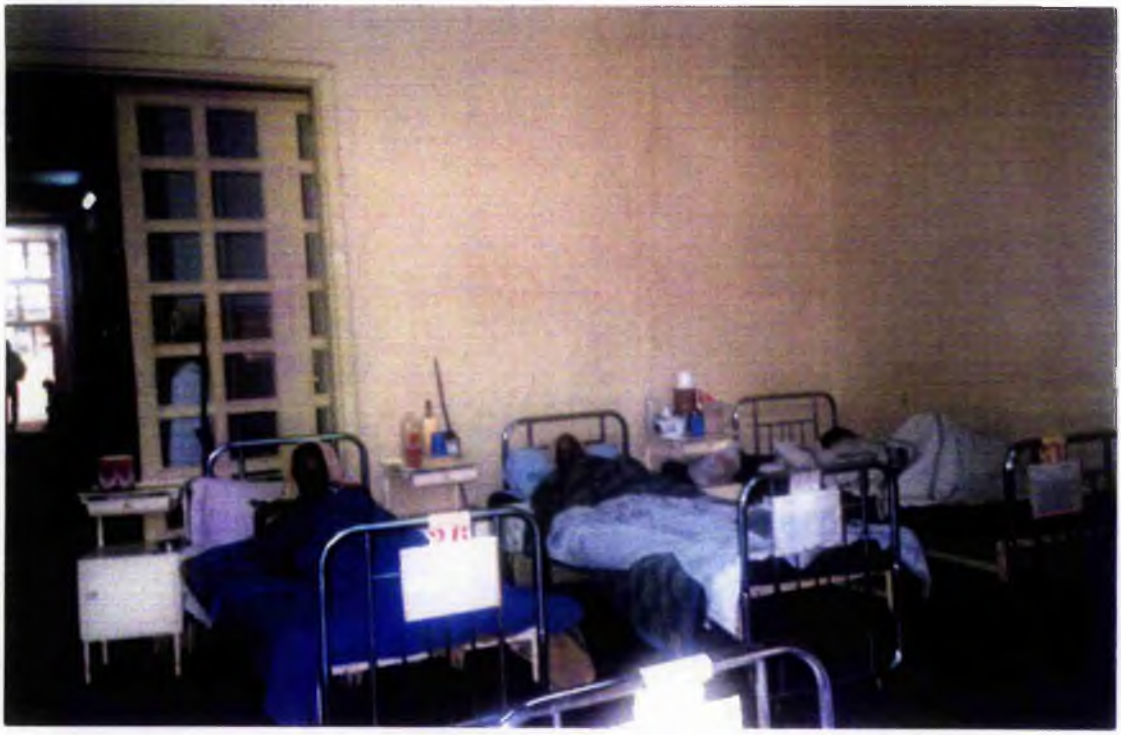
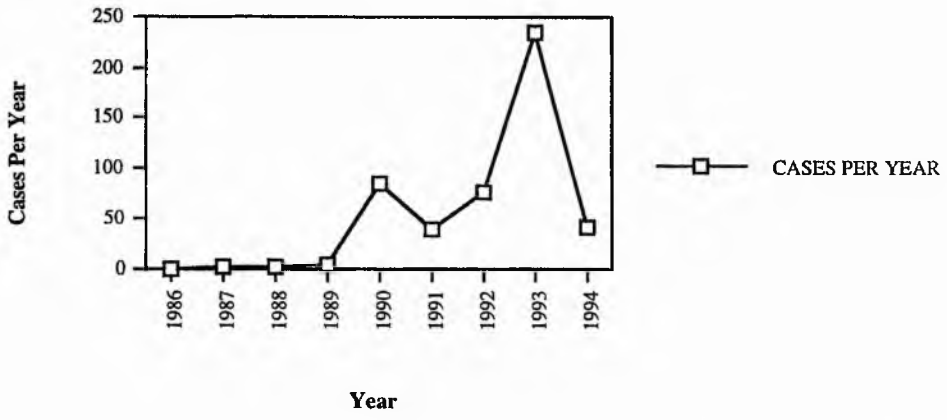


Figure 8-7: Paediatric Ward at St. Peter's Sanatorium

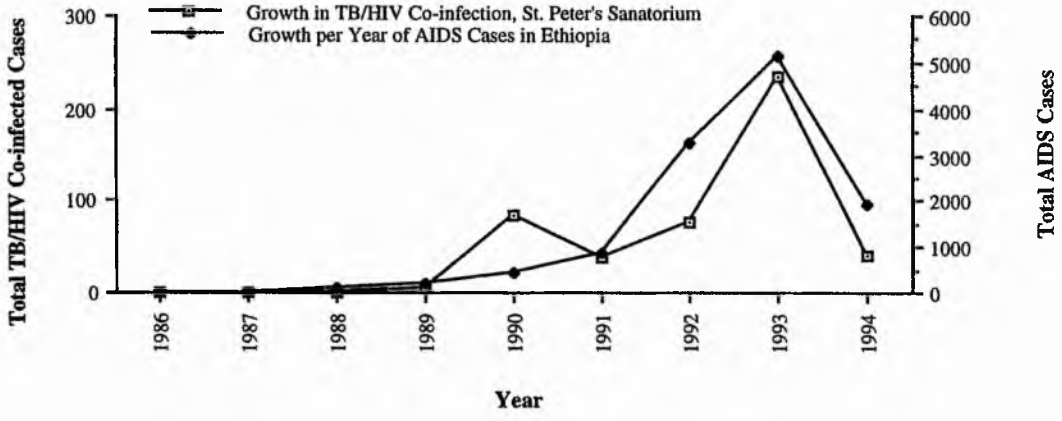
TB/HIV co-infection has a striking impact on patients in this sanatorium. Figure 8-6 shows a room in the male ward of St. Peter's Santorium where both HIV and thiacetazone drug reactions are not uncommon. TB/HIV co-infection can also be devestating for those around the patient. One of the boys in Figure 8-7 is one of two children whose mother had TB. On top of this their mother died of AIDS related causes (unknown if it was in fact TB) the day this photograph was taken.

Figure 8-8: Total TB/HIV Co-Infected Cases per Year at St. Peter's Sanatorium*



*1994 data is not complete

Figure 8-9: A Comparison Between Total TB/HIV Co-Infected Cases per Year at St. Peter's Sanatorium with Total Growth per Year of AIDS Cases in Ethiopia*



*1994 data is not complete

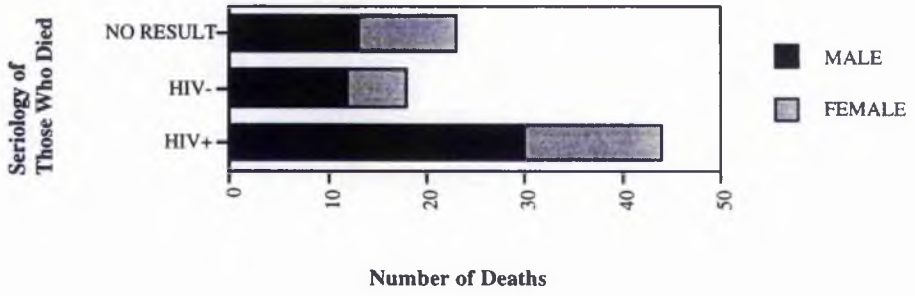
Data in Figure 8-8 starting in 1986, show growth in TB/HIV co-infected patients. This closely reflects HIV growth per year illustrated in Figure 7-5 in Section 7-4. A comparison of these two

growth rates is made in Figure 8-9. Except for the rise in patients in 1990 at St. Peter's Sanatorium, the growth between these proves to be quite similar (the reader is again reminded that data for 1994 in both cases are incomplete, reflecting the deceptive drop in the curves of these figures). Such curves suggest that the growth of HIV will continue to provide more and more TB/HIV co-infected cases in the future.

8-1:5a Death and TB/HIV Co-infection

Of those HIV screened patients who died, 18 (21%) were HIV-seronegative, and 44 (51%) were HIV-seropositive and in 23 (27%), no result could be determined. In these results, over half of those screened who died were HIV-positive, which might reflect that a large proportion of those with TB who die, die from HIV-related causes: either TB or other infections, as shown in Figure 8-10.

Figure 8-10: HIV-Serology of Patient Deaths St. Peter's Sanatorium



8-1:6 Drug Resistance at the Sanatorium

Resistance causes problems in treating patients at the St. Peter's Sanatorium and proves to be higher than in health centres because many patients' TB has become critical due to repeated default. Dr. Heiwot, the medical director at St. Peters states that resistance to isoniazid, thiacetazone, and streptomycin is commonly observed, but she has observed rising levels of rifampicin resistance. Patients are suspected of resistance based on their history and lack of response to two months of treatment. If a patient has previously received 2-3 months of treatment of a particular drug, then other types of drugs are substituted. Resistance is estimated in approximately 10-20% of cases, but it is difficult to culture these samples because results take 8 weeks when often the patient has already become smear-negative. When resistance is suspected, 5 different drugs are administered for the first 2 months, and a continuing dose of four drugs in the third month and with a culture after one year.

Some doctors only give rifampicin and isoniazid, however, which contributes to a greater resistance selection, especially if the patient was already resistant to these drugs.

8-1:7 Summary of Section 8-1

Out of a total of 762 patients treated in 1993, a total of 235 patients were HIV positive. This represents approximately 30% of all patients treated, which proves to be quite close to statistics on HIV/TB co-infection in other African countries, but these statistics are somewhat unclear. Although TB/HIV co-infection was only 16.43% in nationally reported AIDS cases, an extra 67.90% suffered from a persistent cough, 1.42% suffered from night sweats and an added 0.21% suffered from a loss of appetite: all symptoms of other diseases, but also symptoms of tuberculosis. TB/HIV co-infection probably accounts for a much higher percentage of patients considering that TB often develops in patients before any AIDS defining illnesses appear.

The percentage of those TB cases that can be attributed to HIV is difficult to calculate. Some estimates can be made from TB/HIV co-infection national AIDS data, but these are inaccurate. More accurate estimates can be determined from greater screening of TB patients to catch asymptomatic HIV cases, but this is unlikely to occur unless patients are critical. The TB/HIV co-infection rate is an important epidemiological determinant in explaining changes in the TB data in the era of HIV, and in illustrating the burden of disease of HIV on TB.

The fact that the medical director observed an average of 10-20% of resistance in patients to the ordinary treatment is alarming, considering the fact that there is little isolation between patients at the sanatorium, allowing for the spread of primary resistance to normally drug-sensitive TB cases. The cost of using five drugs to treat resistant patients increases the drug cost of treatment, but also TB treatment costs are increased because of longer associated hospitalisation of patients. In addition, there is the cost of more deaths due to resistant TB.

Section 8-2

THE NATIONAL TUBERCULOSIS CENTRE IN ADDIS ABABA: COST CONSIDERATIONS IN DIAGNOSTIC PROCEDURES

In this section, the approach to TB screening primarily at the National Tuberculosis Centre in Addis Ababa is analysed. The sex, TB type (extra-pulmonary, smear-positive, smear-negative) and age structure of the case load which was comprised of a sample size of 29 295 screened patients between 1992 and 1993 can be used as an estimate of the general incidence and manifestation of TB in Addis Ababa and outside the city. An analysis of the cost of screening for TB in both the TB centre and in other areas of the public health sector in Addis Ababa is presented with possible recommendations for improving screening from a cost perspective. This analysis is meant to show those elements in the diagnosis of TB that influence cost and is further designed to support the analysis in the next section.

The National Addis Ababa Tuberculosis Demonstration and Training Centre (TB Centre) at one time was completely responsible for treating almost all cases of TB in its area which account for several thousand (See Figures 8-11 and 8-12). This is a centre that has come under considerable criticism because of its inability to maintain patient compliance after initial diagnosis of tuberculosis. The overwhelming numbers of patients that came to the TB Centre for diagnosis were simply too difficult to manage. As this centre was the only public institution designed for treating TB in its area, it was ill equipped to treat so many patients by virtue of its small size and funding. Hence, the centre had a caseload that it could not realistically deal with, resulting in patients receiving two months of intensive treatment and being discharged for their continuous phase treatment with little follow-up. Indeed, the centre suffered with a record default rate of 86% meaning that even by a generous estimate, its cure rate averaged at only around 30%. The TB Centre continued to suffer from mismanagement and problems in tracing patients until only recently when the task of treating TB was delegated to local health centres and hospitals. Recent improvements, with the support of the WHO emergency fund, has allowed for the treatment within health centres with short course chemotherapy as well as a more accessible non-pilot programme for treatment with the standard drug regimen. The TB Centre has been integrated into this treatment programme for those that live locally. It still diagnoses TB in patients from outside of Addis Ababa. Now the TB centre has a more manageable caseload, but by far, still diagnoses the greatest number of cases in the area and surrounding areas. Their caseload, however, remains heavy because of a widespread belief by those seeking care that the centre is either still the only treatment centre, or that they are somehow better than local health centres. Due to such a large caseload diagnosed at the National TB Centre in Addis Ababa. It is possible to see a large

Figure 8-11: Nurses at the TB Centre in Addis Ababa

Figure 8-12: The X-Ray Machine and X-Ray Technician at the TB Centre

sample distribution of cases of TB over the past years in Ethiopia. In addition, the diagnostic procedures will also be discussed in detail.

8-2:1 Caseload at the TB Centre

Between September 1992 and September 1993, the TB Centre screened over 29 295 patients for tuberculosis. Of this group, only 5353 (18%) of those were diagnosed with TB, resulting in an extra cost of 23 942 (82%) screened that did not have TB. Of those with TB, a total of 39% were smear-positive, 58% were smear-negative and 3% were extra-pulmonary tuberculosis cases as illustrated in Figure 8-13.

Figure 8-13: Smear Classification of TB Patients from the TB Centre in Addis Ababa from September 1992-September 1993.

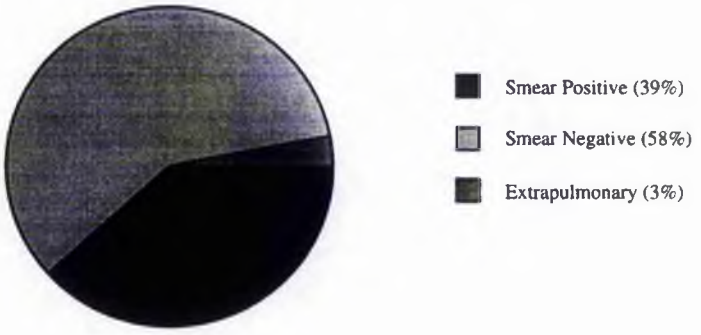
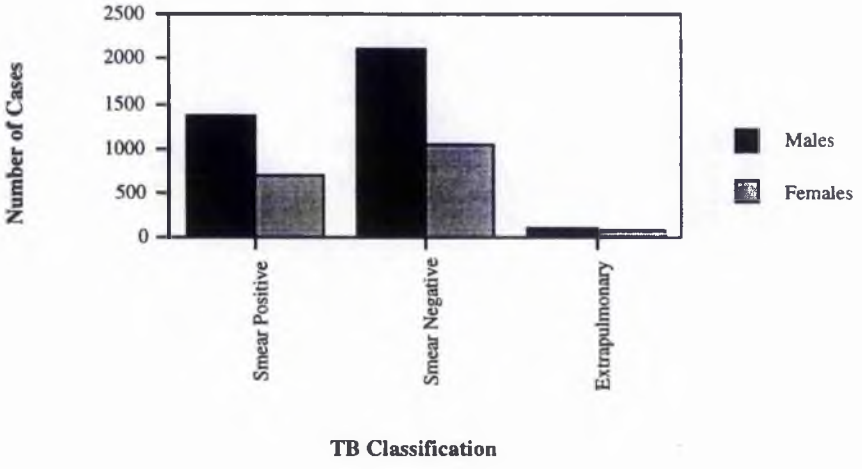


Figure 8-14: Smear Status According to Sex

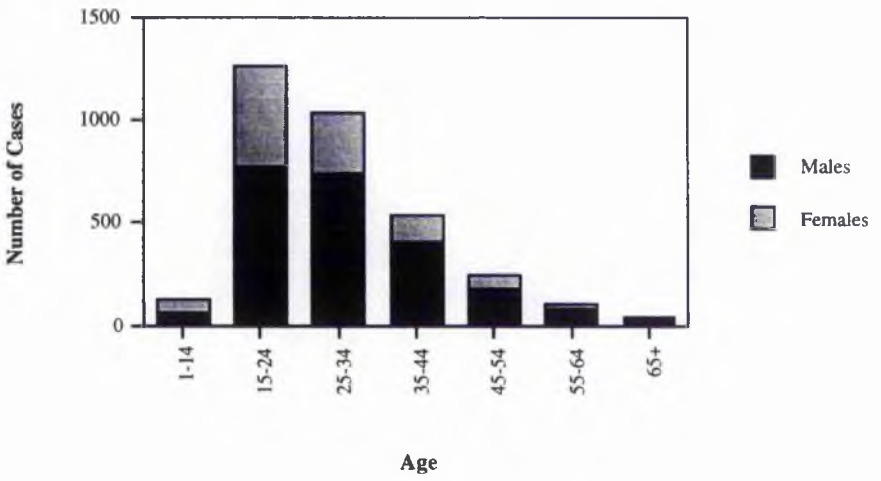


Again a large proportion of these proved to be males rather than females. On average there were 2 males for every one female treated for tuberculosis. 66% males to 34% females in the smear-positive

smear-positive, 67% males to 33% females in the smear-negative group, and 59% males to 41% females in the extra-pulmonary group as can be seen in Figure 8-14.

Indeed, tuberculosis affects more males than females, as has been the case in other countries. For unknown reasons, TB seems to strike in males more than females (See Figure 8-15). This could possibly be exacerbated by the fact that more males seem to be HIV-positive as described in Section 7-4 and more males have a greater incidence of TB/HIV co-infection . This disease is far more costly in economic terms from the perspective of a society if males are the major producers and wage earners of that society.

Figure 8-15: Age and Sex Distribution at the TB Centre from All Available Reports from September 1992 to September 1994



8-2:2 Diagnostic Procedures

It is the policy of the TB Centre in Addis Ababa to screen all patients by giving them a smear test and a chest x-ray (See Figure 8-12). Indeed, although a chest x-ray (CXR) can reveal some information about a patient, it has to be used in conjunction with other diagnostic tools and patient symptoms in order to diagnose tuberculosis. CXRs are essential for use in paediatric age groups, especially when they have had contact with a tuberculosis patient, a TB/HIV co-infected patient, a miliary tuberculosis patient or a pleurisy patient. However, as was revealed in Chapter 5, there is no definitive chest x-ray particular to tuberculosis. Chest x-rays are difficult to read and x-rays of TB infected cases can be quite similar to other chest diseases. They cannot be the sole indicator of tuberculosis but need other clinical support. Nevertheless, since this diagnostic tool is relatively technologically intensive, it is often perceived as better than other diagnostic tools, when in fact this is not necessarily the case. Sputum examination is a cheaper alternative in the diagnosis of TB as compared to chest x-rays, but there are problems in this diagnostic tool as well. Many patients have

difficulty giving sputum samples, often giving useless saliva samples instead of sputum. Nevertheless, for those patients that can be diagnosed smear-positive by sputum examination, this proves to be a cheaper alternative to x-rays.

The use of CXRs in those patients who can be diagnosed as smear-positive by a sputum smear represents a superfluous use of this diagnostic tool, and is a sub-optimum use of resources. In ideal circumstances, a chest x-ray in conjunction with a smear test might be an appropriate aid to a clinician seeking extra information in diagnosis, but not in areas that are so financially constrained. Instead, all patients should undergo a smear test before receiving a chest x-ray in order to isolate those patients who have smear-positive TB. Indeed, if these patients can be diagnosed with TB by a smear test, they do not need a chest x-ray to re-determine this. Instead, by using the CXR on suspected smear-negative and extra-pulmonary cases, it can be used more efficiently to determine tuberculosis.

This superfluous use of x-rays on smear-positive patients proves costly. The costs of x-rays has been calculated to be approximately 15.35 birr from estimates of the cost per x-ray in other local hospitals, including film and reagents, doctor costs, technician costs and machine costs (See Table 8-2).

Table 8-2: Total Value of X-Rays from Smear-positive Cases of Tuberculosis at the TB Centre from Available Data Between 1992-1994

Year	Total Smear + Patients	Costs of X- rays	$ US Dollar Value	This Figure in SCC Patients	This Figure in SDR. Patients
1992-1993	2051	31482.85 birr	$4843.52	119	197
1991 quarter	408	6262.80 birr	$963.51	24	39
1993-1994	2113	32434.55 birr	$4989.93	123	203
TOTAL	4572	70180.2 birr	$10796.95	266	439

Considering this, according to Table 8-2, for the cost of these extra x-rays for smear-positive patients, 266 patients could have been treated with SCC and 439 could have been treated under SDR.

Total lost expenditure for x-rays was estimated to be approximately 70 180.20 Ethiopian birr and $10 796.95 US dollars. These figures may seem like a relatively small amount, but they become far more significant when considering that this amount represents 1% of the 1992 drug and medical supply budget for Addis Ababa, 2% of the 1992 drug and medical supply budget for hospitals and health centres in the remainder of the country, or the monthly salary for 87 doctors or 176 nurses.

8-2:2a Smear Microscopy versus Chest x-rays

Indeed, even if smear microscopy proved to be more expensive than chest x-rays, their use would still be justified for the diagnosis of tuberculosis until the cost of the total amount of incorrect diagnoses from x-rays was less than the cost of correct diagnoses with smear microscopy in smear-positive patients. Smear microscopy is an essential method for quickly identifying the most infectious cases of tuberculosis. It is a more effective method by definition in identifying smear-positive cases due to the fact that a decisive x-ray solely for tuberculosis does not exist. Although it could be said that this is especially true in the HIV era where a large proportion of x-rays for TB/HIV co-infected patients prove to be anormal, this is not that relevant when only a very small proportion of TB/HIV patients are smear-positive.

Obviously, smears are extremely important since in order to decrease the transmission of the disease, identifying smear-positive cases as quickly as possible becomes imperative. An x-ray, a smear test and a culture might be very helpful in determining information about a patient's tuberculosis. Nevertheless, in countries as financially constrained as Ethiopia, where drug treatment and health service are unavailable to a large proportion of the population, quick and effective efforts in determining tuberculosis become the focus for diagnosis. The use of several methods to check for false diagnosis and discover information on the overall nature of a patient's TB proves an unaffordable luxury when the need for low cost diagnosis is demanded.

Table 8-3: Activity Report from Addis Ababa Hospitals, 31 May, 1994

	Menilik	Yekatit	Berla	T.A.H.	E.S.C.H.**	Zewditu	Ras Desta
TB Manifestation							
Smear-positive	120	233	2	236	10	50	29
Smear-Negative	243	76	131	207	194	50	51
EP	39	15	11	180	75	28	17
Total	402	324	144	623	279	128	97
Referred Out							
Pilot Area	212	147	26	227	55	12	16
Non-pilot Area	190	94	64	396	247	198	73
Total	402	241	90	623	302	210	89
Admissions	39	43	29		4*	94	29
Under Follow-up		40	54		All	128	
Deaths	3				1	10	8
Sputum Tests							
Total	1027	1286	6	1516	204	569	
For Diagnosis	5		4	1488	204	502	
For Follow-up	1022		2	28		67	

Courtesy of: Region 14 Health Bureau, Addis Ababa

* From SCC Area Only

**E.S.C.H. Refers Patents for their daily treatment, but tracks follow-up for all patients

8-2:3 Other Local Hospital's Diagnostic Procedures

The use of superfluous, automatic diagnostic tests for patients is not just particular to the TB Centre in Addis Ababa. The Black Lion Hospital in Addis Ababa screens suspected patients with a sputum smear, blood test and x-ray. According to the sputum register, a total of 294 of 2294 patients screened had smear-positive tuberculosis (excluding 24 follow-up tests). Considering that blood tests (CBCs) cost 5 birr and x-rays cost 15.25 birr (costs of each procedure are the courtesy of Region 14 Health Bureau in 1994), extra costs for these 294 patients amount to 1470 birr in blood test costs and 4484 birr in x-ray costs. Likewise at the Saqudito Memorial Hospital, of 1400 screened patients, there were 143 smear-positive patients, and their corresponding blood tests amounted to 715 birr and x-rays amounted to 2181 birr. Indeed, the use of smear microscopy will serve to screen out all smear-positive patients, before x-rays and blood tests need to be used to identify smear-negative patients. The amount saved in each hospital would prove to be relatively small, but considering that this is the policy year after year, in just the TB Centre alone, the excess cost from x-rays would amount to 80 000 dollars over ten years if costs remained constant. On a national scale, if an automatic x-ray policy were adopted for all patients, extra costs would be quite significant. Of the 154 000 cases of TB that were predicted to be detected in 1993, if 69 300 (45%) of those were smear-positive, total x-ray costs would amount to 1 056 825 birr. This 1 056 825 birr amounts to 19% of the total drug and supply budget for Addis Ababa, 25% of the budget for hospitals and health centres in the rest of the country, and 6% of the total 1992 budget for drug supplies.

8-2:4 Optimum Screening Procedures for TB

The process of screening TB itself needs to be seriously re-considered. Indeed, the TB Centre screens an incredible number of patients for TB. At the Addis Ababa TB Centre, analysis of over 7 000 x-rays in 1980 found that only 6.5% had cavitary disease. In contrast a total of 72.9% were normal and 13.4% had pulmonary disease of apparently non-tuberculosis origin (Teklu, Bayu and Kassegn, 1982). Using the number of those screened between September 1992 and September 1993 as a per-year estimate of total screening: of those 29 295, 5 353 (18%) had tuberculosis and 23 942 (82%) were non-TB patients. Subtracting an extra generous 10% diagnosis of non-TB pulmonary disease, this leaves a total of 21 547.8 (72%) normal patients who are needlessly screened per year. Indeed, the patient's piece of mind accounts for some benefits in this screening, but this screening represents 323 217 birr in x-rays, and 145 642 birr in smear costs. This method of deciding if a patient has tuberculosis is inefficient as proven by the TB Centre where 72% of those screened proved normal.

The question arises as to how to selectively reduce the large number of those screened for TB each year without jeopardising efforts to find those with tuberculosis. There are several challenges that

arise in trying to achieve this objective: (1) The more patients that are denied TB screening, the more TB patients will not be found for treatment. In essence, some TB patients will slip through the screening matrix. (2) Screening all patients who walk into a health facility represents wasted resources from needlessly screening normal patients. (3) Indescriminantly distributing broad spectrum antibiotics to all patients requesting screening in order to determine if the patient has another pulmonary infections means that 72% of the group are needlessly receiving antibiotics which will contribute to a problem in resistance, especially when considering large numbers such as 20-30 000. (4) In some instances, patients travel long distances to receive treatment and cannot afford long waiting periods before they are diagnosed. At the TB Centre, for example, many patients come from outside Addis Ababa and have no time to sit about and wait to see if antibiotic treatment works or not. They want to be diagnosed for TB right away so that they can be referred for treatment. A delicate balance has to be found between identifying patients that absolutely do not have TB, those patients who are suspected with TB but also might have another infection, and those that most definitely do have TB.

When considering tests in diagnosing patients for TB: (1) patients should have been suffering from a cough for more than 3 weeks or (2) have blood in their sputum as well or (3) fever, malaise and weight loss. Other pulmonary diseases are equally as common as TB and can sometimes be mistaken for it. For example, pneumonia is ranked as the 4th disease seen in health centres and hospitals and therefore, pneumonia is far more likely to be present in patients experiencing symptoms of pulmonary disease than tuberculosis, which is ranked as 12th (see Table 7-4, Section 7-1). Hence, it is just as likely that those showing symptoms of tuberculosis could also have had pneumonia due to an overlapping similarity between some symptoms of the two diseases.

Those individuals initially appearing at a health centre should be carefully considered by doctors when deciding if they are suspected cases of TB. Unfortunately, with a large caseload, such careful consideration is not always possible. Nevertheless, one option is that instead of automatically using diagnostic tests for patients with a cough for more than 3 week, patients would be given only a smear test. If these smears prove to be positive, then the patient would obviously go on to receive treatment. However, if the patient was negative, a broad spectrum antibiotic would be given for 7-10 days and an appointment would made in 2 weeks to look for improvement. Those patients showing no improvement would then be given a chest x-ray. There are obvious exceptions to this procedure. If a patient shows very critical signs of disease, he or she should immediately be screened for TB with all available diagnostic tools. Likewise, those cases where TB strikes or progresses quickly, such as in children and HIV patients, should be immediately screened for TB with both x-rays and sputum microscopy.

The question arises as to the opportunity cost of the money spent on screening such a large proportion of normal individuals for TB. The national cost of screening normal patients in 1993 is staggering as only 28% of patients are found to have TB or some other respiratory disease. If 72% of screened patients are normal, this would amount to 7 484 400 birr ((6.75)[(0.72)(1540000)]) in sputum smears, 5 544 000 birr ((5)[(0.72)(1540000)]) in blood tests, and 16 909 200 birr ((15.25)[(.72)(1540000)]) in CXRs, making a total of 29 947 600 birr, which translates to $4.6 million US dollars per year. This is enough money to treat 113 309 patients or 74% of the total TB case load for 1993 with SCC, and represents 1.5 times the total budget allocated for drugs and medical supplies in Ethiopia in 1992. Indeed, there must be a less costly method of looking at a patient and predicting whether he or she might have tuberculosis, before screening them. Indeed, the number of and cost of screening normal patients is high. If suspected TB patients could be more effectively identified, more funds would be free to treat a greater number of TB patients.

8-2:5 Summary of Section 8-2

The large proportion of patients screened for TB offers an unusually large sample in order to analyse the epidemiological patterns of TB in Ethiopia, including the sex and age structure of those affected by the disease as well smear status. When analysing these data, the diagnostic procedures at the TB Centre come into question due to its automatic use of x-rays for smear-positive patients who could be identified by smear microscopy. This represents a large body of wasted resources. It is significant because such automatic use of x-rays for all suspected TB patients is not just particular to the TB Centre, but is also seen in other hospitals in Addis Ababa. In addition to screening techniques, the process of identifying suspected TB patients is inefficient. As much as 72% of those individuals tested for TB are diagnosed as normal, suggesting a great inefficiency in the use of resources and patient time in these tests. A more standardised efficient procedure needs to be established in screening for TB as well as identifying suspected TB patients, or TB programme resources that could be used more optimally in treatment will continue to be wasted.

Section 8-3

A COST-EFFECTIVENESS ANALYSIS BETWEEN SCC AND THE STANDARD REGIMEN IN THE PUBLIC SECTOR OF ADDIS ABABA

In this section, the question of what impact resistance has on the cost of TB treatment in Addis Ababa is answered in a cost-effectiveness analysis of two treatments for TB: SCC and SDR. As well as presenting the impact of resistance on cost, the impact of drug reactions from HIV, non-compliance to treatment and death are shown. The section begins with a description of the organisation of treatment of TB, incidence of TB, management of drug and laboratory supplies and the process of diagnosis within the public health sector of the city. It then proceeds to describe materials and methods used to perform this study, including the number of patients and health centres that participated in the study and their location. The results of the analysis are then given, including the treatment results of those in both the pilot sample and the non-pilot sample, and an analysis of the components influencing the costs of treatment, including resistance. Here the impact of TB resistance on the cost of TB treatment is assessed. Following this, cost-effectiveness ratios are presented for both the pilot and the non-pilot samples along with an incremental analysis. A sensitivity analysis of those factors affecting these results, including the changes in resistance, are then considered. This is followed by a discussion of treatment, supported by interviews from each health centre that participated in this study.

In 1993, in Addis Ababa, tuberculosis remained the leading cause of death in hospitals and the third largest reason for hospital admissions. Tuberculosis is responsible for 1 500-2 000 deaths per year in the city alone. Epidemiological statistics for Addis Ababa present a grave picture of 3 000-4 000 new cases of smear-positive tuberculosis per year, 6 000-8 000 new tuberculosis cases per year, and a 13 200-17 600 total case prevalence of TB per year. Past tuberculosis treatment in the city has been relatively impotent in treating tuberculosis. Treatment was crippled by the fact that the burden of treatment was thought solely to be the task of the Tuberculosis Training and Demonstration Centre in Addis Ababa. Efforts to rectify this problem by putting more of the responsibility of the treatment and follow-up of patients on the health centres and providing each of them with their own laboratory for sputum smear microscopy were wholly ineffective due to poorly designed referral systems and ill defined health regions. To improve this situation, a pilot programme was developed using short course chemotherapy with three years of support from the WHO emergency fund. Likewise, six months later, a non-pilot programme in the remaining regions was initiated for the standard regimen.

8-3:1 The Pilot Programme

In September 1994, the tuberculosis pilot programme was 14 months old, and operating in five hospitals, seven health centres, and one clinic covering 8 woredas (areas). The goal of the programme was to achieve a cure rate of 85% of all smear-positive cases. From each pilot area, one doctor, one nurse and one lab technician were trained for one week as tuberculosis co-ordinators.

It is hoped that this programme can be replicated in the remaining non-pilot health centres covering 20 woredas (areas). The current woredas were chosen for the pilot programme on the basis that they were the most populated areas and would take the greatest case load. Patients are placed on short-course chemotherapy if they are diagnosed as smear-positive and they are placed on the standard drug regimen if they are diagnosed as smear-negative or extra-pulmonary tuberculosis. Short course chemotherapy consists of a two-month intensive phase treatment with pyrazinamide, streptomycin, rifampicin and isoniazid and a continuous phase treatment with isoniazid and thiacetazone or 'TB450' (2SHRZ, 6TH). Severe shortages of drugs were reported in these areas, previous to this study. However, the National Leprosy and Tuberculosis Control Programme, Christian Relief and Development Association, the Goal and Italian Cooperation Tuberculosis Control have been instrumental in helping to secure drugs.

8-3:2 The Non-Pilot Programme

In order to better facilitate the treatment of tuberculosis in the non-pilot areas, a tuberculosis programme had to be established in the remaining 20 areas of Addis Ababa. This became the non-pilot Programme which offers standardised tuberculosis treatment of SDR to patients living in non-pilot areas. Like the pilot programme, one doctor, one nurse and one lab technician were chosen as tuberculosis co-ordinators from each area and were sent on a training course.

Primarily the standard drug regimen is given in the non-pilot programme, and it consists of a two-month long intensive-phase treatment with streptomycin, isoniazid and thiacetazone and a 10-month continuous phase treatment with isoniazid and thiacetazone, 'TB450' (2STH/10TH). The programme is designed so that all patients receive the standard drug regimen regardless of their smear classification. Ethambutol is substituted for thiacetazone in all cases of adverse drug reactions or those patients suspected as likely to have a reaction (usually suspected TB/HIV co-infected cases). Short-course chemotherapy is very rarely administered as the drugs are difficult for these non-pilot health centres to obtain.

8-3:3 Detection Rates, Incidence and Prevalence

The programmes report an 85% detection rate, which is quite high. Part of this high rate of detection could be due to the fact that health service coverage is low and facilities for treating tuberculosis in rural areas within a reasonable travel distance are inadequate. Hence, many travel from outside of the city to receive treatment, making the detection rate seem artificially high. Ignoring this urban bias, real detection rates are more inclined to be 50%. This is likely to be true when even considering that there might be more cases in Addis Ababa because of such a high population concentration (which allows the disease to spread more easily). As shown in Tables 8-4 and 8-5, the total population that these health facilities cover is 2 451 493. This gives a total incidence in this area of 13 074. Hence, there are 436.8 reported cases per 100 000. This means that there is a 0.44% incidence of detected cases per 100 000 population and a 0.88% prevalence of detected cases per 100 000 population. The real incidence is estimated to be twice these values, assuming a detection rate of 50%.

Table 8-4: Estimated Epidemiological Indices in the Non-Pilot Woredas (Areas) in 1994

Health Centre/Clinic	Population	Smear-positive Cases	Smear-negative Cases	Incidence	Prevalence
Arada	70 783	86	103	189	378
T/Haimanot e	103 571	125	150	275	550
Addis Ketema	121 438	147	176	323	646
	97 612	118	142	260	520
TB Centre	118 976	144	173	317	634
Gefersa	91 546	111	133	244	488
Gulele	66 930	81	97	178	356
	92 594	112	134	246	492
Kazanchis	86 056	104	125	229	458
Yeka	81 164	98	118	216	432
Higher 17	114 984	139	167	306	612
Higher 19	86 675	105	126	231	462
Kirkos	118 127	143	172	315	630
Lideta	51 101	62	74	136	272
Higher 23	93 120	113	136	249	498
	113 609	137	164	301	602
Kolfe	75 667	92	110	202	404
Akaki	94 011	114	137	251	502
Kality	57 538	70	84	154	308
Kotebe	31 647	38	46	84	168
Total	1 767 149	2 139	2 567	4 706	9 412

*Some health centres and clinics function for two areas, running a non-pilot programme and a pilot programme: this is the case for K19

Table 8-5: Estimated Epidemiological Indices in the Pilot Woredas (Areas) in 1994*

Health Centre/Clinic	Population	Smear-positive Cases	Smear-negative Cases	Incidence	Prevalence
Arada	55 341	70	84	154	308
T/Haimanot and Beleteshchew	111 830	135	162	297	594
Shiromeda and Entoto	106 236	129	155	284	568
Entoto No. 1	67 666	82	98	180	360
Higher 13	84 865	103	124	227	454
Baata and Zewditu Hospital	86 536	105	126	231	462
Higher 18	74 406	90	108	198	396
Higher 19	97 464	118	142	260	520
Total	684 344	832	999	1 831	3 662

*Some health centres and clinics function for two areas, running a non-pilot programme and a pilot programme: this is the case for Higher 19

8-3:4 Drug and Laboratory Supplies in the Non-Pilot and Pilot Areas

The amount of drugs consumed in the pilot programme is shown in Table 8-6. From this table, a large deficit can be observed between projected demand and the actual amount of TB drugs consumed. The proportion of drugs actually consumed outweighs the projected amount by a very large margin in all but three cases. It seems that the supply of HT combinations is not as much a problem as other drugs, possibly due to their lower cost. Also of note is that only a very small proportion of projected consumption of $R_{300} + H_{150}$ was consumed. This is possibly due to the fact that a majority of patients are under weight and are given the $R_{150}+H_{100}$ dosage instead of the expected $R_{300}+R_{150}$ dosage. The largest deficit was for ethambutol. This is attributed to an unexpected low intolerance to thiacetazone whereby ethambutol had to be substituted in many patients.

Table 8-6: Consumption of Drugs as a Proportion of Projected Consumption in the Pilot Programme

Serial Number	Item	Quantity Received (Tins)	Consumed (Tins)	Amount Consumed as a Percentage of Estimated Consumption	Estimated Consumption (Tins)
1	$R_{300} + H_{150}$	1152	250	27.74%	901
2	$R_{150} + H_{100}$	1203	962	751.56%	128
3	Z	233	202	104.66%	193
4	S	1177	911	108.45%	840
5	E	189	163	776.19%	21
6	HT	529	484	98.17%	493
7	$H_{100}+T_{150}$	140	9	14.28%	63

Courtesy of: Region 14 Health Bureau, Addis Ababa

In the non-pilot programme, drug consumption was again projected in a 6 month balance sheet, as seen in Table 8-7. As can be observed in this table, actual drug consumption was observed to be much

higher than what was projected for Streptomycin, but lower for HT and the paediatric combination of $H_{100}+T_{50}$.

Table 8-7: Consumption of Drugs as a Proportion of Projected Consumption in the Non-pilot Programme

Serial Number	Item	Quantity Received (Tins)	Consumed (Tins)	Amount Consumed as a Percentage of Estimated Consumption	Estimated Consumption (Tins)
1	S	1412	649	110.75%	586
2	HT	-	238	67.61%	352
3	$H_{100} + T_{50}$	-	2	7.69%	26

Courtesy of: Region 14 Health Bureau, Addis Ababa (unpublished)

The anticipation of future drug supplies has been calculated from the estimation of past cases. Future drugs needed for one year are calculated from Table 8-8. As can be observed, current stocks only represent 13-42%, leaving 58-87% yet to be obtained.

Table 8-8: Estimated Anti-TB Drug Requirement for 1995

Serial Number	Item	Current Stock	Quantity Required for the Next Year	Estimated Difference
1	$R_{300} + H_{150}$	902	313	589 (65.30%)
2	$R_{150} + H_{100}$	241	1200	959 (79.91%)
3	Z	31	252	221 (87.70%)
4	S	266	1138	872 (76.63%)
5	E	86	205	119 (58.05%)
6	HT	125	505	380 (75.25%)

Courtesy of: Region 14 Health Bureau, Addis Ababa (unpublished)

Table 8-9: Laboratory Supplies Issued in Addis Ababa, Health Region 14 According to a 6-month Review

Item	Quantity Received	Pilot	Non-Pilot	Total	%
Sputum Cups	7976	4670	2050	6720	84.53%
Solution A (500ml)	123	74	32	106	86.18%
Solution B (500ml)	108	52	25	77	71.30%

Courtesy of: Region 14 Health Bureau, Addis Ababa

8-3:4a Laboratory Supplies

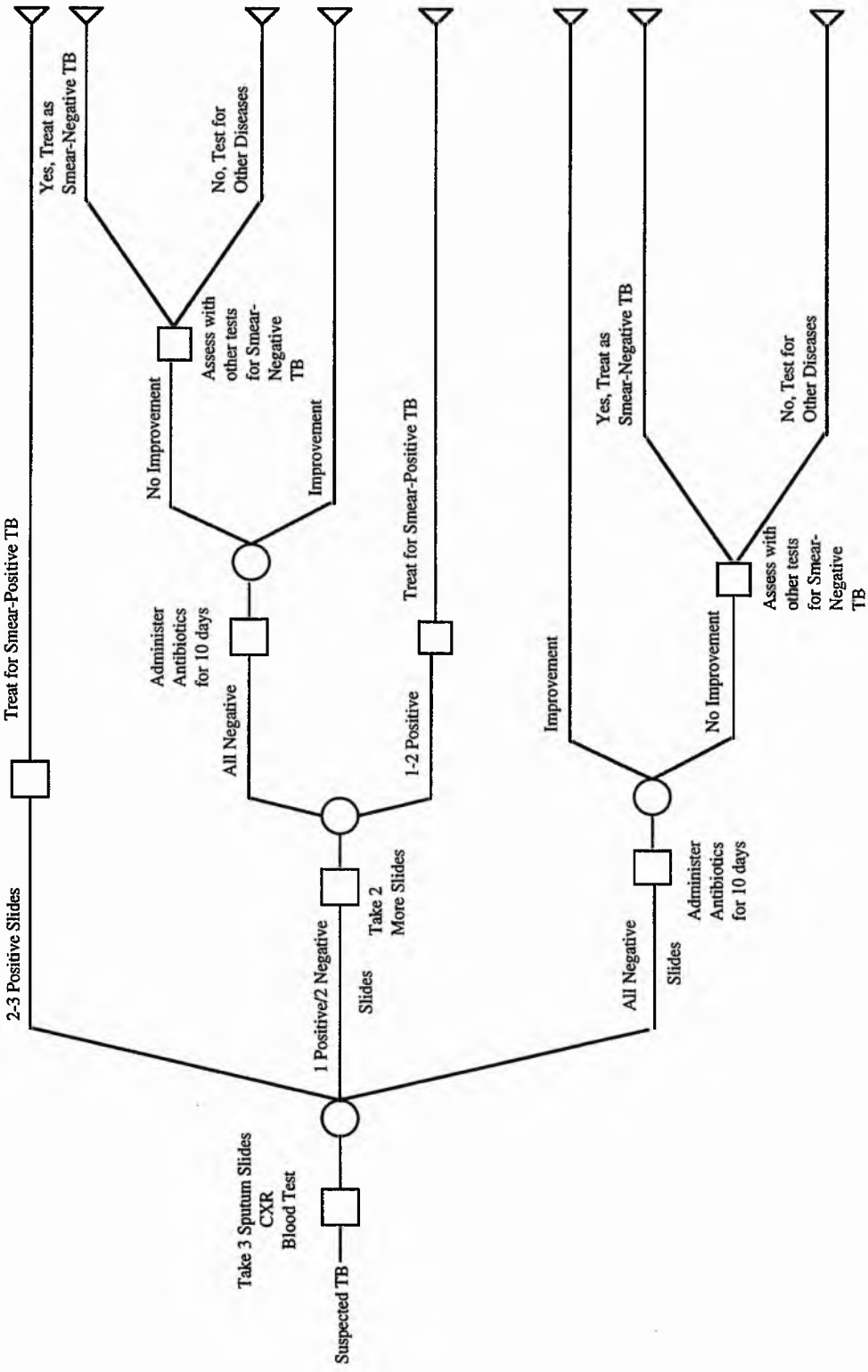
A consistent store of laboratory supplies is essential in the proper diagnosis of smear-positive tuberculosis cases. In the pilot and non-pilot Areas, between 71-80% of laboratory supplies received were used as depicted in Table 8-9. The extra 20-30% accounts for a buffer to meet any unexpected

arising laboratory supply needs. Nevertheless, there are still some problems in obtaining some of the necessary supplies such as the diamond pencil.

8-3:5 Treatment and Diagnosis of Patients

The majority of patients in the health centres and clinics (approx. 85%) are diagnosed at hospitals in Addis Ababa and then referred to the health centre or clinic closest to the patient's house. In contrast, only a small percentage are diagnosed in the health centre. If a patient comes to the hospital complaining of a persistent cough for three weeks or more, he or she is given a blood test, a chest x-ray, and a sputum smear test. Patients are classified according to how many sputum tests out of three are positive: (1) 2 or more positive smears, (2) 1 positive smear, or (3) all three negative smears, as shown in the diagnosis algorithm in Figure 8-16. Those in group (1) who have at least two positive sputum tests are assumed to be sputum positive and are referred to their nearest health centre or clinic for treatment. Here, he or she receives an 8-month or 12-month treatment depending on whether their area is designated as pilot or non-pilot.

Figure 8-16: Algorithm of TB Diagnosis



Those patients in group (2), with only one positive sputum slide, are given two more sputum tests and are considered sputum positive if one or more of these subsequent tests is positive. If these subsequent tests prove to be negative, the patient is then sent away and given general antibiotics for 10 days. An appointment is made for the patient to be seen again after 2-4 weeks where if he or she has not improved and still has one or more positive sputum smears, he or she is treated as a smear-positive patient. In contrast, if this patient is still negative but has not improved, then he or she undergoes a chest x-ray if he or she has not already had one and with other clinical support, the likelihood of the patient having TB is evaluated. Lastly, those patients in group (3), who have three negative sputum smears, are classified as smear-negative, and as in group (2), are given antibiotics for 10 days and then reviewed after 2-4 weeks. If they do not responded to the antibiotics, they are then given another 3 sputum smears and if one or more is positive, they are classified as a smear-positive patient. Again, if the patient is still sputum negative, his or her chest x-ray is examined and together with other clinical evidence, it is decided as to whether the patient has smear-negative TB or another illness.

8-3:6 Methods for Analysis

A sample size of 1 504 TB patients was observed from 6 non-pilot health centres, 6 pilot health centres and one health centre that included both a pilot and a non-pilot programme. Non-pilot health centres included Kolfe Health Centre, Kazanchis Health Centre, Addis Ketema Health Centre, Kefetegne 17, Kefetegne 23 and Kefetegne 19. The pilot health centres were Kefetegne 18, Kefetegne 19, Kefetegne 13, Entoto Health Centre, Tekelhamanot Health Centre and Shiromeda Health Centre. These health centres serve a total of approximately 1 178 101 million people.

Information on the course of each patient's treatment was recorded from tuberculosis record books and treatment cards at each health facility in August and September of 1994 (See Appendix D for patient recording forms). Patients were identified according to the treatment regimen that they received: SCC, SDR, retreatment or isoniazid-ethambutol regimens. These patient's response to treatment was subsequently recorded according to 5 categories: cured, defaulted, death, drug reaction or bacteriologically positive (BAC^+). From this, a cure rate was established for those patients receiving SCC in the pilot areas and SDR in the non-pilot areas.

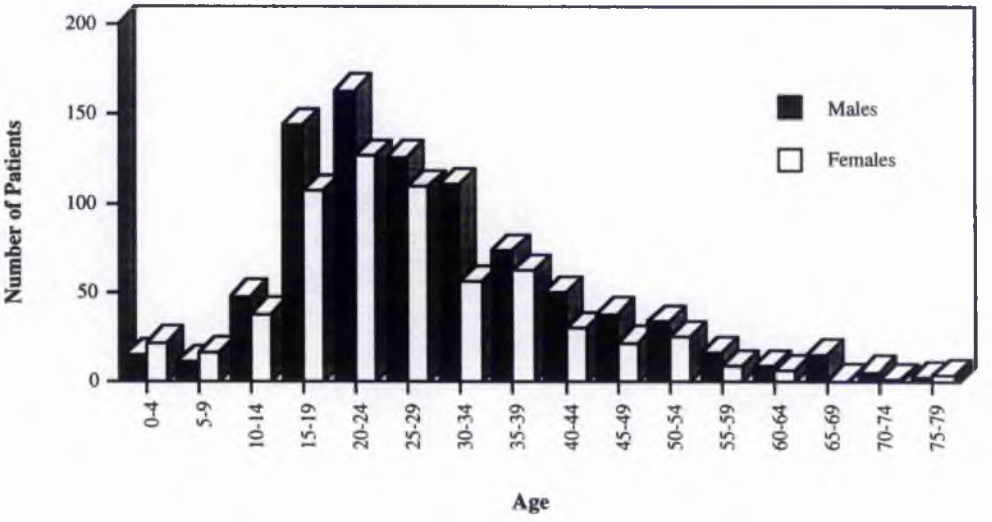
All costs relevant to each treatment regimen in each area were gathered with the co-operation of the epidemiology department of the Region Health 14 Bureau, responsible for health administration and support in Addis Ababa. These costs were then used in conjunction with the cure rates to calculate the cost-effectiveness of the treatments in terms of cost per cure. In addition, the cost per death averted and the cost per life year saved were also calculated.

8-3:7 Results

8-3:7a Non-Pilot Area

In the non-pilot group, 632 patients were studied of which 384 (60.76%) were male and 248 (39.24%) were female, with an average age of 29 years, as illustrated in Figure 8-17. Out of this sample, 233 (36.87%) were smear-positive, 328 (51.90%) were smear-negative, 67 (10.60%) had extra-pulmonary tuberculosis and 1 (0.16%) had both pulmonary and extra-pulmonary tuberculosis, leaving the smear classification of 7 (1.10%) unknown. Also, 37 (5.85%) died, 98 (15.51%) defaulted from treatment, and 62 (9.81%) transferred out. All but 95 (12.03%) patients were placed on a standard regimen of 2STH/10TH. 76 patients were placed on Isoniazid-Ethambutol instead of Isoniazid-Thiacetazone (2SHE/10HE), 8 were on short-course chemotherapy, and 11 were on a retreatment regimen. A further 20 (3.16%) suffered adverse drug reactions primarily to thiacetazone.

Figure 8-17: Known Age and Sex Distribution of TB Patients in Addis Ababa Pilot and Non-Pilot Areas (N=1499)



8-3:7b Pilot Area

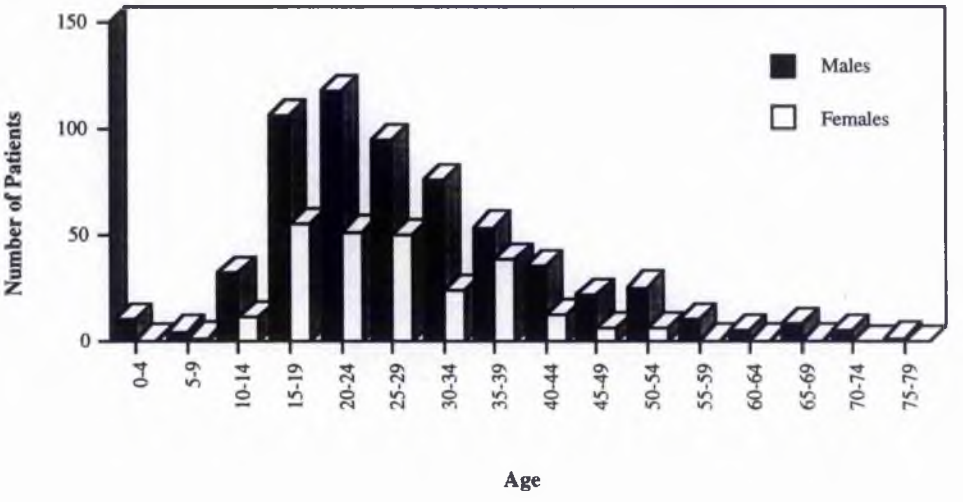
Similarly, in the pilot group, 872 patients were studied, with an average age of 27 years, with 481 (55.16%) males and 390 (44.72%) females. Out of this sample, 402 (46.10%) were smear-positive, 375 (43.00%) were smear-negative, 94 (10.78%) were extra-pulmonary, 2 were both extra-pulmonary and pulmonary (0.23%), and in 6 (0.69%), classification was unknown. Instead of the short course or standard regimen, there were 40 (4.59%) on Isoniazid-Ethambutol (HE) instead of Isoniazid-Thiacetazone (TB450) and 4 (0.46%) on Isoniazid-Rifampicin instead of Isoniazid-Thiacetazone. A further 8 (0.92%) patients were on a retreatment regimen.

As shown in Table 8-10, of the total patients, there were 60 (6.88%) deaths, 116 (13.30%) defaulters and 47 (5.39%) transfers. 47 (5.39%) experienced drug reactions primarily to thiacetazone.

Table 8-10: Results of Patient Treatment

Category	Pilot #	Pilot %	Non-Pilot #	Non-Pilot %
Total Number	N=872		N=632	
Mean Age	27.46		28.73	
Total Males	481	55.16%	384	60.76%
Total Females	390	44.72%	248	39.24%
Smear-Positive (P+)	402	46.10%	233	36.87%
Smear-Negative (P-)	375	43.00%	328	51.90%
Extra-Pulmonary (EP)	94	10.78%	67	10.60%
P & EP	2	0.23%	1	0.16%
Unknown	6	0.69%	7	1.10%
Deaths	60	6.88%	37	5.85%
Default	116	13.30%	98	15.51%
Transfers	47	5.39	62	9.81%
HE Continuous Phase	40	4.59%	76	12.03%
SCC in Non-pilot Area			8	1.26%
HR Continuous Phase	4	0.46%		
Drug Reaction	47	5.39%	20	3.16%
Retreatment	8	0.92%	11	1.74%

Figure 8-18: Age and Sex Distribution of Smear-Positive Patients in Addis Ababa



8-3:7c Ethambutol Substitution for Thiacetazone (HT-HE)

The high percentage (12.03%) of those patients placed on HE treatment in the non-pilot area as compared to the pilot area could account for the lower number of drug reactions to thiacetazone observed in the non-pilot (3.16%) as opposed to the pilot area (5.39%). Those patients initially placed on HE or HR treatment suggests the amount of patients suspected or known to be HIV-seropositive.

Clinical evidence shows that HIV patients are far more likely to have an adverse drug reaction to Thiacetazone than those who are HIV-seronegative (Kelly *et al.*, 1994). Thiacetazone, although a relatively cheap drug, is not an effective drug in the treatment of patients who are HIV-seropositive. Some of the doctors in Addis Ababa that were interviewed thought that Ethiopians in general could not tolerate thiacetazone, but in actuality, HIV patients cannot tolerate it, influencing the perceived tolerance of the total population. Nevertheless, little is known about the number of the TB/HIV co-infected patients in this sample because HIV screening is not only too expensive, but also would place a further stigma on TB treatment, making it appear a completely AIDS-related disease. Such a stigma would hamper case-finding in TB because patients would be inclined to wait until their TB was quite life-threatening before risking or being forced into the perceived disgrace of treatment.

8-3:7d Age Correlation with Productivity

Looking at the respective average ages of 27 and 29 for the pilot and the non-pilot programmes in addition to the overall age distribution (see Figure 8-17) would suggest that TB strikes those in Addis Ababa at their most economically productive stage of life: a time when they are expected to raise children and act as community leaders in society. Figure 8-18 clearly illustrates that the highest age range for TB occurs in the age-group between 15-24 years, followed by 25-34 years, 35-44 years and 45-54 years. TB is clearly an illness that primarily strikes between the ages of 15-55. Several reasons could be attributed to this such as BCG effectiveness in childhood, greater accessibility to the health care system increasing detection and undoubtedly, tuberculosis's association with AIDS in this age group.

8-3:8 Results of Smear-Positive Cure Rates between SCC and SDR

There were 233 smear-positive cases of tuberculosis in the non-pilot study. Of these, 34 (14.59%) had not finished treatment, 5 (2.15%) were on SCC chemotherapy and 19 (8.16%) were on isoniazid and ethambutol instead of TB450, 19 had transferred (8.16%) and 1 (0.43%) was on a retreatment regimen. This left a total of 155 (66.52%) patients on SDR whose results of treatment were known. Of these 155, 10 (6.45%) died, 47 (30.32%) defaulted, 0 were bacteriologically positive (failures), and 7 (4.52%) had adverse drug reactions primarily to thiacetazone. This left a cure rate of 91 (58.70%) not including those in the default group who were cured and 105 (67.74%) including those in the default group who were cured.

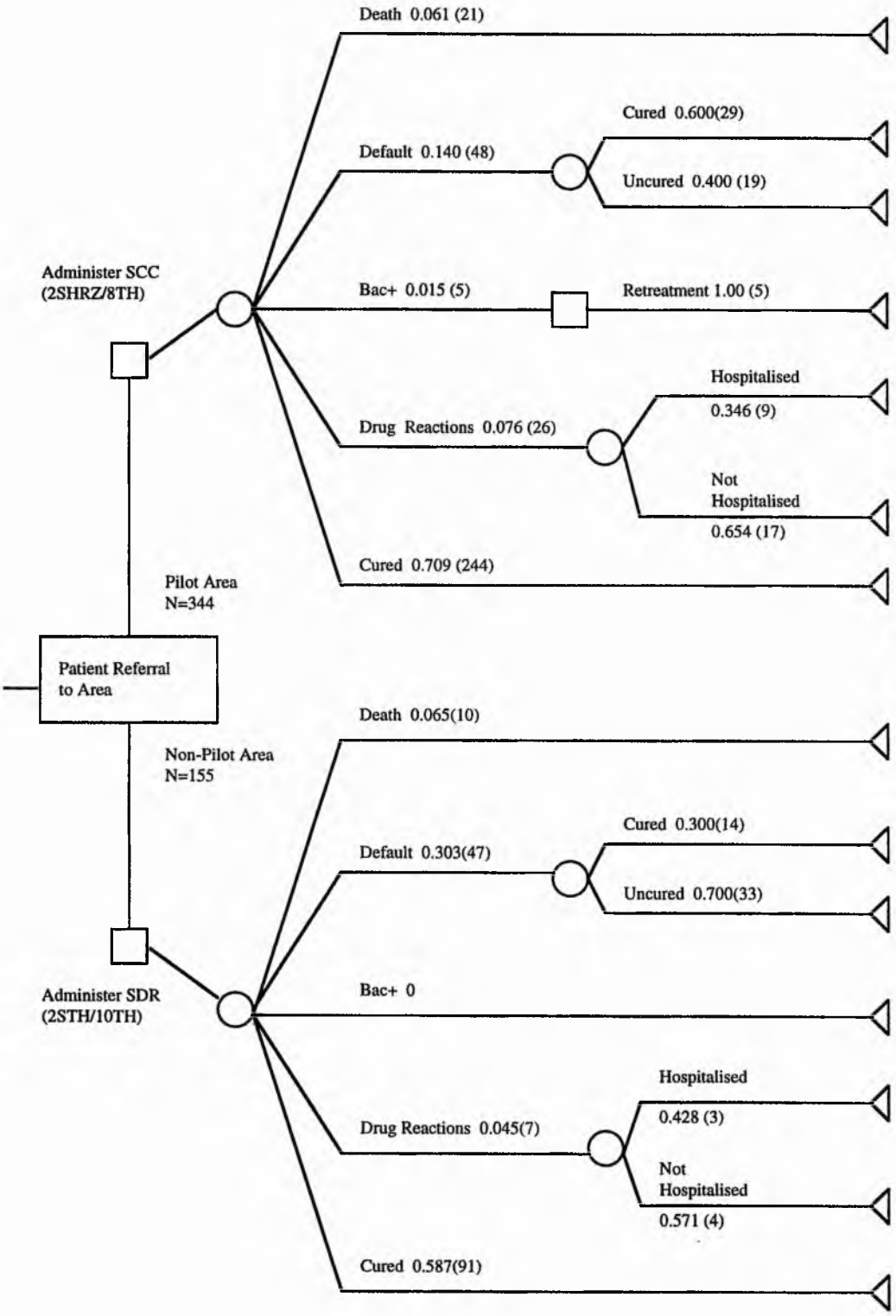
In the pilot Group 402 patients were smear-positive. Of these patients, 9 (2.24%) were unfinished with treatment, 23 (5.72%) were on isoniazid and ethambutol instead of TB450, 2 (0.49%) were on isoniazid and rifampicin instead of TB450, 19 (4.73%) transferred to other areas, and 5

(1.37%) were on a retreatment regimen, leaving 344 (85.57%) smear-positive patients on SCC who had finished treatment. In these 344 patients, 21 (6.10%) died, 48 (13.95%) defaulted, 5 (1.45%) were bacteriologically positive, and 26 (7.59%) had adverse drug reactions primarily to thiacetazone. From this, 244 (70.93%) were cured, not including those in the default group, and 273 (79.36%) patients were cured, including those in the default group. Cured patients in both the SCC and SDR samples were defined as having completed treatment with a follow-up smear to verify conversion, although a follow-up smear could not be obtained for some patients in this group. Results of treatment are shown in Table 8-11 (See Appendix A for all data for Non-Pilot and Pilot Groups).

Table 8-11: Results of Smear-Positive Treatment

Category	Non-pilot # (SDR)	Non-pilot %	Pilot # (SCC)	Pilot %
	N=233		**N=402**	
Smear-positive	233		402	
Smear-positive on SCC/SDR regimens with known results	155	66.52%	344	85.57%
Unknown	34	14.59%	9	2.24%
HE Treatment	19	8.16%	23	5.72%
SCC Treatment (in non-pilot Areas) HR Treatment (in pilot Areas)	5	2.15%	2	0.49%
Transfers	19	8.16%	19	4.73%
% Transfers Uncured	0.33(19)= 6.27 0.7(6.27)= 4.39	1.88%	0.33(19)= 6.27 0.7(6.27)= 4.39	1.09%
Retreatment Cases	1	0.43%	5	1.37%
		L_d=155		**L=344**
Death Rate	10	**D_d=6.45%**	21	**D=6.10%**
Default Rate	47	30.32%	48	13.95%
% Defaulters Uncured	0.7(47)=32.9 ≈33	**F_d=21.29%**	0.4(48)=19.2 ≈19	**F=5.52%**
Bac.+ (Failures)	0	**B_d=0**	5	**B=1.45%**
Drug Reactions	7	**R_d=4.52%**	26	**R=7.59%**
Cure Rate w/o added default calculations	91	58.70%	244	70.93%
Cure Rate inc. Default % Cured	**N_d=105**	**67.74%**	**N=273**	**79.36%**

Figure 8-19: The Algorithm of TB Treatment in Both the Pilot and Non-pilot Areas



8-3:9 Differences Between Treatment Groups Determining Smear-Positive Cure Rates

Cure rates were estimated to be 74.40% for SDR and 85.84% for the SCC treatment. The difference in these cure rates was thought to be primarily dependent on the high rate of default experienced in the standard regimen. Figure 8-19 shows the algorithm for treatment of smear-positive patients in both the pilot and the non-pilot group. Most default occurred after two months and therefore, for this analysis, this was the time estimated for all defaulters. As taken from Murray, Styblo and Rouillon, (1993) after two months, 40% of defaulters were assumed uncured for SCC and 70% of defaulters were assumed uncured for SDR.

Most treatment results are a reflection on the ability of SCC to decrease default. Default rates in this study were much higher for SCC and much lower for SDR than past studies (Murray *et al.*, 1991; Arandottir, 1993; Kamolratanakul, 1993). However, this is an unusual case where both of these studies were performed in the same environment. As suspected in Murray *et al* (1991) and Kamolratanakul (1993) where SCC results appeared to be taken from a very controlled atmosphere, likely to have been run by an NGO and then compared to an SDR programme that was run on a wider scale for a longer time by each country's ministry of health. Unlike these, results for SCC and SDR came from a programme implemented in the same area, in identical facilities by the same body. Hence, cure rates are closer.

8-3:10 Costs

Costs of both the pilot and the non-pilot treatments were calculated from all stages of treatment and diagnosis. Costs included variable costs, such as labour, supplies, stationary and drug costs, and fixed costs, such as equipment and buildings. Costs were derived from the laboratory costs, drug costs, nursing time, doctor time, technician time, pharmacist time, administration time, screening costs and administration. As is illustrated in Table 8-12 treatment costs were divided into categories. Screening costs were calculated from the fact that only approximately 10% of 15 040 of those screened actually had TB and approximately half of these were smear-positive (See Appendix B for a more thorough description of costs). Indirect costs represent the total cost of death from lost earnings, assuming an average age of 27 and a daily wage of 3 birr. This was thought to be a fair assessment because a proportion of patients were employed. Of 201 recorded patients at K19, 32% were employed whereas 68% were unknown. The cost in lost earnings were subsequently expressed as indirect costs in the total cost of deaths. The average incremental cost was estimated as the sum of variable and fixed costs divided by the total number of patients treated.

All but one serious drug reaction proved to be exfoliative dermatitis to thiacetazone rather than other adverse reactions, (one case was isoniazid hepatitis). For this reason, in the analysis, all drug

reactions were assumed to be reactions to thiacetazone in TB450. The cost of drug reactions was calculated from the cost of prednisolone and chlorpheniramine treatment, the cost of switching over a patient to HE instead of TB 450, and the cost of hospital treatment in approximately 33% of cases. This value was then multiplied by the number of drug reactions and then divided by the total number of patients cured.

8-3:10a Overview of Costs

In looking at Table 8-13 of costs, one can note that the highest cost is from death, however, a high proportion of costs are determined by labour, screening and drugs. Because of daily streptomycin injections for the first two months and the fact that there are nurses and health assistants who solely work in tuberculosis, labour costs are high. In addition, is the cost of screening per smear-positive patient. These costs reflect that only approximately 10% of those patients screened for tuberculosis actually have the disease and even fewer are smear-positive. Finally, as mentioned before, the major differences in costs between treatments are dependent on the cost of each drug regimen and the cost of retreatment for defaulters. Variables that will be the primary determinants of the cost-effectiveness of each will depend on drug costs and rates of default.

8-3:11 The Impact of TB Resistance on the Cost of TB treatment

All smear-positive defaulters either remain infectious, die or seek retreatment. In this analysis, it was assumed that all defaulters would seek retreatment. Defaulters were assumed to be isoniazid susceptible so that TB450 could be used in their retreatment regimen. The cost of H-susceptible retreatment was 434.55 birr in drugs making a total cost of 790.69 birr. Therefore, retreatment costs were calculated by multiplying the cost of retreatment per patient with the number of defaulters and dividing this by the number of patients cured.

For the non-pilot group, no bacteriologically positive cases were found, but 5 cases (1.45%) in the pilot group were BAC^+. This is possibly because of the fact that some chronic cases do not always reveal the fact that they have received prior treatment, and since until recently, record keeping was less than ideal, these patients' treatment is difficult to document. Chronic cases are usually defaulters who begin treatment and then stop it when they feel better. Hence, these cases can move from facility to facility receiving some treatment and then disappearing (for instance to the country), only to reappear when their TB again becomes a problem. There is also the potential for chronic patients to be incorrectly referred to SCC instead of a retreatment regimen. In addition, the smear-positive sample in the pilot region was over twice the size of the non-pilot region, partially accounting for the fact that more resistant cases were found.

Retreatment costs for bacteriologically positive patients were estimated by multiplying the cost per case of retreating BAC^+ cases with the number of BAC^+ patients and subsequently dividing this figure by the number of patients cured. Those who were bacteriologically positive were assumed to be at least resistant to isoniazid because of repeated supervised treatment with no result. The cost of treating these drug resistant patients was higher than H-susceptible treatment due to the fact that more expensive drugs had to be used. The cost of the H-resistant retreatment regimen was estimated to be 603.38 birr in drugs and 959.52 birr in total cost. The treatment of these patients included 90 days of R, H, Z, E and S and then continued with R, H and E for a further 64 days. H-susceptible retreatment drug regimens cost 60% more than SCC. However, more significantly, the cost of and H-resistant regimens cost 378.05% of SDR and 228.29% of SCC. Hence, in terms of drugs costs, for every one resistant TB case that is treated, 3.78 SDR patients and 2.28 SCC patients could be treated. In terms of total treatment, excluding screening and fixed costs, 5.70 SDR patients and 3.52 SCC patients could be treated for the cost of treating one drug-resistant patient. In some cases, not only are more drugs required, but more expensive drugs are required, depending on the drug that a patient's TB becomes resistant to. In many cases, regimens in Ethiopia use cheaper drugs such as thiacetazone, streptomycin and isoniazid to treat susceptible cases, leaving only more expensive drugs to treat resistant TB cases.

In addition to this are the costs from past treatment where TB resistance originated (assuming secondary resistance) and costs from increased deaths from resistant TB cases. The time a patient stops treatment and develops resistance is variable as is the number of treatment regimens that he or she receives before developing resistance. However, assuming a patient defaults from treatment after two months and then must receive a retreatment regimen, the cost of treating this patient not only includes the retreatment regimen, but also the forgone costs of the initial treatment when the patient was first diagnosed. For this case, forgone drug costs of the initial treatment would be an extra 147 birr for SDR and 258 birr for SCC.

It is difficult to assess the death rate from resistance to various drugs, but it is known that combined resistance to R and H has a 40-60% death rate associated with it according to Bloom and Murray (1992). Assuming a 50% death rate from multi-drug resistance, if in this study there was the hypothetical scenario where all cases were multi-drug resistant, the total cost of death would become 7.75 and 8.91 times the total cost of death observed from susceptible SDR and SCC cases in this study (SDR: [(155/2)44844]/448440 = 7.75) (SCC: [(344/2)44844]/941724 = 8.91).

In summary, the impact of each resistant case is such that it raises TB treatment cost to at least 3.52-5.70 times the treatment of susceptible TB, depending on the regimen it is compared to (SCC or SDR). This is because of the fact that treatment of TB resistance requires more drugs, more resources and more time.

Table 8-12: A Breakdown of Costs for SDR and SCC in the Non-Pilot and Pilot Areas (in Ethiopian Birr)

Type of Cost	SDR	SCC
Screening Costs/Smear+ Patient		
microscopy cost	53.49	53.49
lab technician	14.1	14.1
x-ray cost	150	150
x-ray technician	1.88	1.88
x-ray machine	1.71	1.71
Total Cost per Successfully Screened Smear+ Patient	221.18	221.18
Total Screening Costs of Treatment	**S_d=34282.9**	**S=60382.14**
Variable Costs per Patient (excluding screening)		
microscopy	3.08	2.33
drugs	P_d=159.6	P=264.3
printing formats & registration books	1.64	1.64
stationary	2.26	2.26
telephone	0.45	0.45
electricity	0.75	0.75
water	0.45	0.45
Total Variable Costs per Patient	168.23	272.18
Total Variable Costs of Treatment	**V_d=26075.65**	**V=74305.14**
Fixed Costs per Patient (excluding screening)		
microscope	0.82	0.82
labour	41.08	40.14
administration	3.40	3.89
pharmacy administration	0.49	0.49
building cost per patient	2.23	2.23
Total Fixed Cost Per Patient	48.02	47.08
Total Fixed Costs of Treatment	**X_d=7443.1**	**X=12852.84**
Direct Costs (including screening) per Patient	437.43	540.54
Cost Per Death in Lost Earnings	44 844.00	44 844.00
Total Death Cost for all Deaths	**D_{dc}=448440**	**D_c=941724**
Cost of Retreatment for Defaulters		
Drug Cost	434.55	434.55
Total Cost per Retreatment	790.69	790.69
Total Retreatment Costs for all Retreatment Cases	**M_d=26092.77**	**M=15023.11**
Retreatment for BAC^+ (Resistant) Cases		
Drug Cost	603.38	603.38
Total Cost of Retreatment for BAC^+	959.52	959.52
Total Retreatment Costs for all BAC^+ Cases	**B_{dc}=0**	**B_c=4797.6**
Cost of Drug Reactions		
Hospitalisation Cost/Treatment		
HE Drug Substitution Cost	1140.75	1140.75
	4.08	2.04
	(1140)(2.31)	(1140)(8.58)
Total Cost of All Hospitalised Drug Reaction Cases	**R_{hd}=2635.13**	**R_h=9787.64**
	(4.08)(7)	(2.04)(26)
Total Cost of All HE Drug Substitution Cases	**R_{hed}=28.56**	**R_{he}=53.04**
TOTAL COST OF TREATMENT (Including Costs from Default, Death, BAC+ and Drug Reactions)	**C_{SDR}=544998.11**	**C_{SCC}=1118925.51**

8-3:12 Cost-Effectiveness of Treatments

8-3:12a Cost per Cure

The average total cost per cure when using each treatment's respective cure rates, was estimated to be 5190.46 birr (US $798.53) for SDR and 4098.63 birr (US $630.56) for SCC These were calculated from all costs to treatment, and then divided by the number of patients that were cured. The difference between these two ratios represents a 1091.83 birr (US $167.97) difference in cost per cure.

8-3:12b Cost per Death Averted

Data on individuals who have not received treatment before in the modern age in developing countries are sparse. Hence, the cost per death averted was estimated using data from an article by Fox (1990) in India, where 50% of those who never received treatment died. The actual death rate that occurred with treatment in this study was then subtracted from this value in order to obtain the total amount of deaths averted as shown in the following equations for cost per death averted for SCC (CDA_{SCC}) and cost per death averted for SDR (CDA_{SDR}):

$$CDA_{SCC} = \frac{T_{SCC}}{[(.50)(L)] - D_{scc}}$$

Where:

T_{SCC} =Total cost of treating all SCC patients

L =Total Patients Treated

D =Number of patients that died in the SCC sample

$$CDA_{SDR} = \frac{T_{SDR}}{[(0.50)(L_d)] - D_{sdr}}$$

Where:

T_{SDR} =Total cost of treating all SDR patients

L_d =Total Patients Treated

D_{sdr} =Number of patients that died in the SDR sample

Hence, from this, the cost per death averted was estimated to be 8074.05 birr ((544998.11)/(77.5-10)) or $1242.16 US dollars for SDR and 7410.10 birr ((1118925.51)/(172-21)) or $1140.02 US dollars for SCC. The difference in cost per death averted between SCC and SDR is 663.95 birr or US $102.15.

If the hypothetical situation arose whereby all cases were multi-drug resistant, assuming all other variables are held constant, this same analysis above could be used when considering averted deaths

from multi-drug resistance through correct treatment because of the same survival rate associated with both no treatment and multi-drug resistant TB. If the patient develops multi-drug resistance (resistance to both H and R) using a 50% death rate from Bloom and Murray (1992) (the same as untreated TB) one can see that the cost per TB deaths from multi-drug resistance averted through properly implemented SCC and SDR is also approximately 248.61 birr and 663.95 birr, respectively.

8-3:12c Cost per Total Death Averted, Including Transmission

This is the amount of death that would occur if all smear-positive cases in this study were to remain untreated and continue to infect others. According to Murray *et al.* (1991), each smear-positive case will go on to cause 5.6 deaths and 3.8 discounted deaths over a cycle of 18.5 years. The number of patients (defaulters) that would remain uncured and infectious for each treatment was calculated and multiplied by 3.8 and then subtracted from 3.8 times the number of patients that would have hypothetically remained infectious without treatment (subtracting those who died in the sample). To this was added the number of deaths in the sample that were averted (from the previous paragraph). Hence the equations used for calculating cost per death averted for SCC ($CDA_{t_{SCC}}$) and cost per death for SDR ($CDA_{t_{SDR}}$) were the following:

$$CDA_{t_{scc}} = \left[(N - D_{scc})(3.8)\right] - \left[3.8F_{scc}\right] + \frac{T_{SCC}}{\left[(0.50)(L)\right] - D_{scc}}$$

Where:

N =The number of patients cured

D_{SCC} =the number of patients that died in the SCC sample

F_{scc} =the number of patietns that defaulted in the SCC sample

T_{SCC} =the total cost of treating all patients in the SCC sample

L =the total number of patients treated

$$CDA_{t_{SDR}} = \left[(N - D_{sdr})(3.8)\right] - \left[3.8F_{sdr}\right] + \frac{T_{SDR}}{\left[(0.50)(L_d)\right] - D_{sdr}}$$

Where:

N =The number of patients cured

D_{sdr} =the number of patients that died in the SCC sample

F_{sdr} =the number of patients that defaulted in the SCC sample

T_{SDR} =the total cost of treating all patients in the SCC sample

L =the total number of patients treated

According to this, in the non-pilot programme, there would be 493.1 total deaths averted and in the pilot programme, there would be 1306.20 total deaths averted. From this, the total cost per total death averted is 1105.24 birr (544998.11/493.1) (US $170.04) for SDR and 856.63 birr (1118925.51/1306.20) (US $131.80) for SCC.

8-3:12d Cost per Life Year Saved in the Non-Pilot and Pilot Samples

The cost per life year saved was difficult to calculated due to difficulty in establishing a life expectancy for each year of life. Life expectancy is estimated to be between 46 and 53.4 years at the age of birth in Ethiopia in 1992 (World Bank, 1993; Cross and Millar, 1994; Transitional Government of Ethiopia, 1992). For this analysis, it was estimated that by 1994, the life expectancy at birth would be at least 53.

The cost per life year saved was calculated for each treatment according to the potential years of life lost (PYLL), standard expected years of life lost (SEYLL) and the period expected years of life lost (PEYLL). Three approaches were used because no one method seemed to be ideal for the calculation. Cohort expected years of life lost could not be calculated due to problems in getting specific data on cohort age groups of those in Ethiopia. For the PYLL and the PEYLL methods, a potential life expectancy of 53 was used based on lower past estimates by the World Bank and other sources from 1992 (See Table 8-14 for a comparison of life years lost without treatment according to different methods).

With the PYLL method the cost per life year saved was calculated using a fixed life expectancy of 53 for both the pilot and non-pilot area. For the pilot area, a total of 3790 years of life were saved and in the non-pilot area, 1488 years of life were saved. From this, the cost per life year saved was 295.23 birr (US $45.42) for the pilot area and 366.26 birr (US $56.35) for the non-pilot area. SCC is 71.03 birr (US $10.93) less than SDR per life year saved according to the PYLL method.

Table 8-13: Derivation of an Ethiopian Model Life-Table

Age	Female Age Fraction from West Level 26 (A)=Life Expectancy @ Age/82.5	Male Age Fraction From West Level 26 (B)=Life Expectancy @ Age/82.5	Female Ethiopian Life Expectancy Fraction From Graph (C)	Ethiopian Male Life Expectancy Fraction From Graph (D)	Female Ethiopian Life Expectancy (E)=(C)(53)	Male Ethiopian Life Expectancy (F)=(D)(53)
0	0.000	0.000	1.000	1.000	53.000	53.000
1	0.012	0.013	0.992	0.992	52.576	52.576
5	0.061	0.063	0.945	0.942	50.077	49.939
10	0.121	0.125	0.885	0.880	46.891	46.64
15	0.182	0.188	0.824	0.818	43.698	43.334
20	0.242	0.250	0.765	0.755	40.524	40.041
25	0.303	0.313	0.705	0.693	37.370	36.749
30	0.364	0.375	0.646	0.631	34.222	33.463
35	0.424	0.438	0.586	0.570	31.080	30.183
40	0.485	0.500	0.528	0.508	27.965	26.924
45	0.545	0.563	0.469	0.447	24.875	23.698
50	0.606	0.625	0.412	0.387	21.836	20.531
55	0.667	0.688	0.356	0.329	18.868	17.437
60	0.727	0.750	0.301	0.273	15.951	14.449
65	0.788	0.813	0.248	0.219	13.131	11.594
70	0.848	0.875	0.196	0.170	10.407	8.997
75	0.909	0.938	0.149	0.127	7.889	6.738
80	0.970	1.000	0.108	0.093	5.718	4.936

By using the SEYLL method, life lost due to premature death from tuberculosis in the pilot and non-pilot group was found. Years of life lost were calculated by multiplying life expectancy and then subtracting the year of premature death, using increments of 5 as a midpoint. According to the SEYLL method of calculating life lost due to premature death, tuberculosis in this sample was responsible for 3824.61 male and 4051.97 female years of life saved, making a total of 7876.58 years of life saved by SCC. In the non-pilot group, 2015.52 male and 1184.99 female years of life saved gave a total of 3200.51 years of life saved by SDR. This is assuming a 50% death rate from tuberculosis without treatment. From this, the cost per life year saved for SCC is 142.06 birr (US $21.85) and the cost per life year saved for SDR is 170.28 (US $26.20): SCC is 28.22 birr (US $4.34) less per life year saved according to the SEYLL method.

Since there is no current life table specific to Ethiopia, in order to use the PEYLL method, a table had to be derived as shown in Table 8-13. The table was derived by condensing the West Level 26 table to correspond to a life-expectancy of 53. There are undeniably inconsistencies between this table and the morbidity patterns experienced in Ethiopia. Child mortality, for instance, would be much higher than that experienced in many industrialised countries. Nevertheless, in absence of data on life expectancies at each age, this table is the closest representation of the premature burden of death in Addis Ababa because it takes into account the life years lost from the elderly.

Table 8-14: Total Life Years Lost Without Treatment According to PYLL, SEYLL and PEYLL Methods of Calculating Years of Life Lost Due to Premature Mortality

Area	PYLL All	SEYLL Males	SEYLL Females	PEYLL Males	PEYLL Females
Pilot					
Died/ Defaulted /Drug Reactions /Bac+	2449.000	2791.070	2467.450	1762.846	1463.217
Cured	6607.000	6345.59	7212.360	4088.399	4718.049
Total	**9056.000**	**9136.660**	**9679.810**	**5851.245**	**6181.266**
Non-pilot					
Died/ Defaulted /Drug Reactions /Bac+	1501.000	1927.850	1368.130	1310.661	878.917
Cured	2252.000	3152.870	1619.000	2088.750	994.454
Total	**3753.000**	**5080.720**	**2987.130**	**3399.411**	**1873.371**

Using the derived Ethiopian model life-table in Table 8-13, the cost per period expected life year saved was derived (See Appendix E for the derivation of this model life-table). In the pilot region, 2449.33 male and 2587.36 female years of life formed a total of 5036.81 years of life saved. In the non-pilot region, 1348.55 male and 743.17 female years of life formed total of 2091.72 years of life saved. With these values, the cost per period expected life year saved was 222.15 (US $34.18) for the pilot area and 260.55 (US $40.08) for the non-pilot area. The difference between these cost per life years saved is 38.40 birr (US $5.91).

8-3:13 Summary of Cost-Effectiveness Ratio Results

In all cases, cost-effectiveness ratios for SCC were observed to be lower than SDR. As observed in Table 8-15, the largest difference in cost-effectiveness was in the cost per cure followed by the cost per death averted. Cost per life year saved ratios varied between 28.03 and 70.57 according to the method used to measure life years lost due to premature mortality. Difference were attributed to the fact that the number of life years saved in the SEYLL method produced the most years of life lost, followed by the PEYLL method and the PYLL method. All these results, except for the cost per total death averted, were not discounted because tuberculosis treatment is an intervention where the benefits and costs occur immediately.

Table 8-15: A Summary of Cost Effectiveness Between SDR and SCC (Ethiopian Birr)

Cost-Effectiveness Measure	SDR	SCC	Difference	More Cost-Effective Regimen
Average Total Cost per Cure Excluding Cost of Deaths	5190.46 birr	4098.63 birr	1091.83birr US $167.97	SCC
Total Cost per Death Averted				
Per Death	8074.05 birr	7410.10 birr	663.95 birr US $102.15	SCC
Per Total death (including Indirect Death from Smear-Positive Transmission)	1105.24 birr	856.63 birr	248.61 birr US $38.25	SCC
Cost per Life Year Saved of Entire Smear-positive Group				
Potential Years of Life Lost (PYLL)	366.26 birr	295.23 birr	71.03 birr US $10.93	SCC
Standard Expected Years of Life Lost (SEYLL)	170.28 birr	142.06 birr	28.22 birr US $4.34	SCC
Period Expected Years of Life Lost (PEYLL)	260.55 birr	222.15 birr	38.40 birr US $5.91	SCC

8-3:14 Incremental Analysis

A summary of incremental cost-effectiveness ratios are shown in Table 8-16. The differences in cure rates including drug reactions were 11.6% and the difference in total cost was 573927.39 birr. The average cost per patient was 3516.12 for SDR and 3252.69 for SDR. With an incremental analysis, the incremental cost for SCC was estimated to be 3416.23 birr (573927.39/168). This means that each extra cure from the short course regimen costs 3416.23 birr (US $525.57). Incremental cost per death averted of SCC over SDR is 6873.38 (573927.39/83.5); (US $1057.44) and per extra total death averted of SCC over SDR is 705.85 birr (573927.39/813.1); (US $108.59). The incremental cost according to the PYLL method is 249.32 birr (573927.39/2302); (US $38.36), according to the SEYLL method is 122.74 birr (573927.39/4676.07); (US $18.88) and according to the PEYLL method is 194.88 birr (573927.39/2945.09); (US $29.98).

Table 8-16: Incremental Cost Effectiveness of SCC over SDR

Measure	Incremental Cost
Incremental cost per cure	3416.23 birr/US $524.28
Incremental cost per death averted	6873.38 birr/US $1057.44
Incremental cost per total death averted	705.85 birr/US $108.59
Incremental cost per PYLL	249.32 birr /US $38.35
Incremental cost per SEYLL	122.74 birr/US $18.88
Incremental cost per PEYLL	194.88 birr/US $29.98

8-3:15 Sensitivity Analysis

In order to find the sensitivity of these cost-effectiveness results, the cost per cure threshold values were found using the programme Mathcad©, holding all other variables constant using both the equations for calculating the cost per cure ratio for SCC,

$$CE_{SCC} = \frac{S + V + X + D_c + M + R_{he} + R_h + B_c}{L(1.0 - [D + F + B + R])}$$

Where:

S =Total Screening Costs for All patients

V =Total Variable Cost for All Patients

X =Fixed Cost for All Patients

D_C =Total Cost of Deaths

M = Total Retreatment Cost for all Defaulters

B_C =Total Retreatment Cost for All Bac^+ Cases

R_{he} =Total HE Replacement Cost for all Drug Reaction Cases

R_h =Total Cost for all Drug Reaction Cases that Required Hospitalisation

L =Total Number of Patients Treated

D =Death Rate

F =Default Rate

B =Bac^+ Rate

R =Drug Reaction Rate

and the cost per cure ratio for SDR

$$CE_{SDR} = \frac{S_d + V_d + X_d + D_{dc} + M_d + R_{hed} + R_{hd} + B_{cd}}{L_d(1.0 - [D_d + F_d + B_d + R_d])}$$

Where:

S_d =Total Screening Costs for All patients

V_d =Total Variable Cost for All Patients

X_d =Fixed Cost for All Patients

D_{cd} =Total Cost of Deaths

M_d = Total Retreatment Cost for all Defaulters

B_{cd} =Total Retreatment Cost for All Bac^+ Cases

R_{hed} =Total HE Replacement Cost for all Drug Reaction Cases

R_{hd} =Total Cost for all Drug Reaction Cases that Required Hospitalisation

L_d =Total Number of Patients Treated

D_d =Death Rate

F_d =Default Rate

B_d =Bac^+ Rate

R_d =Drug Reaction Rate

Table 8-17: Actual Values and Threshold Variables for SCC and SDR in the Pilot and Non-Pilot Areas

Variable	Actual Value for SCC	Threshold Values for SCC*	Actual Value for SDR	Threshold Values for SDR**
Total Screening Costs for All patients	60382.14	<358451.72	34282.9	>-80359.24
Total Variable Cost for All Patients	74305.14	<372374.72	26075.65	>-88566.49
Fixed Cost for All Patients	12852.84	<310922.42	7443.1	>-107199.04
Total Cost of Deaths	941724	<1239793.58	448440	> 333797.86
Total Retreatment Cost for all Defaulters	15023.11	<313092.69	26092.77	>-88549.37
Total HE Replacement Cost for all Drug Reaction Cases	53.04	<298122.62	28.56	>-114613.58
Total Cost for all Drug Reaction Cases that Required Hospitalisation	9787.63	<307857.22	2635.13	>-112007.01
Total Retreatment Cost for All Bac^+ Cases	4797.6	<302867.18	0	>-114642.14
Death Rate	0.0610	<0.2278	0.0645	>-0.1158
Default Rate	0.0552	<0.2220	0.2129	> 0.0326
Bac+ Rate	0.0145	<0.1810	0.0000	>-0.1803
Adverse Drug Reaction Rate	0.0759	<0.2427	0.0452	>-0.1350

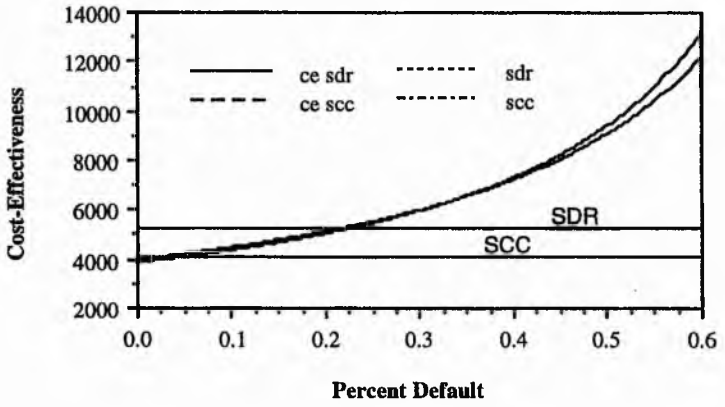
*Values for SCC must remain smaller (<) than these threshold values to maintain cost-effectiveness conclusion
**Values for SDR must remain greater (>) than these threshold values to maintain cost-effectiveness conclusion

In the case of SCC, once variables increase above these threshold variables, SCC will no longer be more cost-effective. Likewise, once values for SDR decrease below the SDR threshold variables, the cost-effectiveness ratio will no longer be valid. As is depicted in Table 8-17, threshold values for SDR are implausible for all but the cost of death per patient cured and the rate of default. For SCC, the only variable that is close to its threshold value is the total cost of deaths (difference of 296 245). The

SCC death rate, default rate, BAC^+ rate, and the drug reaction rate must rise by approximately 16.64% in order to shift the cost-effectiveness ratios to favour SDR in cost-effectiveness.

In order to look at the sensitivity of the cost-effectiveness ratios of both SCC and SDR, these respective variables are compared to those used to calculate cure rates in other studies (Murray *et al.*, 1991; Kamolratanakul, 1993; and Arnadottir, 1992). In these studies, the highest death rate for SCC was 6.5% whereas the lowest was 1.5%, well within the range of sensitivity shown in Table 8-17. For bacteriologically positive cases, the range was 1.3% to 2.4% from other studies, also placing the value in this study well within the range of SCC sensitivity shown in Table 8-17 Side effects for SCC could only be obtained from one study (Thailand) and it was 25%, whereas the value in this study was only 7.59%. However, values above the threshold value of 24.27% for drug reactions would make this cost-effectiveness ratio no longer valid, if all other variables were held constant. The rate of default found in differing studies ranged between 2.2% and 25%. As the SCC rate of default in this study needs to rise above 22.20% to no longer be cost-effective, a 25% default rate would make the cost-effectiveness ratio of SCC more than SDR. For SDR, the only cure rate variable that its cost-effectiveness ratio could possibly be sensitive to was the default rate. Ranges for the literature place default at between 15.7% and 73%. As the threshold value for SDR default must fall below 3.26% to become more cost-effective than SCC and the actual default rate was 21.29%, this is considered well within the limit of the given range from the literature. The rate of default in patients for both the SCC and SDR sample as a function of cost per cure are shown in Figure 8-20.

Figure 8-20: Default of SCC and SDR as a Function of Cost-Effectiveness



In looking at costs, it was estimated that the cost of death was the variable that this analysis was the most sensitive to, perhaps because it is so large in comparison to the other costs. The cost-effectiveness ratio of both SDR and SCC were perceived to be sensitive to changes in the total cost of deaths. The function for the cost of death as a function of cost per cure are shown in Figure 8-21 for SCC and Figure 8-22 for SDR. In these figures, the influence of cost of death on the cost per cure are illustrated. Nevertheless, the cost for each patient who died was the same for both SCC and SDR and considering that the death rates were the same, it is unlikely that different calculations of the cost per death will change the overall analysis considerably. Substantiating this, the cost per cure excluding the cost per death, was 649.09 birr for SCC and 919.60 for SDR. Hence, even without the cost per death, SCC still is more cost-effective than SDR. This is significant because there is the argument that the cost of death of an Ethiopian is not worth a day labourer's wages lost from the time of premature death to life expectancy.

Figure 8-21: Cost of Death as a Function of SCC Cost-effectiveness (CE)

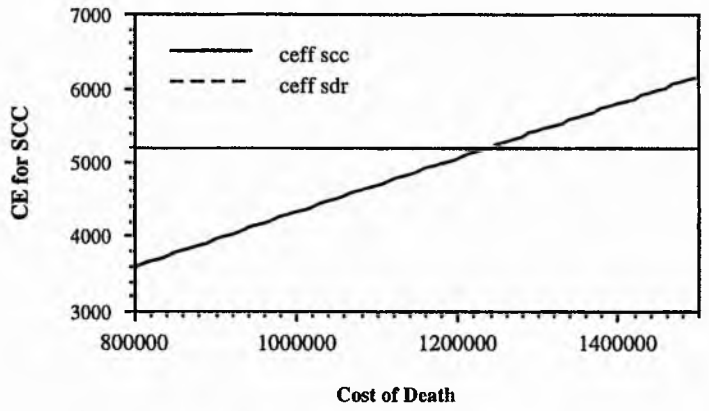
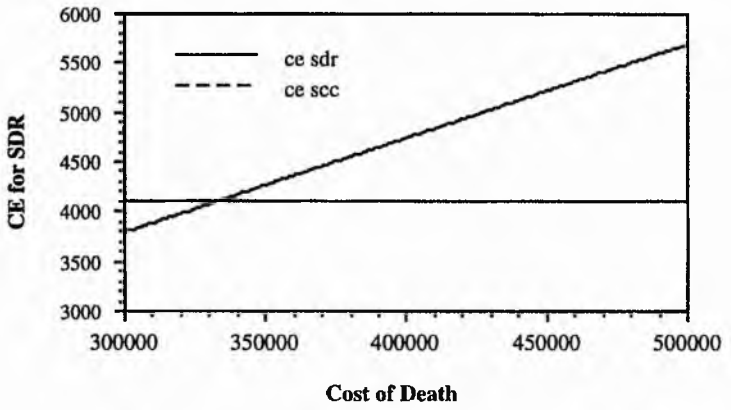


Figure 8-22: Cost of Death as a Function of SDR Cost-effectiveness (CE)



The cure rate variables for SDR are considered on the low end of the possible range of variables in the literature. Death rates, default rates, and failure rates are all low. Likewise, for SCC, the cure rate variables are considered to be on the high end of the range of variables in available literature, and indeed, death rates, default rates and failure rates all prove to be high. However, for the rate of adverse drug reactions, both SDR and SCC have relatively low rates compared to the reported rates of approximately 18-25% in available literature (Kelly *et al,* 1994: Kamolratanakul *et al.*, 1993). These values are primarily dependent on HIV and the amount of substitution in HIV patients of ethambutol for thiacetazone. Since both regimens in this study use thiacetazone, and most reactions occur within the first two weeks, the rate of drug reactions for both regimen should logically be the same. Excluding the cost of drug reactions and the rate of drug reactions experienced, cost per cure becomes 4863.95 for SDR and 3877.45 for SCC. It can only be surmised, but it is possible that there were more HIV patients in the pilot group because of the higher rate of drug reactions. It should be noted that including drug reactions, the cost-effectiveness ratios between these two treatments still finds SCC more cost effective, even when drug reactions to it are higher. This is extremely relevant for the future when the rate of TB/HIV co-infection is expected to rise.

The possibility of a false-positive diagnosis has not been discussed so far in this analysis because it could not be measured. It should be noted that more often than not, there would be a high proportion of false negatives due to the fact that patient often give saliva rather than sputum. However, although this phenomenon occurs making case detection low, estimates on this are completely unavailable. In contrast, false-positive diagnosis suggest that a patient is incorrectly diagnosed and then treated for TB when he or she does not have the disease. Assuming, for instance, that 5% (as observed by Murray *et al.* , 1991) of those diagnosed and cured were false positive, leaving 13.75 needlessly treated patients

in the SCC sample and 5.25 patients needlessly treated in the SDR sample, cost-effectiveness for false positive diagnosis can be calculated for SCC with:

$$CE_{SCCfp} = \frac{13.75(s+v+x)+C}{N-13.75}$$

Where

s =screening cost per patient successfully screened in SCC sample

v =variable cost per patient in SCC sample

x =fixed cost per patient in SCC sample

N =total patients cured in SCC sample

C =total cost of SCC

and for SDR:

$$CE_{SDRfp} = \frac{5.25(s_d+v_d+x_d)+C_d}{N_d-5.25}$$

Where:

s_d =screening cost per patient successfully screened in SDR sample

v_d =variable cost per patient in SDR sample

x_d =fixed cost per patient in SDR sample

N_d =total patients cured in SDR sample

C_d =total cost of SDR

This raises the cost per patient cured by SDR to 5548.66 and the cost per patient cured by SCC to 4335.27.

The cost per cure when only considering the drugs, the major predictor of the difference in costs between treatments, was also calculated. The cost per patient for drugs was 159.6 (US $24.55) for SDR and 264.30 (US $40.66) for SCC, making a difference of 104.7 (US $16.10) in drug cost per patient. When only drug costs were calculated, excluding screening costs, all other variable costs, fixed costs and costs of death, the cost per cure for SCC was 441.69 birr (US $67.95) and for SDR, 509.47 birr (US $78.38). The difference between these values in treatment is 61.10 birr (US $9.4).

It was assumed in this analysis that all defaulters would seek retreatment. In actuality, some would seek retreatment, some would continue to infect others and some would die. Since the cost of death and the cost of treating those subsequently infected with TB is so much higher than retreatment costs, and since there are so many more defaulters in the SDR group, a change in this assumption is not estimated to affect the conclusion that SCC is more cost-effective than SDR.

Another estimate was that all patients were diagnosed in hospital. It was difficult to measure this, but in actuality, only 80-90% are thought to be diagnosed in hospital, the other 10-20% are diagnosed in the health centres. This might affect the overall screening costs, decreasing them slightly. However, screening costs are identical for both the SCC and the SDR regimen and since screening costs for SCC have to rise above 358451.72 birr or those for SDR have to drop below -80359.24 birr to nullify SCC's better cost-effective ratio, the cost-effectiveness ratio is not sensitive to changes in this assumption. With the removal of screening costs, the cost per cure ratio was 4863.95 for SDR and 3877.45 for SCC (See Table 8-18 for a summary of sensitivity measures).

A possible bias in this study might have developed from the small sample size of SDR compared to the size of the SCC sample. The sample size of SDR proved to be smaller because the programme had a longer treatment period and had been started later than the SCC programme. Data from before the non-pilot project was started would definitely suggest that SCC was more cost-effective because cure rates ranged from 20-50% at most. Nevertheless, to preserve the integrity of this study, patient results from a similar environment were used. Indeed, both programmes were new, both programmes occurred in the same environments and in the same area.

8-3:15a Sensitivity of Cost per Cure Ratios to Resistance

The assumption was made that all retreatment cases after default would be isoniazid sensitive and all BAC^+ cases would be isoniazid resistant. Although unlikely, if all BAC^+ cases were actually H-susceptible, this would decrease the cost of SCC because of the use of the H-susceptible retreatment regimen. However, considering the current amount of BAC^+ cases, this would have a very insignificant impact on the cost per cure for SCC.

A range for bacteriologically positive cases of 1.3% to 2.4% was found from other studies presented in Chapter 6. This places the value in this study well within the range of SCC sensitivity as shown in Table 8-17. Costs for resistant cases of SCC must rise above 302867.18 birr for the SDR cost per cure to be less than SCC. The BAC^+ rate, or assumed resistance rate must rise above 18% in order for SDR to become more cost-effective However, this is assuming that resistance is not occurring to drugs in the SDR regimen (also contained in the SCC regimen).

There is the possibility that a proportion of defaulters will develop resistant TB because of their receiving intermittent therapy. If all retreatment cases were drug resistant and had to be given the more expensive H-resistant regimen, this would increase the cost of SDR over SCC, since there are far more defaulters in this group. When all SCC and SDR retreatment cases are resistant, retreatment costs rise 21%. In addition, the cost per cure ratios for SCC change to 4111.38 birr from 4098.63 birr and for SDR change to 5243.52 birr from 5190.46. Hence, cost per cures rise 3.11% for SCC and

1.02% for SDR. Hence, it can be seen that changes in retreatment assumptions have some impact on these respective cost-effectiveness ratios. However, changes in retreatment assumptions in this analysis have little impact on the conclusions of the cost-effectiveness analysis of these two treatments in this study. Hypothetically, if resistance were to rise significantly, this would start to have substantial consequences on the cost of treatments and possibly on the cost-effectiveness ratios of these treatments.

Table 8-18: A Summary of Sensitivity Measures

	SCC	SDR	More Cost-Effective Regimen
Minus Total Death Costs	649.09	919.601	SCC
Minus Total Screening Costs	3877.45	4863.95	SCC
Minus Drug Reaction Costs	4099.69	4842.14	SCC
Looking at Drug Costs (minus total screening, variable, fixed and death)	441.69	509.47	SCC
With a False Positive Diagnosis of 5%	4335.27	5486.66	SCC
If all Retreatment Cases Prove H-Resistant	4110.38	5243.52	SCC

8-3:15b Summary of Sensitivity Analysis

SCC proves to be cost effective in all relevant instances when parameters of the study are changed. Both SDR and SCC could be sensitive to changes in the cost of death if they were to differ from each other. For SDR, the only plausible cure rate variable that could affect these results was the default rate and it was not considered sensitive to changes as its threshold value is so very low that it is unlikely that it could be achieved. SCC could possibly be sensitive to large changes in the default rate and the drug reaction rate, but this is unlikely. Looking at costs, the SCC cost per cure remains more cost-effective even with the elimination of screening costs, death costs, and drug reaction costs. It also remains more cost-effective when there is a 5% false positive diagnosis, when eliminating death costs, screening costs, fixed costs and all variable costs except for drugs, and it when retreatment cases are isoniazid resistant.

8-3:16 Summary of Cost-Effectiveness

The improvements of SCC over SDR on the cure rate is primarily a function of the high default rate experienced in SDR. Because of this high default rate and the cost associated with it, it is likely that SDR will continue to have a higher cost per cure associated with it. Nevertheless, efforts to

maintain case holding have been effective, even in SDR. By standardising treatment, increasing efforts of defaulter tracing and implementing an effective NTP programme, this programme in Addis Ababa has produced amazing results. Looking at data from the Arsi project in 1992 in Table 8-19, one can see that default rates were 25% and 72% for SCC and SDR respectively, making cure rates a sparse 66% for SCC and 18.1% for SDR. Likewise, default rates around this same time in Addis Ababa reached 80%. The administration and management of treatment has not only improved SCC treatment results, but also has improved SDR results.

Table 8-19: Results of SCC and SDR Treatment reported by Arnadottir's for the IUATLD in Ethiopia, 1992

	SCC	SDR
Total Treated	72	121
Total Cured	48 (66%)	22 (18.1%)
Treatment Complete	2 (2.7%)	4 (3.3%)
Failure	1 (1.4%)	1 (0.8%)
Died	3 (4.2%)	1 (0.8%)
Lost	18 (25%)	88 (72%)
Transferred	1 (1.4%)	5 (4.1%)

8-3:17 Discussion of Treatment in the Pilot and Non-Pilot Areas

8-3:17a Drug Reactions

Drug reactions to thiacetazone are predominant among the number of patients that experience drug reactions. For instance, the non-pilot area in the May 1994 Annual Review Report by Region 14, showed 65 total drug reactions so far and out of these, 5 (7.6%) were to Streptomycin, 1 (1.5%) was to Isoniazid, and 59 (90.77%) were to thiacetazone in TB450. According to the TB coordinator doctor at the Black Lion Hospital, most thiacetazone reactions occur within the first 14 days. Indeed, in a survey of thiacetazone reactions at St. Peter's Sanatorium, a large proportion of reactions occurred within the first 20 days. Unfortunately, because of the inexpensive nature of this drug, even the SCC regimen implements it.

HIV tolerance to thiacetazone has proven to be relatively low. In some studies, the percentages of drug reactions has been as much as 25% and in screened HIV patients, reactions in one study in Zambia (Kelly *et al.*, 1994) reached 18.7%. If the cost of thiacetazone drug reactions rise enough, using this drug will no longer prove cost-effective, even though it is such an inexpensive drug. In this study, efforts to substitute ethambutol for thiacetazone in drug regimens for those suspected of HIV is probably the determining factor in the comparatively low rate of drug reactions in this study. Also, as these reactions are primarily associated with HIV , it is possible that fewer HIV cases in Ethiopia mean fewer drug reactions as compared to other African countries. Thiacetazone drug reactions are the significant problem in drug reactions to tuberculosis treatment. Should the rate of drug reactions rise

so that their overall cost is greater than the cost of the regimens, then it will prove more cost effective to substitute ethambutol for thiacetazone in all regimens. The only other alternative would be to screen all patients for HIV, which would also prove costly.

8-3:17b Over-Utilisation of Secondary Care

The high numbers of patients diagnosed in hospitals reflects the patients' over-dependence on secondary care rather than on primary care, a pattern observed in other areas of health in Ethiopia. Treatment could be made cheaper and more cost effective if more patients were given the incentive (i.e. monetary) to seek diagnosis on the primary level as opposed to the secondary level. Indeed the benefits of this would be two-fold due to the lessened expense of primary care, as well as the cheaper smear microscopy method of diagnosing TB in the health centres rather than the blanket method of initially giving all patients x-rays, blood tests and smear microscopy in hospitals.

8-3:18 Health Centre Interviews

In all health centres surveyed, a tuberculosis coordinator was interviewed and a laboratory technician (where possible) in order to ascertain the approach to treatment in each health facility (See Appendix C for Health Centre Interviews). Laboratories are relatively basic, using a microscope and staining solutions to identify sputum positive samples (See Figure 8-23 and 8-24). For laboratory supplies, there were problems getting the diamond pencil, wire loop, and solution A and B (for bacilli analysis). There is also a problem in getting sputum samples from some patients who cannot produce them. In some cases, only saliva is given instead of sputum. Laboratory technicians keep a detailed laboratory register of sputum samples and sputum follow-ups. A proportion of technicians at the health centres visited were trained in Cuba during the Dergue regime.

Drug supplies in general were not a problem. Drugs were organised, often according to the supplier (MOH, Other External Aid, WHO), in a large room by the pharmacist (See Figure 8-25 and 8-26). Some coordinators in the pilot area observed that ethambutol and rifampicin were difficult to obtain in some of the non-pilot areas. Since drugs had been made free for all patients approximately two months before treatment, they were observed to no longer be a problem in treatment. All those interviewed said that drugs were ordered from their last quarterly report and that drug needs were rising.

Another of the problems observed was the process of referral of patients from hospital. Some of those interviewed said that patients often arrived with wrong or incomplete information, or the wrong drug regimen prescribed for the referral area. Extremely critical patients arriving referred from the hospital was another problem. Dr. Yocabel at Kezanchez Health Centre said that sometimes patients

arrive at the health centre on stretchers when the health centre has no beds to take care of these patients. In contrast, a doctor interviewed at Yekatit Hospital said that he was eager to get TB patients out of the hospital as quickly as possible because there is no isolation between most patients. In any given hospital, for some classes of treatment, there will be 20 people in one room, each with a different infectious disease (See Figure 8-27 and 8-28). A trip to the hospital might make one sicker than they were beforehand. Referring a patient back to a hospital was another problem. Sometimes there was no room, patients were HIV positive and therefore had less (unspoken) priority, or a patient would pay a large sum to travel to the hospital just to be told to come back the following day, which he or she could not afford in travel costs.

All patients who transferred to another area were given a referral note, however, those in their intensive phase were not given any treatment, but those in their continuous phase were given up to two months of treatment. Case finding was primarily passive, and the predominance of patients were referred from hospital. Patients often wait longer to be treated at a health centre because they are ignorant of their symptoms. One boy of 15 that I spoke to, who works in one of the main Italian shopping areas, has had a bad cough for more than two years. When I asked him if he had ever thought about having this treated, he said that he did not think he could afford it, nor did he know where he could be treated. He said that not only does he have a cough, but he suffers from night sweats. At 15, this boy was not more than five feet tall. If he did in fact have tuberculosis, he could have been treated free of charge at a local health centre. Another problem is that patients seek help from traditional healers before seeking care from a health centre. The man in Figure 8-29 and 8-30 is a traditional healer and he sold me what resembled a small mixture of dirt and pieces of bark that he claimed would help my 'TB' if I boiled it and drank it like tea twice a week. This is not to discount traditional healing, but there is no traditional cure for TB. Mohammed Abadir Mussee estimates that a large proportion of individuals seek care from traditional healers before approaching a recognised health facility.

Defaulter tracing usually consisted of the coordinator nurse giving the patient or person responsible for the patient a call, or calling a local administration centre in the area of a patient and having a worker from there go to the patient's house (many patients do not have telephones). A problem in defaulter tracing is the fact that patients who desperately want treatment give false telephone numbers and addresses. In some cases such as at K13, defaulter follow-up was poor because there was no coordinator nurse there. Dr. Kidist at this health centre observed that tuberculosis was not a popular area to work in because nurses were afraid of getting the disease, and although this was rare, the TB coordinator doctor at K18 could not be interviewed because she was being treated for TB. In other instances, such as Tekelehamanot, the coordinator Nurse Negassa was so good that he would

walk to the house of the defaulter to find them. At Entoto, the health centre director had obtained bicycles from UNICEF and had given them to the local administration offices where workers there would ride them, get defaulters and ride back together (double) to the health centre. Also at Entoto, in order to make treatment more convenient, a health station was built by the Italian government because it is a more rural part of Addis Ababa (See Figure 8-31). The director of the Entoto Health Centre said that she recommends that patients consume three eggs per week (≈1 birr for three), unfortunately, travel to and from Entoto #1 is more than this cost. The construction of this health station nearer to many of these patients allows them to receive treatment for less cost. Travel to various health centres varies because some are in relatively populated areas, whereas others are in more sparsely populated areas, as shown in Figures 8-32 and 8-33.

There is no environmental control of tuberculosis spread nor TB patient isolation. TB patients, especially smear-positive patients, are encouraged to cover their cough at all times when they are infectious. Educational posters in TB treatment rooms and health personnel emphasise this (See Figure 8-34). At the Shiromeda Health Centre, as depicted in Figure 8-35, 8-36 and 8-37, patients come to receive treatment during their intensive phase each day and wait outside covering their cough until they can be injected and be given their pills.

In all but one health facility in this study, syringes and needles were boiled or sterilised in an oven, unless the patient was suspected to be HIV-positive (See Figures 8-38, 8-39 and 8-40). Patients had the option to buy new syringes if they could afford them. Disposable syringes were reused up to 5 times and reusable syringes were used over 100 times. Many of the nurses commented on how dull the syringes became and this was also evident in observing treatment.

Figures 8-23 and 8-24: Laboratories and Lab Technicians from the Pilot and Non-Pilot Areas

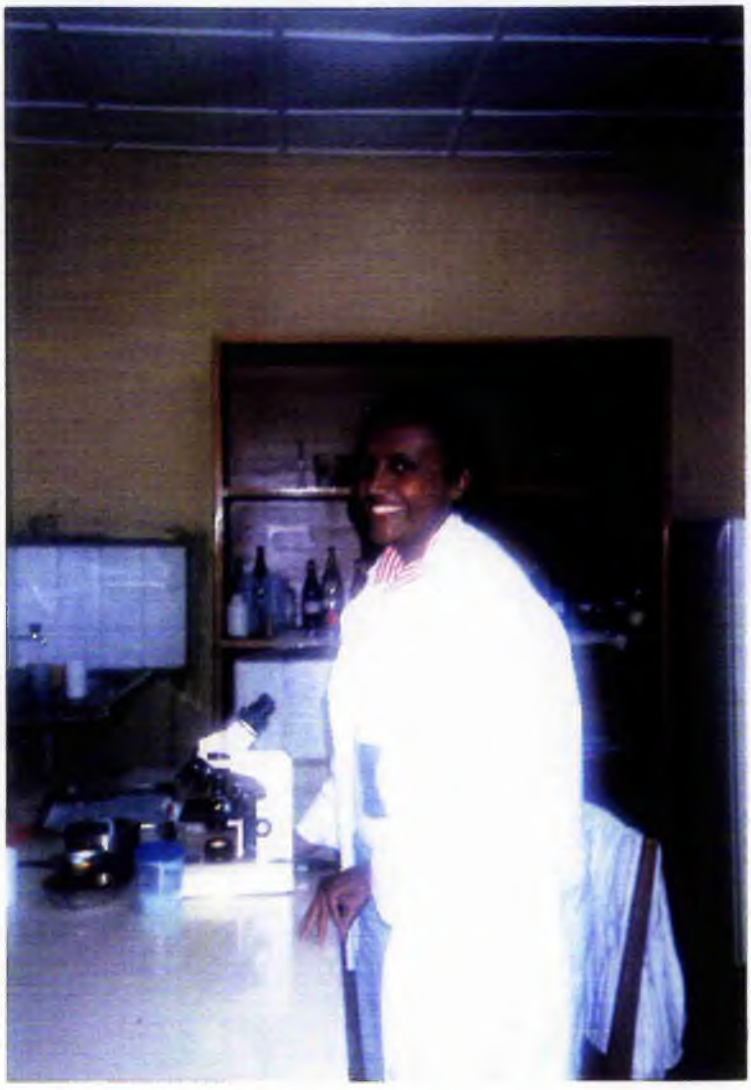


Figure 8-25: Kazanchez Health Centre

Figure 8-26: An Example of Drug Supply Organisation at Kazanchez: Pink Slips indicate Drugs from the Ministry of Health, Blue slips indicate drugs from aid organisations and yellow slips (on wall not shown) indicate drugs from the WHO

Figure 8-27: Yekatit Hospital

Figure 8-28: Average Hospital Room for Poor Patients Accommodating Over 20 Patients With Different Diseases

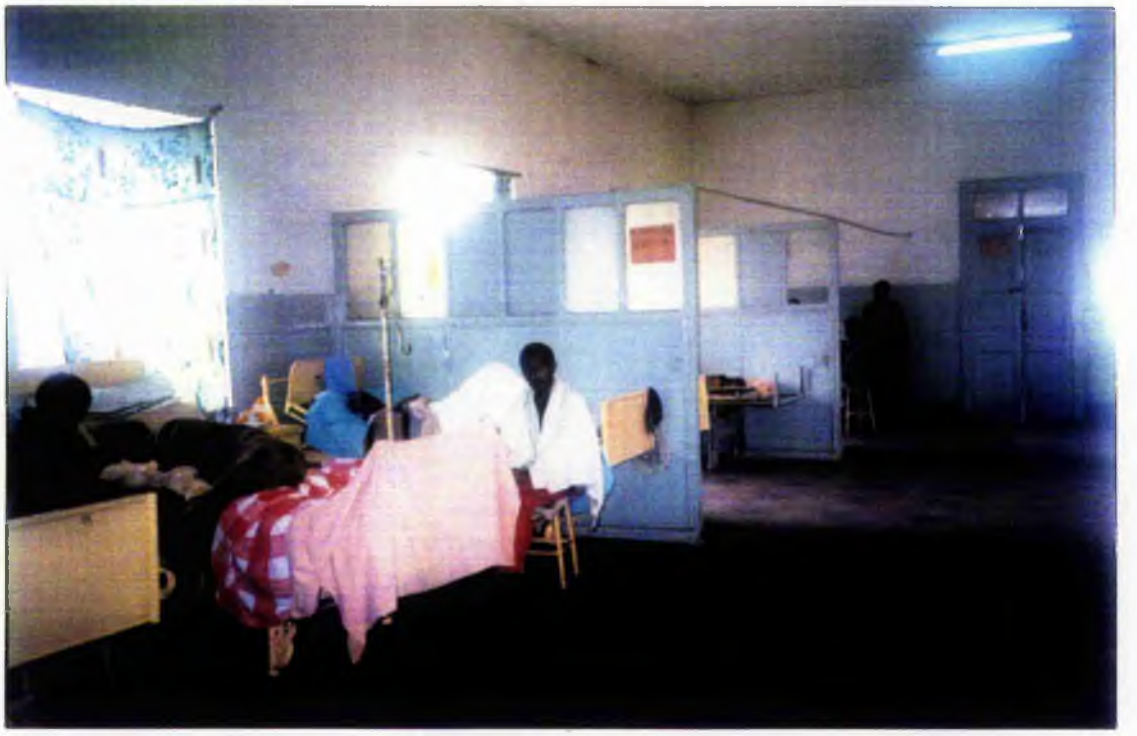


Figure 8-29 and 8-30: A Local Traditional Healer Near the Main Mosque in the Addis Ketema Area

Figure 8-31: Health Station for Entoto #1 Health Centre

Figure 8-32: Higher 23 Health Centre

Figure 8-33: Outside Addis Ketema Health Centre

Figure 8-34: Informational Poster in Amharic Telling TB Patients to Cover their Cough

Figure 8-35: Shiromeda Health Centre

Figure 8-36: Treatment Nurse and Patients Awaiting Treatment at Shiromeda Health Centre

Figure 8-37: Patients Waiting to Receive Treatment at Shiromeda Health Centre

Figure 8-38: Nurses Removing Syringes from a Boiler in Order to Begin Treating the Day's Patients

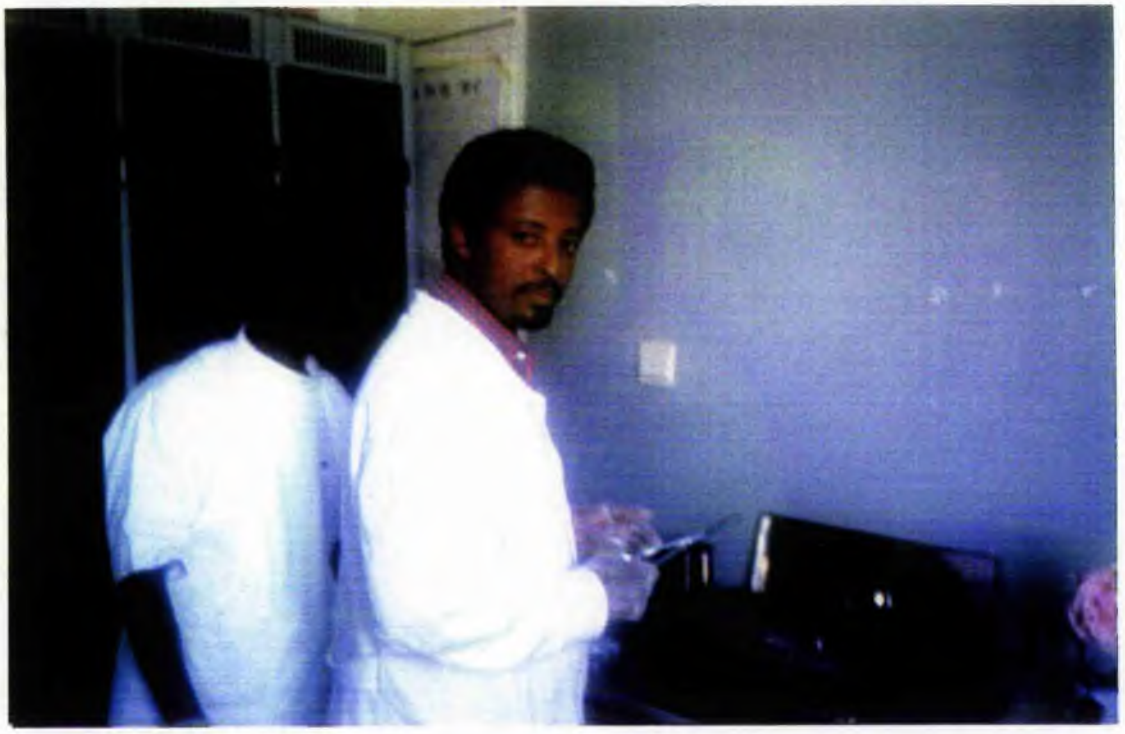
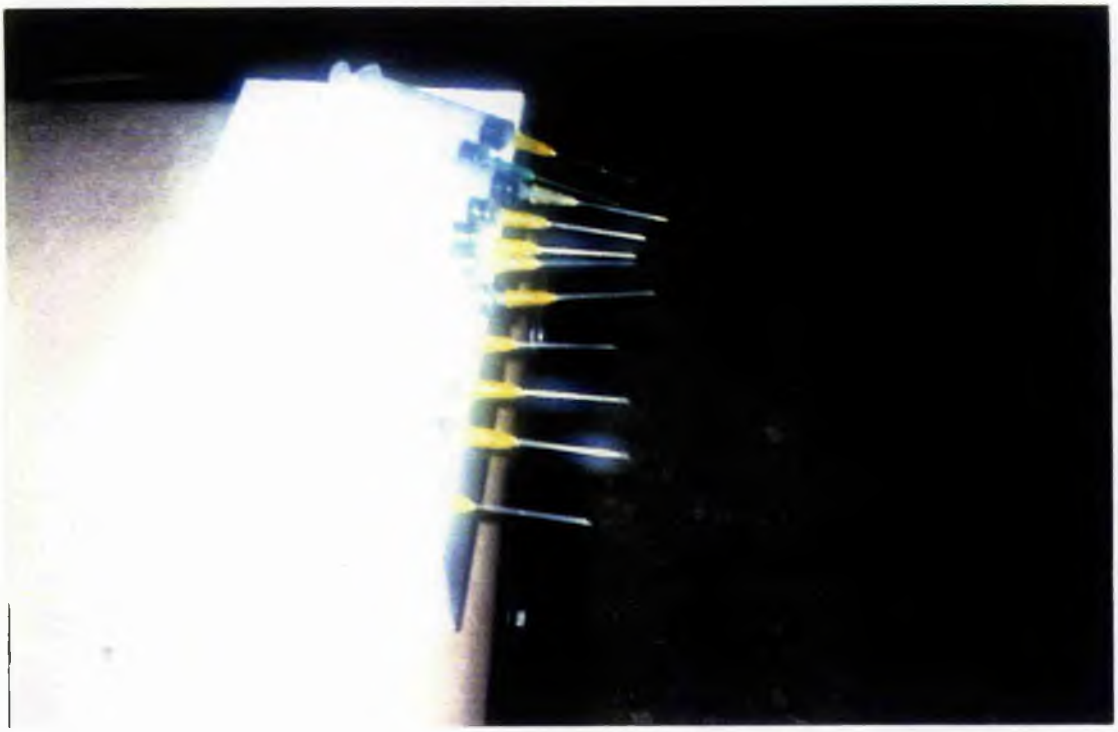


Figure 8-39: Common Boiler for Syringes

Figure 8-40: Used Syringes after Injection



8-3:19 Summary to Section 8-3

In a study of 499 smear-positive patients in the public health sector of Addis Ababa, short course chemotherapy and the standard drug regimen were compared. It was in this context that it was shown that resistance to anti-TB drugs does indeed, have an impact on the cost of TB treatment. Retreatment costs for resistance can raise costs of treatment to 2.28-3.78 times the cost of susceptible cases and when including variable costs, to 3.52-5.70 times the cost of treating susceptible cases. This study also showed that resistance has an impact on cost-effectiveness ratios, but conclusions from this study are not sensitive to resistance until resistance for SCC rises above 18%.

Short Course Chemotherapy, although a more expensive regimen for tuberculosis proved to be a more cost-effective regimen in all measures of cost per cure, cost per death averted and cost per life year saved. SDR has a higher non-compliance rate because its treatment time is 4 months longer than SCC. Because of this high rate of non-compliance for SDR, treatment with SDR incurs the added costs of retreatment of all defaulters. This is a major determinant of cost-effectiveness ratios between these treatments. If the ultimate goal for TB treatment is to treat as many patients as possible, then SDR is the answer, however, if the goal is to cure more patients, then SCC is the more ideal regimen. Objectives of treatment must be defined, but because of the costs incurred by treating patients and not curing them, increased cures must be the final objective of an NTP.

Rates of drug reactions to thiacetazone are high and could prove to threaten the cost-effective use of thiacetazone in HIV patients. Treatment of drug reactions proves to be costly. Also, affecting costs is the possibility for isoniazid resistant tuberculosis in defaulters increasing retreatment regimens by 21%. The implementation of a standardised tuberculosis control programme has had some problems in drug supply, laboratory supply and patient defaulter tracing. Nevertheless, the increase of these cure rates shows remarkable results from just two years ago, due to the presence of an effective National Tuberculosis Programme in Ethiopia.

Section 8-4

CONCLUSION TO CHAPTER EIGHT

The effects of HIV are starting to be felt more acutely in the area of tuberculosis. At the St. Peter's Sanatorium, TB/HIV co-infection is becoming more and more common, making TB more difficult to treat, especially in critical patients. Screening for HIV in TB patients is uncommon and is only done in hospitalised patients. The rate of TB/HIV co-infection in hospitalised patients tested at St. Peter's Sanatorium was approximately 30%. This is an interesting reflection of the synergistic action between these two diseases, but it is unknown whether this value is a representation of TB/HIV co-infection in the general population due to the small sample size of those screened and the critical nature of their disease. Anti-TB drug resistance at the St. Peter's Sanatorium was estimated at 10-20%.

St. Peter's Sanatorium functions as the hospital for critical TB patients from the TB Centre in Addis Ababa. The TB Centre Screens an astounding number of patients per year for TB, but its approach to diagnosis is less than optimal. Unnecessary costs are incurred in chest x-rays for smear-positive patients. On closer analysis, other local hospitals also use a technique of automatic smear microscopy tests, chest x-rays and blood tests for patients suspected of TB. A proportion of this screening expenditure could be saved if all patients were given a smear test to separate smear-positive patients and the remainder were then given chest x-rays and blood tests. These costs can be significant because over 85% of patients are diagnosed in a hospital and then referred to a health centre for treatment. This also reflects patients' over-dependence on secondary care for initial contact for diagnosis, which could be done more inexpensively at a health centre. Another striking feature of diagnosis is the large proportion of normal patients that are screened for TB. Of those screened, only approximately 10% actually have any form of TB.

Optimisation of TB treatment was shown in a study of 499 smear-positive patients in a pilot and non-pilot programme in Addis Ababa. SDR, a less expensive treatment regimen, is often the regimen of choice in developing countries, nevertheless, the final cost per cure of this regimen was proven to actually be higher than the more expensive but more effective regimen, SCC. In choosing the correct treatment, the objective should not always be to treat as many patients as possible, but to cure as many patients as possible. In this example, short course chemotherapy is the optimal choice for TB treatment and control of its spread.

In addition, resistance to anti-TB drugs was shown to increase the cost of TB treatment because it increases the drug costs and variable costs of treatment. This increased cost represents a potential burden for the public sector of health in Addis Ababa. This sector depends on the ERRP and other external aid in order to maintain all of its SCC regimens and a large proportion of its SDR regimens.

Should the incidence of TB resistance rise, the cost of giving more and more patients retreatment regimens for resistance will have to be met. In some cases there will be the problem whereby those with resistant TB will be unable to obtain the proper regimens from health facilities, leaving a poor prognosis for survival. As almost all TB resistance arises from improper use of the drugs, in order to contain resistance, it is extremely important for TB case holding to be strongly enforced, education in drug use to be widened and drug quality to be ensured. Likewise, drug supplies must be well regulated so that patients can get a consistent supply of drugs, not intermittent therapy.

CHAPTER NINE
CONCLUSION

Developing countries are faced with a continuing challenge of providing an efficacious health care system with available funds that is suitable to its needs. Health is an imperative investment because of its influence on well-being and productivity. Health and development are closely related, and investment in health is investment in human capital. The relationship between health and productivity is circular in developing countries. As health increases, productivity can increase and as productivity increases, living environments improve and as living environments improve health increases. Increased health status is a fundamental human need and allows for stronger future generations, greater stamina, better child health and mental acuity. Improved health status not only increases the amount of human capital available, but by extending an individual's life, increases the amount of time that he or she can work.

Unfortunately, most developing countries have extremely poor health service coverage with a large concentration of health facilities only located in cities. In several of these countries, only a small amount per capita is spent on health. Investment in health can often take a low priority and depending on the government, is sacrificed for investments, such as military hardware and urban growth. For this reason, medical supplies and drugs are quickly depleted and there are not enough trained health personnel to meet health care demands. Impeding bureaucracy is rampant and all transactions can take much longer. The health care system can therefore be riddled with an over-concentration on rules, paperwork, systems and guidelines that never allow anything effective to be done. Referral systems in developing countries are poor: for many in developing countries, if individuals manage to travel to one health facility, those that they are referred to are virtually inaccessible to these patients due to cost and transportation. Transportation is difficult and patients seeking care may have to travel across extremely rural areas that can only be travelled by foot. Where there are roads, mostly dirt, they can be flooded and impossible to drive. Facilities for providing health care are often dilapidated and overwhelmed. Patients may find themselves in hospitals with several other patients with other

infectious diseases. In some of these hospitals patients must rely on their family to feed them. In addition, many are rushed out of hospital in order to make room for new patients. Also, those patients who need care may not receive it because they cannot afford it, or a there is no room for them at a health facility.

Health problems that are seldom seen in industrialised countries are highly visible in developing countries. In many cases the very ill lie on crowded city streets because they have no other place to go. Death and morbidity are a more common part of life, especially in low income countries. In poor countries, many come from extremely large families and most have lost a brother, mother, sister, father, daughter, son, aunt, uncle, niece or nephew from a premature death.

This thesis has approached the rationalisation of health care in relation to infectious bacterial disease, and namely, the effect of the cost of resistance on tuberculosis treatment in developing countries. Chemotherapy was a large focus for this thesis because of its high cost-effective impact as a health intervention. Drugs have the potential to be well regulated, well organised and appropriately utilised. They are an ideal intervention for developing countries because in many cases they can be consumed away from a health facility with little effort or discomfort. The paradigm is antibiotics. The use of antibiotics for bacterial diseases proves to be extremely rewarding in terms of their high cures for their cost. Antibiotics represent a low-technology intensive intervention that is far more effective than many other drugs and procedures. The benefits of these drugs are not only experienced by individuals but also by society. Antibiotics can easily cure an infection and in the case of an infectious bacterial disease, can work to quickly and effectively contain its spread. The savings in costs of these indirect benefits are difficult to measure, but they undoubtedly have a significant impact on society.

Unfortunately, with the use of antibiotics there comes bacterial resistance to them, rendering some antibiotics useless in treating infections. This is an inevitable negative externality of use, but this should not be accepted in the case of inappropriate antibiotic use. Inappropriate use is most often the cause of TB resistance. Resistance of other diseases to antibiotics is not only due to inappropriate use, but due to use itself because of the development of exogenous resistance. This is not the case with anti-tuberculosis drugs because the bacilli can only develop endogenous resistance, meaning resistance primarily develops through improper treatment. Indeed, some antibiotics are so important and resistance is such a threat in their treatment of life-threatening diseases, that they should only be used for these indications.

Most health care problems in developing countries can be illustrated with the example of tuberculosis. It is a disease that is viewed as such a strong health threat that in many cases, treatment for patients is provided by the government free of charge. The costs of tuberculosis are grave, expressed not only in the illness and premature death of individuals, but in that it can spread quickly

and affect individuals in their socially and economically most productive part of life. Tuberculosis is a disease that thrives in the poor sanitation, malnutrition, HIV and crowded conditions of developing countries. It is a curable disease that has a very virulent impact in terms of morbidity and mortality. It can be effectively and relatively inexpensively treated and is ranked by the WHO on the top of the list of effective health care interventions. While this thesis was written, tuberculosis once again has become prominent in international news and there is suddenly rising pressure for containment efforts.

Efforts to start systematic standardised national tuberculosis programmes have in some cases been impotent because of poor financial backing. Priorities are often skewed and very little is given by the governments themselves to support TB programmes: a scenario that inevitably ends in failure to control the disease. For example in Ethiopia, although it had a programme aided and instigated by the support of the WHO, only recently did this programme really start to be effective when it was supported by a new government. Drug management has been poor and drugs are often obtained from expensive sources. Also, the regulation of these drugs is not well controlled so that drugs are inappropriately used for other infections, contributing to the development of resistance. In other cases, drugs necessary for treatment are not available or are intermittently given, amounting to treatment, but no cure and again resistance.

Resistance has been a real threat to tuberculosis chemotherapy because once multi-drug resistance occurs, the prognosis for the disease is a 40-60% death rate, the same as untreated tuberculosis. Resistance in TB is attributed to many factors including poor administration, poor patient compliance, poor drug quality and incorrect use. Efforts to control tuberculosis have also been hampered by the inability to manage treatment. Without proper patient tracing, patients are treated for the disease for a short period of time only to default. Administration of this disease is reliant on recording patient information in order to calculate future demands in treatment.

The impact of HIV on TB also cannot be ignored. More than any other disease, TB is able to exploit the growth of HIV to its own advantage. Where many diseases that affect those with HIV find HIV-negative individuals unsusceptible, tuberculosis can affect both populations. As a third of the global population is estimated to be already infected with the disease, TB can grow in the TB-infected who contract HIV and in those with HIV who become infected with TB.

The management of tuberculosis and problems encountered with it were shown in Ethiopia. Here, where GNP per capita per year at most reaches $110 US dollars and the average life expectancy is only approximately 50, poverty is an accepted part of their life. Tropical diseases plague Ethiopia which has several different climates due to its altitude, and therefore, complex epidemiological patterns of disease: these disease patterns mean that the system of health care delivery must be versatile. Investment in health is still less than $1 US dollar per capita, health service coverage, at

most, amounts to 50% of the population, and the urban concentration of health facilities is high. Correlating with this, total expenditure for medical supplies and drugs in 1992 amounted to approximately $3.2 million dollars, meaning that there has been less than US 5 cents spent per person in this area. However, in this environment, infectious disease is the greatest health challenge to the health care system and therefore, a sound priority for interventions. All complications to health care delivery in bacterial diseases, such as HIV and drug resistance, consume resources which could be used more efficiently to treat more patients in the absence of these complications.

Tuberculosis for Ethiopia is a very visible health threat with an annual risk of infection of 1.5%. HIV infection is starting to grow in Ethiopia threatening not only the population, but tuberculosis control. At the St. Peter's Sanatorium, an estimated 30% of screened patients were TB/HIV co-infected. Although this cannot be generalised to all TB patients, the high rate of drug reactions to thiacetazone, primarily a phenomenon in HIV patients, is evidence that HIV is creeping into the TB case loads of health facilities. Efforts to establish a powerful TB control programme have become more effective and tuberculosis eradication has become a more prominent goal in Ethiopia, especially in the urban areas where administration for the disease involves those who only work in TB. Management of tuberculosis containment has been forced to be resourceful. Problems in treatment that are difficult to address, due to poor funding, have been dealt with in the most inexpensive but effective way. Case holding, one of the greatest challenges to tuberculosis treatment has been aided by the efforts of conscientious nurses, doctors and medical directors who will go to the houses of defaulters to find them. Unfortunately tuberculosis treatment is at risk from the lack of supplies. Recently, drug supply in Addis Ababa has been consistent with the strong support of the WHO, but other supplies, such as syringes and needles must be re-used and boiled. In contrast, in areas outside of Addis Ababa, drug supply is not consistent. Because the support of these programmes are so dependent on WHO funding, they are in a precarious position.

The system of referral for patients is weak because of the poor quality and capacity of secondary health care facilities. Hospitalisation of critical patients in Addis Ababa has also proved a problem. Health facilities are eager to get their patients into hospital, but there is sometimes no room. Hospitals on the other hand try to get TB patients out of secondary care as soon as possible and in many cases, prematurely. Critical patients arriving on stretchers at health care centres, who have no facilities for this, are not uncommon.

The system for information recording has been improved with the use of a tuberculosis registrar, patient treatment cards, quarterly reports, annual reports, and sputum laboratory record books. Utilisation of health care facilities has been eased by the building of health stations near patients in the more rural parts of the city. However, many patients still have little knowledge of the existence of this

free and comprehensive tuberculosis treatment and many rely on traditional healers. Case finding is still passive, which is unlikely to change considering the available resources.

Since the change in government, and the instigation of SCC, the potential for better treatment has developed. However, this is likely to bring in resistance to those drugs in the SCC drug regimen that are not used in the SDR regimen. Resistance to drugs like rifampicin, pyrazinamide and ethambutol, which were not used to any large degree before, is likely to become a larger health threat, also allowing the potential for multi-drug resistance. However, with a good implementation of a tuberculosis programme, ensuring only limited amounts of default, resistance to these drugs can be contained. Tuberculosis is a disease that is curable and its resistance is primarily determined by human actions in implementing treatment. Poor treatment leads to resistance which was shown to increase tuberculosis treatment costs, because more drugs and more time and resources must be used to treat these patients. Not including the cost of treatment before resistance has been detected in a patient, approximately 3-5 more susceptible patients may be treated than drug resistant patients, depending on the regimen chosen. In addition, as costs rise, so do the relative cost per cures and other measures of cost-effectiveness for SDR and SCC. However, SCC still remains more cost-effective than SDR until resistance to SCC rises to 18% (assuming resistance to SDR remains constant).

Choices, Priorities and Decision Making

Better organisation and administration of health care is demanded in developing countries and this is where health care management can be instrumental. By examining each situation and instigating a simple, but workable management plan, diseases and health problems can be more readily attended to.

Making choices in drug treatment is another area where TB is a relevant example to the rationalisation of chemotherapy. This is an area that is closely tied to deciding the ultimate objectives of an intervention. It seems that all too often, low income countries compromise the quality of treatment for the quantity of those treated. In essence, the desire to treat as many patients as possible for as little expenditure as possible has become an end in itself. This emphasis has overshadowed the need to treat patients with effective results. Drug treatments and interventions are either valued because of the fact that they integrate some high and often inappropriate technology or because they are inexpensive. Developing countries are proud of the abilities of their staff in hospital to perform highly technical procedures such as open-heart surgery, when for the price of such interventions and technology, thousands could be saved with something as fundamental as ORT. In Ethiopia at the TB Centre and in hospitals in Addis Ababa, there is an over-reliance on chest x-rays for the diagnosis of tuberculosis in smear-positive patients when much could be saved by first using smear microscopy in

order to screen these patients out of the group of patients will all types of TB. For the amount of money that is used sub-optimally on x-rays for TB diagnosis a large proportion of patients could receive short-course chemotherapy. The high emphasis on treating, rather than curing the most patients was expressed by the case of tuberculosis drug therapy. SDR has been used extensively in many developing countries, especially sub-Saharan Africa. The question has, nevertheless, arisen as to how effective it is in dealing with the threat of tuberculosis. In this thesis, SDR was shown to be inferior in curing tuberculosis when compared with SCC. In fact, for the price paid for each cure, SCC was approximately $170 US dollars less. It also proved cheaper in deaths averted, total deaths averted and the cost per life year saved (no matter which method was used in calculating years of life lost).

Developing countries must balance their efforts in order to optimise the effects of their expenditure. It is essential that priorities be set for interventions in order that appropriate technology, training, supplies, drugs and infrastructure can be established. It is making these decisions in priorities that becomes difficult. One of the most appropriate tools for this decision making is the use of health economic analysis and tools to explore the best combination of options that will minimise opportunity costs and maximise the desired benefits from expenditure. Available funds are scarce and since the greatest benefits are desired for the amount of expenditure, there is no better tool for analysing this than health economics. Health economic analysis was shown in this thesis to be a superior method for identifying the optimal health care interventions and concentrations. It is also an area that is under-utilised.

This thesis showed that in Ethiopia, resistant cases of tuberculosis increase the cost of tuberculosis treatment. This is a country that is one of the very poorest of developing countries. Until only recently, it was relatively isolated from those around it, possibly explaining its lower levels of HIV and resistant TB. Unlike more resource-rich developing countries, Ethiopia has only just begun to develop a standardised treatment for tuberculosis. Therefore in many places, resistance to drugs, especially those particular to the SCC regimen, is non-existent because of little use. If programmes are not implemented correctly, it is likely that with greater implementation of tuberculosis treatment, resistance will also rise to the levels observed in other countries. If TB resistance rises, the cost of treatment will also rise.

Although Ethiopia has been relatively isolated until recently, and although particular TB treatments have not been in use for as long as those in other developing countries, the conclusions of this thesis are not entirely context-dependent. In other developing countries, if tuberculosis resistance requires the use of a greater number of drugs and a greater amount of time and resources, then the cost of treating this resistance will also rise, likewise representing a larger economic burden for these countries. Indeed, this may not only be the case for tuberculosis. If other resistant bacterial diseases

require more drugs and resources, then the cost of treating these will also rise. Indeed, resistance has the potential to present a grave challenge in containing costs of infectious diseases, an effect for which in developing countries with their limited resources, will have serious consequences.

APPENDIX A

NON-PILOT DATA*

*Data will appear starting from the first patient recorded in the patient register at each representative health facility. Each patient number appears on the sheet according to how it appears in the patient register as does his or her age, sex and smear classification

GUIDE TO SYMBOLS USED ON THE NON-PILOT DATA SHEET

#	Patient number
S	Sex
1	Male
0	Female
E	Extra-pulmanary Tuberculosis
P	Pulmonary Tuberculosis
2	Second Month Smear
5	Fifth Month Smear
8	Eighth Month Smear
12	Twelfth Month Smear
C	Treatment Complete
c	Cured
D	Died
F	Defaulted
T	Transferred
HE	Ethambutol-Isoniazid Substitution
Drug React	Drug Reaction
TB-450	Reaction to Thiacetazone
Place	Health Facility Location
K17	Kefetegne 17
KEZ	Kezanchez
ADD	Addis Ketema
K23	Kefetegne 23
K19	Kefetegne 19
K25	Kefetegne 25 (Kolfe)

7	SEX	Age	PS	2	5	8	12	C	c	D	F	T	HE	DRUG REACT	PLACE
1	1	29	2+	-	-	-			c						KEFETEGNE-17
2	0	26	2+	-	-	-			c					TB450-HE	K17
3	0	40								D					K17
4	1	36	3+	-	-	-			c				HE		K17
5	0	10											HE		K17
6	0	25										T		TB450-Hhep/T	K17
7	0	36										T			K17
8	1	29									F				K17
9A	0	10													K17
9B	1	30	+	-	-						F				K17
10	1	37											HE		K17
11	1	20													K17
12	1	25	2+	-	-	-			c				HE		K17
13	1	20											HE		K17
14	1	37								D					K17
15	1	10										T			K17
16	1	23	3-	-	3+							T			K17
17	1	17	+	-	-						F				K17
18	1	36	+									T			K17
19	1	47	3+	-	-				c						K17
20	0	48								D					K17
21	1	46	3+	-										TB450-HE	K17
22	1	29												TB450-HE	K17
23	0	35	+	-	-				c						K17
24	0	42										T			K17
25	0	24											HE		K17
26	1	28	2+								F				K17
27	1	75								D					K17
28	0	35											HE		K17
29	0	30	+	-	-				c					TB450-HE	K17
30	0	39	3+								F				K17
31A	1	15	?												K17
31B	1	32													K17
32	1	39													K17
33	1	17	3+	-	-				c						K17
34	0	20													K17
35	1	39											HER		K17
36	0	26	3+	-	-				c						K17
37	0	42	3+	-	-				c						K17
38	0	30	2+	-	-				c				HE		K17
39	0	11												TB450-HE	K17
40	1	24	2+	-	-				c				HE		K17
41	1	20													K17
42	0	27											HE		K17
43	1	23												TB450gastr-HE	K17
44	1	52	+								F				K17
45	1	49								D					K17
46	1	14									F				K17

47	1	23												TB450-HE	**K17**
48	0	26											HE		**K17**
49	1	11											HE		**K17**
50	0	28													**K17**
51	1	18													**K17**
52	0	22	3+	-						D					**K17**
53	0	28											HE		**K17**
54	1	36	2+	-					c				HE		**K17**
55	0	20	3+	-							F				**K17**
56	1	32													**K17**
57	1	33	3+	-					c						**K17**
58	0	32											HE		**K17**
59	1	28	2+	-											**K17**
60	1	68													**K17**
61	1	35	2+	-						D					**K17**
62	1	38													**K17**
63	1	48													**K17**
64	0	30													**K17**
65	1	26									F				**K17**
66	0	26	2+	-											**K17**
67	0	17	2+	-							F				**K17**
68	1	18	2+	-	-				c						**K17**
1	1	18	+	-	-				c						**KEZANCHEZ**
2	0	26	+	-	-				c						**KEZ**
3	1	32													**KEZ**
4	1	38	3+	-	-				c						**KEZ**
5	1	15	3+	-					c						**KEZ**
6	0	50	4+	-	-				c						**KEZ**
7	0	15	3+	-					c						**KEZ**
8	1	20	2+		-				c						**KEZ**
9	1	9	3+	-					c						**KEZ**
10	1	20	2+	-	-				c						**KEZ**
11	1	39										T			**KEZ**
12	1	18													**KEZ**
13	0	16	2+	-					c						**KEZ**
14	0	23	2+	-	-	-			c						**KEZ**
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16	1	22													**KEZ**
17	1	14	2+	-					c						**KEZ**
18	1	16	+	-											**KEZ**
19	0	30													**KEZ**
20	0	20													**KEZ**
21	1	34	3+								F				**KEZ**
22	1	57									F				**KEZ**
23A	1	48													**KEZ**
23B	0	21													**KEZ**
24	0	21	+	-					c						**KEZ**
25	0	12													**KEZ**
26	1	16	2+	-	-				c						**KEZ**

27	0	3													KEZ
28	0	40	3+	-					c						KEZ
29	0	20										T			KEZ
30	1	30	2+	-					c						KEZ
31	1	34													KEZ
32	1	14	2+	-					c				HE		KEZ
33	0	40										T			KEZ
34	1	19	2+	-					c						KEZ
35	0	30												TB450-HE	KEZ
36	1	27	2+	2+					c						KEZ
37	0	75													KEZ
38	1	28	3+	-										TB450-HE	KEZ
39	1	23										T			KEZ
40	0	56													KEZ
41	0	23													KEZ
42	1	33	3+								F				KEZ
43	1	23											HE		KEZ
44	1	19	2+	-											KEZ
45	1	28	2+	-											KEZ
46	1	37	3+	-											KEZ
47	1	17													KEZ
48	1	45													KEZ
49	0	19	2+										HE		KEZ
50	0	28													KEZ
51	0	35	2+												KEZ
52	1	40	3+	-									HE		KEZ
53	1	29									F				KEZ
54	1	32	2+	-											KEZ
55	0	24	+	-											KEZ
56	0	20													KEZ
57	1	18											HE		KEZ
58	0	28	2+												KEZ
59	1	41	2+	-											KEZ
60	1	37	2+	-									HE		KEZ
61	1	24											HE		KEZ
62	0	45											HE		KEZ
63	0	75													KEZ
64	0	30	3+									T			KEZ
65	1	28	+											TB450-HE	KEZ
1	1	27	+	-	-	-			c						ADDIS KETEMA
2	1	22	+	-	-	-	0		c						ADD
3	1	26													ADD
4	1	49	+	-	-	-			c						ADD
5	0	35											HE		ADD
6	1	22													ADD
7	0	20													ADD
8	0	14	+	-	-	-			c						ADD
9	0	35													ADD
10	1	30	+							D					ADD

11	1	29														ADD
12	0	38														ADD
13	0	14														ADD
14	0	34														ADD
15	0	20								D						ADD
16	1	25	+	-	-						F					ADD
17	1	18														ADD
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20	0	49														ADD
21	1	50	+	-	-						F					ADD
22	1	18	+	-	-				c							ADD
23	1	21	2+	-	-				c							ADD
24	1	7									F					ADD
25	1	25														ADD
26	0															ADD
27	0	50									F					ADD
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29	1	62								D						ADD
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31	1	29														ADD
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33	1	30														ADD
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36	0	30	3+							D						ADD
37	1	60									F					ADD
38	0	25										T		T-HOSPITAL		ADD
39	1	15									F					ADD
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41	1	28										T				ADD
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44	1	18										T				ADD
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46	1	22												TB450-HE		ADD
47	0	20	+	-							F					ADD
48	0	23	+	-	-							T				ADD
49	1	23	+	-	-	-						T				ADD
50	1	49										T				ADD
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55	1	22										T				ADD
56	0	21														ADD
57	1	32	3+	-						D						ADD
58	1	31	3+	-	-	-			c							ADD
59	0	25														ADD

60	1	25	+	-	-	-					F					ADD
61	0	28	2+	-	-	-					F					ADD
62	1	25														ADD
63	1	58								D						ADD
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65	0	40	+	+	-	-			c				HE			ADD
66	1	16														ADD
67	1	32	2+	-							F					ADD
68	0	15									F					ADD
69	1	11														ADD
70	1	29	3+	-							F					ADD
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73	0	35	+	-	-	-			c							ADD
74	0	25														ADD
75	0	20									F					ADD
76	1	33														ADD
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79	1	30	+	-	-	-			c							ADD
80	1	28	+	-	-							T				ADD
81	1	18														ADD
82	1	40	+								F					ADD
83	0	15									F		HE			ADD
84	0	34	+	-	-	-			c							ADD
85A	1	15														ADD
85B	1	32	2+	-	-	-						T	SCC	T-HOSPITAL		ADD
86	1	23	2+	-									SCC			ADD
87	1	15														ADD
88	0	36	+	-	-	-			c							ADD
89	0	27	+								F					ADD
90	1	18									F					ADD
91	1	16	3+								F					ADD
92	1	17									F					ADD
93	1	14										T				ADD
94	1	28	4+	-								T	SCC			ADD
95	1	5											HE			ADD
96	1	18	2+								F					ADD
97	1	30														ADD
98A	1	36	4+	-	-	-					F					ADD
98B	0	46										T				ADD
99	1	22	+	-							F					ADD
100	1	26	+													ADD
101	1	17									F					ADD
102	0	16														ADD
103	1	48	2+						c							ADD
104	1	16	+	-									HE			ADD
105	0	25														ADD
106	0	20	+	-							F					ADD

107	1	25													**ADD**
108	0	4									F				**ADD**
109	0	35	+	-	-	-			c						**ADD**
110	0	40									F				**ADD**
111	0	50									F				**ADD**
112	1	45	+	-	-	-			c						**ADD**
113	0	60													**ADD**
114	1	40										T			**ADD**
115	1	49								D					**ADD**
116	0	20									F				**ADD**
117	0	30	+	-							F				**ADD**
118	0	20													**ADD**
119	1	69													**ADD**
120	0	35	3+	-	-	-			c						**ADD**
121	0	34													**ADD**
122	0	30	+	-	-	-					F				**ADD**
123	0	75									F				**ADD**
124	0	22													**ADD**
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126	0	26	3+							D					**ADD**
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129	1	23													**ADD**
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133	1	30													**ADD**
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135	1	30									F				**ADD**
136	1	32													**ADD**
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138	0	8													**ADD**
139	1	42													**ADD**
140	1	25	2+	-	-	-					F				**ADD**
141	1	20	4+	-								T			**ADD**
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143	1	15													**ADD**
144	0	28	3+	-	-	-					F				**ADD**
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147	1	25	3+	-	-	-			c						**ADD**
148	0	65	4+	-	-	-					F				**ADD**
149	1	29													**ADD**
150	0	36								D					**ADD**
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152	0	15	+	-							F				**ADD**
153	1	31	2+	-	-	-					F				**ADD**
154	0	35	2+	-	-	-			c						**ADD**
155	1	26	+	-	-	-			c					TB450-HE	**ADD**
156	1	21													**ADD**

157	1	33	2+	-							F					**ADD**
158	1	42	+	-								T				**ADD**
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160	0	16														**ADD**
161	1	25									F					**ADD**
162	1	32	+							D						**ADD**
163	0	13										T				**ADD**
164	1	20														**ADD**
165	1	19									F					**ADD**
166	0	19														**ADD**
167	1	40														**ADD**
168	0	14														**ADD**
169	0	19									F					**ADD**
170	1	18									F					**ADD**
171	1	28	+	-	-						F					**ADD**
172	0	62														**ADD**
173	1	35									F					**ADD**
174	1	24									F					**ADD**
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177	1	30														**ADD**
178	0	30	3+	-	-	-					F					**ADD**
179	1	55									F					**ADD**
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181	1	55	3+								F					**ADD**
182	1	20	4+	-	-	-					F					**ADD**
183	0	14	4+	-	-	-			c							**ADD**
184	1	20														**ADD**
185	0	15									F					**ADD**
186	1	12														**ADD**
187	0	32														**ADD**
188	1	45									F					**ADD**
189	1	17	2+								F					**ADD**
190	0	15														**ADD**
191	1	16									F					**ADD**
192	0	2									F					**ADD**
193	0	19	3+	-	-						F					**ADD**
194	1	19	+	-	-							T				**ADD**
195	0	50	3+	-								T				**ADD**
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197	1	36										T				**ADD**
198	0	11										T				**ADD**
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2	0	33														**K23**
3	0	6											HE	PE		**K23**
4	1	49												TB450-HE		**K23**
5	1	16	+	-	-	-			c							**K23**
6	0	30														**K23**

7	1	35												TB450-HE	K23
8	1	36											HE		K23
9	0	40												TB450-HE	K23
10	0	21	3+	-	-				c						K23
11	1	50								D					K23
12	1	12													K23
13	1	61								D					K23
14	1	50								D			HE		K23
15	0	29									F				K23
16	1	53	3+	-	-	-			c						K23
17	1	25													K23
18	1	29	+	-	-	-									K23
19	0	26										T			K23
20	0	25													K23
21	1	15								D			HE		K23
22	1	29	2+	-							F				K23
23	0	34									F		HE		K23
24	0	30													K23
25	1	42													K23
26	0	21	2+	-	-	-			c					TB450-HE	K23
27	0	38													K23
28	1	26	2+	-					c						K23
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30	1	18													K23
31	1	45	3+	-											K23
32	1	30	+	-											K23
33	0	36													K23
34	1	24													K23
35	1	23											HE		K23
36	1	40										T			K23
37	1	4													K23
38	1	24													K23
39	0	19											HE		K23
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43	0	32													K23
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45	1	26	3+	-											K23
46	1	30													K23
47	1	36													K23
48	1	40													K23
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50	1	40	3+	-								T		T-HOSPITAL	K23
51	1	48													K23
52	0	37								D					K23
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54	1	52											HE		K23
55	0	29										T			K23

56	0	28	4+	-											K23
57	1	28													K23
58	1	38	2+	-						D					K23
59	1	33													K23
60	1	35								D					K23
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64	0	18													K23
65	1	12													K23
66	1	22										T			K23
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90	0	20													K23
91	0	20	2+	-											K23
92	1	45													K23
93	1	34											HE		K23
94	1	46	2+	-									HE		K23
95	1	30											HE		K23
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103	0	26											HE		K23
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105	1	35													K23
106	0	16	+	-											K23
107	0	30	+	-											K23
108	0	33													K23
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112	1	26											HE		K23
113	0	28	+	-											K23
114	1	14	+	-											K23
115	1	23	+										HE		K23
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117	0	30	+	-									HE		K23
118	0	29											HE		K23
119	1	28	+	-									HE		K23
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121	0	40	2+	-								T			K23
122	0	16											HE		K23
123	1	28													K23
124	1	30										T			K23
125	1	25													K23
126	1	54													K23

127	0	16													K23
128	1	45													K23
129	0	40	+	-									HE		K23
130	0	20													K23
131	1	24											HE		K23
132	1	23	2+												K23
1	0	23										T			KEFETEGNE 19
2	0	18	+									T			K19
3	1	17									F				K19
4	0	20									F				K19
5	0	46													K19
6	0	15	+										SCC		K19
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9	0	50	+	-	-	-	-				F				K19
10	1	33									F				K19
11	0	50													K19
12	0	20	+	-	-	-			c						K19
13	1	15	+	-	-	-			c						K19
14	1	19	+								F				K19
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16	0	17	+									T			K19
17	1	26						C							K19
18	1	28	+									T			K19
19	1	20	+	-	-	-					F				K19
20	1	67						C							K19
21	1	30									F				K19
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37	1	20									F				K19
38	1	18	+	-	-	-			c						K19
39	1	34									F				K19
40	0	20													K19
41	0	20										T			K19
42	0	45													K19
43	1	55	+	-	-	-					F				K19

44	1	20	+	-	-	-			c						K19:3-1-86
45	1	20										T		T-HOSPITAL	K19
46	1	15	+	-	-	-			c						K19
47	0	38	+	-	-	-					F				K19
48	0	52													K19
49	1	23	+	-	-	-			c						K19
50	0	74										T		T-HOSPITAL	K19
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53	1	52	+	-	-				c						K19
54	0	25													K19
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59	0	42								D					K19
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62	1	31									F				K19
63	0	25	+	-								T		T-HOSPITAL	K19
64	1	50													K19
65	1	24	+								F				K19:26-2-86
66	0	29													K19
67	1	33									F				K19
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69	1	24	+	-	-				c						K19
70	0	24									F				K19
71	1	41	+	-	-				c						K19
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73	0	56													K19
74	1	26									F				K19
75	1	35													K19
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79	0	30													K19
80	1	27	+	-	-				c						K19
81	1	23													K19
82	1	40													K19
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86	1	24	+	-	-						F				K19
87	1	22													K19
88	1	20													K19: 8-4-86
89	1	32								D					K19
90	0	50	+	-	-							T			K19
91	1	42	+	-					c						K19
92	1	35	+								F				K19

93	1	25													K19
94	0	28								D					K19
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97	0	26													K19
98	1	44	+	-	-				c						K19
99	0	19	+	-	-				c						K19
100	1	42	+	-					c						K19
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102	1	32													K19
103	1	31													K19
104	1	36	+	-	-				c						K19
105	1	36													K19
106	1	40													K19
107	1	19	+	-	-				c						K19
108	1	19													K19: 6-15-86
1	1	21													KEFETEGNE-25
2	0	28	2+	-	-	-			c				HE		K25: 12-3-86
3	0	18													K25
4	0	2													K25
5	1	27													K25
6	1	15													K25
7	1	32													K25
8	1	17	3+	-					c						K25
9	0	14	3+	-	-	-			c						K25
10	1	32								D					K25
11	1	8													K25
12	1	30	2+	-					c						K25
13	0	21													K25
14	1	23	2+	-	-				c						K25
15	1	53										T			K25
16	0	49													K25
17	0	35	3+	-	-	-			c				SCC		K25
18	1	57	3+	-	-				c						K25
19	0	1													K25
20	1	29												RETREATMENT	K25
21	0	15													K25
22	0	9													K25: 12-4-86
23	1	16											HE		K25: 21-4-86
24	0	17													K25
25	1	66													K25
26	1	40													K25
27	1	20													K25
28	1	18								D					K25
29	1	16													K25
30	1	14													K25
31	0	25	3+		-				c						K25
32	1	47								D					K25
33	0	20	3+						c						K25

34	0	32								D					K25
35	1	23	3+	-	-				c						K25
36	1	20													K25
37	0	16	3+	-	-				c				HE		K25
38	1	11													K25
39	1	43	3+	-	-				c						K25
40	1	18	2+	-					c						K25
41	0	30													K25
42	1	3													K25
43	1	21											HE		K25
44	0	19										T			K25: 21-5-86
45	0	27										T			K25
46	0	40	2+						c						K25
47	0	20	3+	-	-							T			K25
48	1	21								D					K25
49	0	24											HE		K25
50	1	8										T			K25
51	0	5											HE		K25
52	1	17													K25
53	1	48	3+							D					K25
54	1	23	2+												K25
55	1	26	2+												K25
56	0	25												RETREATMENT	K25
57	1	17	3+												K25
58	1	17													K25
59	1	46										T			K25
60	1	50													K25
60	1	23										T			K25
61	1	45								D					K25
62	0	30											HE		K25
63	1	54													K25
64	0	28	3+	-											K25: 25-6-86
65	0	25													K25
66	1	28													K25
67	1	21													K25
68	1	18													K25
69	1	47	-	2+											K25
70	0	45											HE		K25
71	1	18													K25
72	0	50											HE		K25
73	1	55													K25
74	1	19	2+	-											K25
75	1	14	3+	-											K25
76	0	18													K25: 7-7-86
77	1	27	-	-	-				0				HE		
	384														
		28.7													

PILOT DATA*

*Data will appear starting from the first patient recorded in the patient register at each representative health facility. Each patient number appears on the sheet according to how it appears in the patient register as does his or her age, sex and smear classification

GUIDE TO SYMBOLS USED ON THE PILOT DATA SHEET

no.	Patient number
S	Sex
1	Male
0	Female
E	Extra-pulmanary Tuberculosis
S	Short-Course Chemotherapy
L	Standard Drug Regimen
P	Primary Smear
2	Second Month Smear
5	Fifth Month Smear
8	Eighth Month Smear
x	Treatment Complete
c	Cured
D	Died
F	Defaulted
T	Transferred
HE	Ethambutol-Isoniazid Substitution
Drug React	Drug Reaction
TB-450	Reaction to Thiacetazone
Place	Health Facility Location
K19	Kefetegne 19
K13	Kefetegne 13
TEK	Tekelehamanot
K18	Kefetegne 18
ENT	Entoto #1
SHE	Sheromeda

no.	SEX	AGE	CL	P	2	5	8	C	c	D	F	T	HE	DRUG REACT	PLACE
1		20		2+	-	-	-	x						H/hep T/A.D.	KEFETEGNE-19
2	1	27							c						K19: 13-8-85
3	1	28							c						K19
4	0	28		4+	2+									bac+	K19
5	0	36		4+	+	-		x	c						K19
6	1	38										T			K19
7	1	22		3+	-	-	-	x	c						K19
8	0	13		3+	-	-	-	x	c						K19
9	0	2							c						K19
10	0	13		3+	-	-	-	x	c						K19
11	1	18							c						K19
12	1	4							c						K19
13	0	22		3+	-	-	-	x	c						K19
14	1	20							c						K19
15	0	46		3+	-	-	-	x	c						K19
16	0	18		3+	-				c						K19
17	1	18		3+	-	-	-		c						K19
18	0	22		3+	-	-	-	x					HE		K19
19	1	46		3+	-	-	-	x	c						K19
20	1	43							c			T		T-HOSPITAL	K19
21	1	17		3+	-	-	-	x	c						K19
22	1	4		3+	-	-	-	x	c						K19
23	1	30							c						K19
24	0	26		3+	-	-	-	x	c						K19
25	1	27		3+							F				K19
26	1	30		3+	-	-						T			K19
27	0	27		3+	-	-	-	x							K19
28	0	34							c						K19
1	1			3+	-	-	0		c						K19
2	0	25							c						K19
3	1	34		3+	-	-	-	x	c						K19
4	0	21							c						K19
5	1	45								D					K19
6	0	15		3+	-	-	-	x	c						K19
7	1	30								D					K19
8	1											T			K19
9	0	18		3+								T		T-HOSPITAL	K19
10	1	34							c						K19
11	0	10										T			K19
12	1	45													K19
13	1	26		4+	-	-	-	x	c						K19
13	0	4													K19: 7-12-85
14	0	29		2+	-						F				K19
15	1	41		2+	-	-		x	c						K19
16	0	17		2+								T			K19
17	1	40													K19
18	1	20		3+	+	0	0				F				K19
19	0	17		4+	-	-	-	x	c						K19

20	1	30									F				K19
21	0	24		3+	-	-	-	x	c						K19
22	0	18										T			K19
23	1	24													K19
24	1	46		3+	-	-	-	x			F				K19
25	1	30									F				K19
26	0	11													K19
27	1	20		2+							F				K19
28	1	20		2+	-	-	-	x	c						K19
29	1	27		2+							F				K19
30	1	66		2+	-	-	-	x	c						K19
31	0	19		3+	-	-	-	x	c						K19
32	0	50		2+	-		-	x	c						K19
33	1	48		2+								T			K19: 3-1-86
34	1	47		3+	-	-	-	x	c						K19
35	1	20		3+	-	-	-	x	c						K19
36	0	23													K19
37	1	52		2+	2+							T		T-HOSPITAL	K19
38	1	35													K19
39	1	20													K19
40	0	11		-					c						K19
41	1	21													K19
42	0	37									F				K19
43	1	17		2+	-	-	-	x	c						K19
44	0	29		+	-	-	-	x	c						K19
45	0	18		3+	-	-	-	x	c						K19
46	1	22		+	-	-	-	x	c						K19
47	0	7		-	-							T			K19
48	0	39													K19
49	1	30													K19
50	1	22		3+	-	-	-	x	c						K19
51	0	45		2+	-	-	-	x	c						K19
52	0	24		4+	-	-	-	x	c						K19
53	1	32									F				K19
54	0	24													K19
55	1	23													K19
56	1	17		2+	-	-	-	x	c						K19
57	0	35													K19
58	0	18		2+	-	-	-	x	c						K19
59	0	20		2+	-	-	-	x	c						K19
60	1	27		-					c						K19
61	0	21		3+	-	-	-	x	c						K19
62	1	73		2+	-	-	-	x						TB450-HE	K19
63	0	3		2+	-	-	-	x	c						K19
64	1	25		2+	-	-	-	x	c						K19
65	1	35		2+	-	-	-	x	c						K19
66	0	24								D					K19
67	1	16		2+	-	-	-	x	c						K19
68	0	32													K19

69	0	32		2+	-	-	-		c						K19
70	0	25													K19
71	1	30													K19
72	1	31		2+	-	-			c						K19
73	0	35		+	-	-	-		c						K19
74	1	23		3+	-	-	-	x	c						K19
75	1	25		3+	-	-			c						K19
1	1	28									F				KEFETEGNE-13
2	1	22	T	2+	-							T			K13: 29-8-85
3	0	35													K13
4	1	60	T												K13
5	1	35	T												K13
6	1	38		3+	-							T			K13
7	1	25		3+	-	-	-		c						K13
8	0	16		4+	-	-	-		c						K13
9	0	20													K13
10	1	16													K13
11	1	34		4+	-						F				K13
12	1	27		2+	-	-	-		c						K13
13	1	37		+	-						F				K13
14	0	19		3+	-	-	-		c						K13
15	0	14	T												K13
16	1	32		3+	-	-	-		c						K13
17	0	18	T												K13
18	1	36								D					K13
19	0	27		3+	-	-	-		c						K13
20	0	11		3+	-	-	-		c						K13
21	0	11													K13
22	1	30									F				K13
23	0	38							c				HE		K13
24	0	20		4+	-	-	-	x						TB450-HE	K13
25	1	49													K13
25	0	20		3+	-	-	-	x	c						K13
26	0	20		3+	-	-	-	x	c						K13
27	0	37							c						K13
28	0	40							c						K13
29	0	16							c						K13
30	0	18		4+	-	-	-	x	c						K13
31	1	16							c						K13
31	0	16	T	2+					c						K13
32	0	27	T	3+	-			x							K13
33	1	17	T								F				K13
34	1	50	T	4+	3+			x	c						K13
35	1	15	T	2+	-				c						K13
36	0	30		3+							?				K13
37	1	70	T								F				K13
38	1	35	T												K13
39	1	33	T	+	-			x							K13
40	1	22	T	3+	-			x							K13

41	1	13	T	3+	-						F				K13
42	1	18	T								F				K13
43	0	25	T	3+	-				c						K13: 3-3-86
44	1	48	T	3+	3+	2+								CHRONIC	K13
45	0	25	T	4+	-			x	c						K13
46	1	29	T	3+	-			x	c						K13
47	1	30			-						F				K13
48	1	21	T	4+	-						F				K13
49	0	55	T												K13
50	0	24	T	3+	-			x						RETREATMENT	K13
51	1	15	T												K13
52	1	38	T	2+	-			x		D					K13
53	1	52	T	+	-			x	c						K13
54	1	2	T												K13
55	1	20	T	2+	-			x			F				K13
56	0	22	T	+	-			x	c						K13
57	1	16	T												K13
58	0	33	T	3+	-			x		D					K13
59	1	22	T												K13
60	1	14	T						c						K13
61	0	22	T												K13
62	1	31	T												K13
63	1	12	T												K13
64	0	48	T	2+	-			x	c						K13: 14-4-86
65	1	11	T												K13
66	1	20	T												K13
67	0	10	T						c						K13
68	1	20	T						c						K13
69	1	54	T												K13
70	0	20	T												K13
71	0	9	T								F				K13
72	0	11							c						K13
73	0	24													K13
74	0	70													K13
75	1	53								D					K13
76	1	40		3+	-			x	c						K13
77	0	25		3+	-			x	c						K13
78	0	12	T						c						K13
79	0	30		2+							F				K13
80	1	16	T												K13
81	1	5													K13
82	1	23													K13
83	1	32								D					K13
84	0	50													K13
85	0	22													K13
86	0	23								D					K13
109	1	30													K13: 30-6-86
110	1	26													K13
111	0	38													K13

112	1	28													K13
113	0	45													K13
114	1	26													K13
115	0	29										T		T-HOSPITAL	K13
116	0	20		+	-			x	c						K13
117	1	48													K13
118	0	38		3+	-			x			F				K13
119	0	32	T	2+				x	c						K13
120	0	38		2+				x	c						K13
121	1	35		2+								T			K13
122	1	31													K13
123	0	18		3+				x	c						K13
124	0	--	T											TB450-HE	K13
125	0	22						x							K13
126	1	31													K13
127	1	23													K13
128	0	5												TB450-HE	K13
129	1	70													K13
130	0	30													K13
131	0	28		+							F				K13
132	1	28													K13
133	1	67													K13
134	1	28		+				x	c						K13
135	0	28													K13
136	1	19		+	+			x	c						**K13: 27-7-86**
137	1	30													K13
138	1	29		+	-			x						TB450-HE	K13
139	0	55													K13
140	0	16												TB450-HE	K13
141	0	30		+	-			x						TB450-HE	K13
142	0	45													K13
143	0	45		+							?				K13
144	1	27		+							F				K13
145	0	23													K13
146	1	18													K13
147	1	21		2+	-			x		D				TB450-HE	K13
148	1	50	R	2+	-			x						R	K13
149	1	39		+	-			x	c						K13
150	1	67									F				K13
151	0	19		+	-			x						TB450-HE	K13
152	1	38													K13
153	0	54								D					K13
154	0	24		3+	-			x	c						K13
155	1	14		2+	-			x	c						K13
156	0	23		+	-			x	c						K13
157	1	23													K13
158	0	21		+							F		HE	UNCOOPERATIVE	K13
159	1	35								D					K13
160	1	21												TB450-HE	K13

161	0	27												TB450-HE	K13
162	0	28													K13
163	1	21													K13
164	0	20						x							K13
165	0	23													K13
166	1	28		+							F				K13
167	0	--												TB450-HE	K13
168	0	19		+				x	c						K13
169	0	17													K13
170	1	60													K13
171	0	36		+				x	c						K13
172	1	46		+				x		D					K13
173	0	25		+										TB450-HE	K13
174	1	45								D					K13
175	1	45													K13
176	0	28													K13
177	1	40		+				x	c						K13
178	1	42										T			K13
179	0	19		+				x	c						K13
180	1	19		+				x							K13: 22-9-86
181	0	30		+				x	c						K13
182	1	20		+				x	c						K13
183	0	18									F				K13
184	1	32										T			K13
185	0	58									F				K13
186	1	23		+				x			F				K13
187	0	35		+				x		D			HR		K13
188	0	23													K13
189	1	11						x							K13
190	1	67									F				K13
191	0	20		+				x	c						K13
192	1	10						x							K13
193	0	9						x							K13
194	1	45													K13
195	0	30									F				K13
196	0	32													K13
197	0	25		2+							F				K13
198	0	36		2+							F				K13
199	0	60		+				x	c						K13
200	0	22		3+				x	c						K13
201	0	4													K13: 15-10-86
202	1	22		3+				x							K13: 15-10-86
203	0	4						x							K13
204	1	4						x							K13
205	1	26						x							K13
206	0	25													K13
207	1	25		2+											K13
208	0	25		2+				x			F				K13
209	1	30		2+					c						K13

210	1	46		3+					c						K13
211	1	21						x							K13
212	0	16													K13
213	1	23													K13
214	1	40													K13
215	0	37		3+							F				K13
216	0	2	T												K13
217	1	20													K13
218	0	8	T	3+				x			F				K13
219	1	36	T												K13
220	0	0.83													K13: 16-12-86
1	0	7							c						TEKELHAMANOT
2	0	35		+	-	-	-	x	c						24-9-85
3	0	21							c						TEK
4	1	20		3+	-	-	-				F				TKE
5	1	24		2+	-	-	-	x	c						TEK
6	0	7							c						TEK
7	1	2							c						TEK
8	1	30		2+	-	-	-	x	c						TEK
9	0	25		3+	-	-	-	x						TB450-HE	TEK
10	0	22		2+	-	-	-	x	c						TEK
11	1	19		2+	-	-	-	x	c						TEK
12	0	16		+	-	-	-	x	c						TEK
13	0	19		2+	-	-	-	x	c						TEK
14	1	36		4+	-	-	-	x	c						TEK
15	1	50		3+	-	-	-	x	c						TEK
16	1	15		+	-	-	-	x					HE		TEK
17	1	15		+	-	-	-	x	c						TEK
18	1	36		+						D					TEK
19	1	24		2+	-	-	-	x	c						TEK
20	1	45		2+	-	-	-	x	c						TEK
21	1	18		2+	-	-	-	x	c						TEK
22	0	16							c						TEK: 24-10-85
1	1	33							c						TEK
2	0	28							c						TEK
3	0	11									F				TEK
4	1	34									F				TEK
5	1	59									F				TEK
6	1	18							c						TEK
7	1	18								D				TB450-HE(HIV)	TEK
8	0	25							c						TEK
9	0	20							c						TEK
10	1	30									F				TEK
11	0	32							c						TEK
12	0	17								D					TEK
13	0	40									F				TEK
14	0	23							c						TEK
15	1	14							c						TEK
16	0	50		2+	-	-	-	x	c						TEK

17	1	19							c						**TEK**
18	1	18		3+	-	-	-	x	c						**TEK**
19	0	21									F				**TEK**
20	1	21		+	-	-	-	x					HR		**TEK**
21	0	30		+	-	-	-	x	c						**TEK**
22	0	22									F				**TEK**
23	1	26													**TEK**
23	1	23							c				HR		**TEK**
24	0	30									F				**TEK**
25	1	35							c						**TEK**
26	1	36		+	-	-	-	x	c						**TEK**
27	0	23							c						**TEK**
28	0	20							c						**TEK**

29	0	27							c						TEK
30	1	32		2+	-	-	-	x	c						TEK
31	0	21							c				HE		TEK
32	1	29									F				TEK
33	0	20		2+	-	-					F				TEK
34	1	31									F				TEK
35	0	38							c						TEK
36	1	24		+	-	-	-	x	c						TEK
37	1	20									F				TEK
38	0	23							c						TEK
39	0	20									F				TEK
40	1	61		3+	-	-			c		F				TEK
41	0	30						x							TEK
42	0	23									F				TEK
43	0	35		3+	-	-		x	c						TEK
44	0	16		4+	-	-	-	x	c						TEK: 7-1-86
45	1	22									F				TEK
46	1	18		2+	-	-	-		c						TEK
47	1	18						x							TEK
48	0	27							c						TEK
49	1	25								D				TB450-HE(HIV)	TEK
50	0	20							c						TEK
51	0	23		3+	-	-	-	x	c						TEK
52	1	20		2+	-	-	-	x	c						TEK
53	1	18		2+	-	-	-	x	c						TEK
54	1	18		3+	-	-	-	x	c						TEK
55	0	38		2+	-	-		x	c						TEK
56	1	42													TEK
57	1	35									F				TEK
58	0	8													TEK
59	1	15		3+	-	-	-	x	c						TEK
60	0	25							c				HE		TEK
61	0	12		3+	-	-						T			TEK
62	1	25		3+	-	-						T			TEK
63	1	36										T			TEK
64	0	40													TEK
65	1	51										T			TEK
66	0	10										T			TEK
67	0	24													TEK
68	1	50		2+	-	-	-	x	c						TEK
69	1	22													TEK
70	0	25							c				HR		TEK
71	0	16													TEK
72	1	20													TEK
73	0	16													TEK
74	1	4													TEK
75	1	32									F				TEK
76	0	50									F				TEK
77	1	10		+	-	-	-	x	c						TEK

78	0	18		3+	-	-	-	x	c						TEK
79	1	16													TEK
80	0	18									F				TEK
81	1	55								D					TEK
82	0	15													TEK
83	0	15													TEK
84	0	50													TEK
85	0	23		3+							F				TEK
86	1	25		4+	-						F				TEK
87	1	24													TEK
88	1	28		+	-	+								BAC+	TEK: 9-3-86
89	0	30		3+	-	-	-	x	c						TEK
90	1	20		+	-	-	-	x	c						TEK
91	0	24		+	-	-	-		c						TEK
92	0	20									F				TEK
93	1	22													TEK
94	0	23									F				TEK
95	1	29									F				TEK
96	0	18		+	-					D					TEK
97	1	40													TEK
98	1	35													TEK
99	0	34									F				TEK
100	0	25										T			TEK
101	1	25		+	-	-	-		c						TEK
102	1	22													TEK
103	0	30		2+						D					TEK
104	0	40									F				TEK
105	1	28		2+	-	-	-	x	c						TEK
106	0	18		2+	-	-	-	x	c						TEK
107	1	23		2+	-	-	-	x	c						TEK
108	0	25													TEK
109	1	28													TEK
110	0	22		+	+	+								BAC+	TEK: 30-3-86
111	0	40	T	+						D					TEK: 4-4-86
112	1	65													TEK
113	0	50													TEK
114	1	20							c						TEK
115	0	26													TEK
116	1	28		+	-	-	-	x	c						TEK
117	1	21	R	+	-	-	-	x						R	TEK
118	1	20		3+	-						F				TEK
119	1	21								D					TEK
120	1	20		+	-	-	0	x	c						TEK
121	1	19													TEK
122	0	37													TEK
123	0	49													TEK
124	0	25		+	-	-								TB450-HE	TEK
125	0	37		2+						D					TEK
126	0	35		2+	-					D					TEK

127	0	18		3+	-	-	-	x	c						TEK
128	1	18													TEK
129	1	52	R	3+	-	-				D					TEK
130	1	35													TEK
131	0	50													TEK
132	1	30	R	4+	-	-			c						TEK: 5-5-86
1	0	27		+	-	-	-	x	c						KEFETEGNE-18
2	1	32		+	-	-	-	x	c						K18: 20-8-85
3	0	16		+	-	-	-	x	c						K18
4	1	27		+	-	-	-	x	c						K18
5	0	48							c						K18
6	1	16							c						K18
7	1	40													K18
8	1	19													K18
9	1	57										T			K18
10	0	38		+	-					D					K18
11	1	17							c						K18
12	1	15		2+	-	-	-	x	c						K18
13	1	13							c						K18
14	0	46							c						K18
15	1	14									F				K18
16	1	25		+	-	-	-	x	c						K18
17	0	19							c						K18
18	1	35		+	-	-	-	x	c						K18
19	1	36		2+							F				K18
20	1	70													K18
21	0	29		+	-	+	-	B+						RETREATMENT	K18
1	0	20							c						K18:2-11-85
2	1	32											HE		K18: 21-11-85
3	1	17									F				K18
4	1	26									F				K18
5	0	13		+	-	-	-	x	c						K18
6	0	15		+	-	-	-	x	c						K18
7	0	25													K18
8	1	20		2+	-	-	-	x	c						K18
9	1	49								D					K18
10	1	30								D					K18
11	1	18		+	-	-	-	x	c						K18
12	0	16													K18
13	1	28													K18
14	1	25		2+	-	-	-	x	c						K18
15	1	18		+	-	-	-	x	c						K18
16	0	18		+	-	-	-	x	c						K18
17	0	14													K18
18	0	25		3+	-						F				K18
19	0	25		3+	-	-	-	x	c						K18
20	1	27		2+	-	-	-	x	c						K18
21	1	48									F				K18
22	1	58													K18

23	1	22													**K18: 15-2-86**
24	1	25		+						D					**K18**
25	0	22		+	-					D					**K18**
26	0	30												TB450-HE	**K18**
27	1	3													**K18**
28	0	19		2+	-	-	-	x	c						**K18**
29	0	16		2+	-	-	-	x	c						**K18**
30	1	30		3+	-	-	-		c						**K18**
31	0	20													**K18**
32	1	44								D					**K18**
33	1	26													**K18**
34	0	27										T		HOSPITAL	**K18**
35	1	14		+	-	-			c						**K18**
36	0	30								D				TB450-HE(HOS)	**K18**
37	1	36													**K18**
38	1	42												TB450-HE(HOS)	**K18**
39	0	23		+	-	-	-	x	c						**K18**
40	1	28		+	-	-			c						**K18**
41	0	20		2+	-	-								TB450-HE	**K18**
42	0	12													**K18**
43	0	8													**K18**
44	1	12													**K18**
45	0	17		+	-	-				D					**K18**
46	1	6									F				**K18: 6-5-86**
47	1	39	TD							D					**K18**
48	1	15		+	-	-			c						**K18**
49	1	31													**K18**
50	1	40		2+	-							T			**K18**
51	1	23		3+	-						F				**K18**
52	1	22		+	-	-			c						**K18**
53	0	39		3+	-	+			c						**K18**
54	0	18		2+						D					**K18**
55	0	22													**K18**
56	1	20		2+	-					D					**K18**
57	0	40													**K18**
58	0	5													**K18**
59	1	19		2+	-	-		C	c						**K18**
60	0	1	T								F				**K18**
61	1	36								D	F				**K18**
62	0	30		2+	-	-		C	c						**K18**
63	0	43		+	-	+		C	c						**K18**
64	0	58									F				**K18**
65	1	27													**K18**
66	1	3													**K18**
67	1	10													**K18: 21-7-86**
1	1	15												TB450-HE	**ENTOTO #1**
2	0	28		2+	-	-	-	x	c						**ENT: 7-8-85**
3	1	62									F				**ENT**
4	1	21		2+	-	-	-	x					HE		**ENT**

5	0	50													ENT
6	0	16		3+	-	-	-	x	c						ENT
7	1	24		2+	-	-	-	x	c						ENT
8	1	19													ENT
9	0	22													ENT
10	0	28													ENT
11	0	18		3+	-	-	-	x	c						ENT
12	1	26									F				ENT
13	1	26		3+	-	-	-	x	c						ENT
14	1	26									F				ENT
15	1	35									F				ENT
16	1	18		2+	-	-	-	x	c						ENT
17	1	22											HE		ENT
18	1	17													ENT
19	0	55									F		HE		ENT
20	0	35		3+	-	-	-	x	c						ENT
21	1	19		2+	-	-	-	x	c						ENT
22	1	22													ENT: 11-10-85
23	1	30		2+	-						F				ENT
24	0	35		2+	-	-	-	x	c						ENT
25	1	50		2+	-	-	0	x	c						ENT
26	1	37		3+	-	-	-	x	c						ENT
27	1	22		2+	-	-	-	x	c						ENT
1	1	52		2+	-	-					F		HE		ENT
2	0	35		2+							F				ENT
3	0	25									F				ENT
4	1	10													ENT
5	0	25									F				ENT
6	0	26													ENT
7	1	13													ENT
8	0	18													ENT
9	0	40									F				ENT
10	0	13		2+	+	-	-	x	c						ENT
11	0	18									F				ENT
12	1	38		3+								T	HE		ENT
13	1	47		2+	-	-	-	x	c						ENT
14	0	2													ENT
15	1	14		2+	-	-	-	x	c						ENT
16	1	52											HE		ENT
17	0	17		3+	-	-	-	x	c						ENT: 11-12-85
18	0	5		3+	-	-	-	x	c						ENT
19	1	47		2+	-	-	-		c						ENT
20	1	37		2+	-	-	-	x	c						ENT
21	0	35													ENT
22	1	22		3+	-	-	-	x	c						ENT
23	0	20		2+	-	-	-	x	c						ENT
24	0	40										T			ENT
25	1	18													ENT
26	1	37													ENT

27	1	17													ENT
28	0	50													ENT
29	0	19		3+	-	-	-	x	c						ENT
30	1	18													ENT
31	1	45		2+	-	-	-	x	c						ENT
32	1	72		2+	-	-					F		HE		ENT
33	1	25		2+	-	-	-	x	c						ENT
34	1	31													ENT
35	0	20		3+	-	-	-	x	c						ENT
36	0	28		2+	-	-	-	x	c						ENT: 25-1-86
37	1	14													ENT: 1-2-86
38	1	23		2+							F				ENT
39	1	28		3+	-	2+					F				ENT
40	1	28		2+	-	-		x	c						ENT
41	0	3													ENT
42	1	6													ENT
43	1	52									F				ENT
44	1	12		2+	-	-			c						ENT
45	1	22		3+	-	-			c						ENT
46	0	23		2+	-	-	-	x					HE		ENT
47	0	28								D					ENT
48	1	22													ENT
49	1	36													ENT
50	1	57		2+						D					ENT
51	0	50								D					ENT
52	0	35		2+	-	-	-	x	c						ENT
53	1	30		3+	-			x	c				HE		ENT
54	1	77													ENT
55	1	50										T			ENT
56	1	22		3+								T			ENT
57	0	18													ENT
58	0	23								D					ENT: 14-3-86
59	0	4										T			ENT
60	1	18													ENT
61	0	50													ENT
62	1	20									F				ENT
63	1	54		2+	-	-	-	x	c						ENT
64	1	17		3+	-	-		x	c						ENT
65	0	16		2+	-				c						ENT
66	1	20		3+	-			x	c						ENT
67	1	60								D					ENT
68	1	30		3+							F				ENT
69	1	32										T			ENT
70	1	50													ENT
71	0	20		3+	-	-	-	x	c						ENT
72	1	26		3+	-					D					ENT
73	1	7													ENT
74	0	25													ENT
75	1	28		2+	-	-		x	c						ENT

76	0	42		2+	-	-		x	c						ENT
77	1	18													ENT
78	1	65													ENT
79	1	29		3+	-					D				TB450-HE	ENT
80	1	39		2+	-	-	-	x	c						ENT: 15-4-86
81	1	52													ENT: 15-4-86
82	0	33		2+	-	2+	-		c						ENT
83	0	18		2+	-	-	-	x	c						ENT
84	0	25													ENT
85	1	35													ENT
86	0	25										T	HE		ENT
87	1	18													ENT
88	1	35	TD							D					ENT
89	0	15		2+	-						F				ENT
90	1	18													ENT
91	0	15		3+	-	-			c				HE		ENT
92	1	30													ENT
93	0	26		3+						D					ENT
94	0	18													ENT
95	1	52													ENT
96	0	40													ENT
97	1	22													ENT
98	1	30		2+	-					D					ENT
99	1	18													ENT
100	1	18		3+	-				c						ENT
101	1	18													ENT: 10-8-86
102	1	-													ENT
103	1	30								D					ENT
104	1	12													ENT
105	0	45		2+							F				ENT
106	0	4													ENT
107	1	37													ENT
108	1	26		3+	-							T			ENT
109	0	16													ENT
110	1	15													ENT
111	1	35													ENT
112	0	15											HE		ENT
113	0	60													ENT
114	0	3													ENT
115	0	40													ENT
116	0	26											HE		ENT
117	0	20													ENT
118	0	39													ENT
119	0	75										T			ENT
120	0	21		2+	-				c						ENT
121	1	22		2+	-				c						ENT
122	0	21		3+	-	-			c						ENT
123	1	58													ENT: 28-6-86
1	1	35									F				SHEROMEDA

2	1	22		2+	-	-		x	c					TB450-HE	**SHE: 20-8-85**
3	1	26		3+	-	-		x	c						**SHE**
4	0	44		+	-	-	-	x					HE		**SHE**
5	1	28												TB450-HE	**SHE**
6	1	28		3+	-	-				D			HE		**SHE**
7	1	34		+	-						F				**SHE**
8	0	12												TB450-HE	**SHE**
9	0	21									F				**SHE**
10	0	23													**SHE**
11	0	45		2+	-							T			**SHE**
12	0	25										T			**SHE**
13	1	53		+	-					D			HE		**SHE**
14	1	19		3+	-	-	-	x	c						**SHE**
15	1	10		2+	-	-		x				T			**SHE**
16	1	25		2+	+	-	-	x	c						**SHE**
17	1	20		3+	-						F				**SHE**
18	0	18											HE		**SHE**
19	1	34		2+	-	-	-	x						TB450-HE	**SHE**
20	1	19		2+	-							T	HE		**SHE**
21	0	23		3+	-	-	-	x	c						**SHE**
22	1	22		+	-	-	-	x	c						**SHE: 3-10-85**
23	1	52		2+	-	-	-	x					HE		**SHE**
24	1	16						x							**SHE**
25	0	16		2+	-	-		x	c				HE		**SHE**
26	0	50		2+	-	-	-	x	c						**SHE**
27	1	40		+	-	-	-	x	c						**SHE**
28	0	4													**SHE**
29	1	33												TB450-HE	**SHE**
30	0	8													**SHE**
31	0	21		3+	+	-	+							BAC+	**SHE**
32	0	20													**SHE**
33	0	25		3+	-	-	-	x	c						**SHE**
1	1	18									F				**SHE**
2	0	16													**SHE**
3	0	17												SENSITIV. TST	**SHE**
4	0	23													**SHE**
5	0	29		3+	-	-	-	x						TB450-HE	**SHE**
6	1	12													**SHE**
7	0	16												TB450-HE	**SHE**
8	1	13													**SHE**
9	1	25		2+	-	-	-	x						TB450-HE	**SHE**
10	1	15		+	-	-	-	x	c						**SHE**
11	1	19		2+	-	-	-				F				**SHE: 3-13-86**
12	0	22													**SHE**
13	0	11		3+	-	-	-	x			F				**SHE**
14	1	19		+	-						F				**SHE**
15	1	19		2+	-	-	-	x					HE		**SHE**
16	0	22													**SHE**
23	0	26										T			**SHE**

18	0	20								D				TB450-HE	**SHE**
19	1	33		+	+	-	-	x	c						**SHE**
20	0	60									F				**SHE**
21	1	25		2+	-	-	-	x						TB450-HE	**SHE**
22	1	21		3+	2+	-	-	x	c						**SHE**
24	1	35		3+	-	-		x	c						**SHE**
25	1	30		2+	+	-	-		c						**SHE**
26	1	20		+	-	-		x	c						**SHE**
27	1	49		3+	-	-	-	x	c						**SHE**
28	0	38		2+	-	-	-	x						TB450-HE	**SHE**
29	1	21		2+	-	-	-	x	c						**SHE**
30	1	20													**SHE**
31	0	0.75									F				**SHE**
32	0	50													**SHE**
33	1	28		3+	-	-		x	c						**SHE**
17	1	59		+	-	-		x	c						**SHE: 28-11-86**
34	0	20		2+	-	-		x	c						**SHE**
35	0	13		2+	+	-		x	c					TB450-HE	**SHE**
36	1	31		3+	-	-	-	x						TB450-HE	**SHE**
37	1	20		2+	-	-	-	x						RETREATMENT	**SHE**
38	0	35		3+	-	-		x	c						**SHE**
39	1	22		2+	2+	-	-	x	c						**SHE**
40	0	27		+	-	-	-	x	c						**SHE**
41	0	25		+	-	-		x	c						**SHE**
42	1	73		+	-	-			c						**SHE**
43	0	17								D					**SHE**
44	1	20		2+	-						F				**SHE**
45	1	3													**SHE**
46	0	38		3+						D					**SHE**
47	0	17		2+	-	-		x	c						**SHE**
48	1	17												TB450-HE	**SHE**
49	1	2													**SHE**
50	1	20													**SHE**
51	1	23													**SHE**
52	0	45		3+					c			T			**SHE**
53	1	4													**SHE**
54	1	18													**SHE**
55	1	22		2+	-				c						**SHE: 9-2-86**
56	0	19		2+	-	-	-	x						TB450-HE	**SHE**
57	0	38		2+	-						F				**SHE**
58	1	1										T			**SHE**
59	1	32		3+	-						F				**SHE**
60	1	18													**SHE**
61	1	31		2+	-	-	-		c						**SHE**
62	0	25		2+	-	-	-	x	c						**SHE**
63	1	54		+	-	-	-	x						TB450-HE	**SHE**
64	0	16													**SHE**
65	1	28		2+	-	-	-	x						TB450-HE	**SHE**
66	1	32		3+	-	-		x	c				HE		**SHE**

67	0	21		2+	-	-		x	c					TB450-HE	**SHE**
68	0	25		-	+									TB450-HE	**SHE**
69	0	14	T												**SHE**
70	0	56		2+	-	-	-	x	c						**SHE**
71	0	22		3+	-	-	-	x	c						**SHE**
72	1	65													**SHE**
73	1	19										T			**SHE**
74	1	19													**SHE**
75	0	28		3+	-	-		x	c						**SHE**
76	1	24	T										HE		**SHE**
77	0	18		2+	-	-	-	x	c						**SHE: 3-3-86**
78	1	18		+	-	-	-	x	c						**SHE**
79	0	30								D					**SHE**
80	0	23													**SHE**
81	1	35		2+	-	-		x	c						**SHE**
82	0	25													**SHE**
83	0	35													**SHE**
84	1	67													**SHE**
85	0	22													**SHE**
86	1	42													**SHE**
87	1	19													**SHE**
88	1	27													**SHE**
89	1	31		+	-	-			c					TB450-HE	**SHE**
90	1	67													**SHE**
91	0	17													**SHE**
92	1	37		3+	-	-		x	c					TB450-HE	**SHE**
93	1	20													**SHE**
94	1	31	R	3+	-	-		x	c					RETREATMENT	**SHE**
95	1	19		+	-	-								TB450-HE	**SHE**
96	1	12													**SHE**
97	1	12										T			**SHE**
98	1	17		3+	-				c						**SHE**
99	0	24	T	+	-				c				HE		**SHE: 12-3-86**
100	0	40													**SHE**
101	0	48													**SHE**
102	0	64													**SHE**
103	1	20		2+	-	-	-	x	c						**SHE**
104	1	10													**SHE**
105	1	28	T										HE		**SHE**
106	1	15													**SHE**
107	1	21		3+	-	-		x	c						**SHE**
108	0	18	T	2+	-	-	-	x					HE		**SHE**
109	1	22		3+	-				c						**SHE**
110	1	15		2+	-						F				**SHE**
111	1	61											HE		**SHE**
112	1	10													**SHE**
113	1	14	T	3+	-			x	c						**SHE**
114	1	28											HE		**SHE**
115	1	41													**SHE**

116	1	40	R											RETREATMENT	**SHE**
117	0	30		3+	-						F				**SHE**
118	1	20													**SHE**
119	1	13													**SHE**
120	1	55													**SHE**
121	1	18													**SHE: 11-7-86**
122	0	35		3+	-				c						**SHE**
123	0	25		3+	-	-	-						HE		**SHE**
124	1	22									F			TB450-HE	**SHE**
125	1	33													**SHE**
126	1	28								D			HE		**SHE**
127	0	18													**SHE**
128	1	20													**SHE**
129	1	32													**SHE**
130	1	18													**SHE**
131	0	55								D					**SHE**
132	1	75		2+	-					D					**SHE**
133	1	26		2+	-	-		x	c						**SHE**
134	0	20											HE		**SHE**
135	0	32		+	-	-		x	c				HE		**SHE**
136	0	25													**SHE**
137	1	24		+	-	-			c						**SHE**
138	0	15		+	-	-		x	c						**SHE**
139	0	37		3+	-	-			c				HE		**SHE**
140	1	39													**SHE**
141	1	26		2+	-	-			c				HE		**SHE**
142	0	40													**SHE**
	481	27.5													

APPENDIX B

LABORATORY COSTS	Item	Unit	Cost (birr)	Per Unit	/Patient: LCC	/Patient: SCC	Total LCC/Area	Total SCC/Area
Screening Cost	Solution A, 500 ml.	/bottle	12.80	(0.2694)(3)=.81				
3X ea.	Solution B, 500 ml.	/bottle	16.90	(0.3557)(3)=1.07				
	Sputum Sample Cups	/ea	0.13	(.13)(3)=.390				
	Cost/Patient Successfully Screened							
				(2.26)(15040)/635	53.49	53.49		
4X LCC	Microscope (last 6-7 years)	/ea	4,257.20	(.33)(4257.2)=1404.88/(268)(6.5)=.82	0.82	0.82		
3X SCC	Micro Slides	/ea	0.04	insignificant				
	Micro Cover Slides	/ea	0.04	insignificant				
Assume 268 Patients	Solution A, 500 ml.	/bottle	12.80	0.2694	1.08	0.81		
per year	Solution B, 500 ml.	/bottle	16.90	0.3557	1.42	1.07		
	Sputum Sample Cups	/ea	0.13	0.13	0.52	0.39		
	Microscope Bulbs (2-3 bulbs/year)	/ea	us.80/5.2b		0.06	0.06		
	Diamond Pencil	UNICEF		re-used repeatedly/unsignificant				
	Wire Loop	UNICEF		re-used repeatedly/unsignificant				
TOTAL								
DRUGS & ASS.	Streptomycin 1 gm	/vial	1.71	60 days @ 1.71/day	102.6	102.6		
	Disposable Syringe: 2 cc w/ needle	/ea	0.23					
	Disposable Syringe: 5 cc w/ needle	/ea	0.26	60 days @ 0.26/day	15.6	15.6		
	Water for injection: 2 cc	/vial	0.48	60 days @ 0.48/day	28.8	28.8		
	Isoniazid: 300 mg	/tab	0.06					
	Isoniazid: 100 mg	/2 tabs	0.04	60 days @ 0.04/day		2.4		
	Rifiampicin: 300 mg	/2caps	1.06	60 days @ 1.03/day		61.8		
	Rifampicin: 100 mg	/2 caps	0.94					
	Pyrazinamide: 500 mg	/4 tabs	0.78	60 days @ 0.78/day		46.8		
	TB 150	/2 tabs	0.06					
	TB 450: 1 Table	/2 tabs	0.07	180/360 days @ 0.035/day	12.6	6.3	159.6	264.3
	Ethambutol: 400mg	/2 tabs	0.28	18 birr/12 birr				
	Vitamin B6: 25 mg	/tab	0.05					
	Boiler 10 years/2680 patients=.559	/ea	1,500.00	syringes assumed new				
	Salvon: 25 liters/2 years=75/536=.13	/bottle	75.00	syringes assumed new				
STAFF COSTS	Nurses	/month	450 birr		20.45	20.45		100.00%
	Lab Tech/screening cost@ hospital				33.4	33.4		
20 min/patient	Lab Technicians @ Health Centres	/month	450 birr		3.76	2.82		
# slides?	Health Assitants	/month	300 birr		13.63	13.63	100.00%	
(1/2 day per week)	Physicians	/month	867.5 birr		3.236	3.236	6.67%	
X-RAY	X-Ray Machine							
(Smear -)	Cost of those successfully X-Rayed	/ea	10-15 birr		150	150		
(from Black Lion and								
Yekatit)								
	X-Ray Technician		450 birr		1.88	1.88		
	(private cost 29-35 birr)							
TOTAT STATIONARY	Printing Formats & Registration Books	total	20,374.80		1.64	1.64		
	Office Stationary	total	14,000.00		2.26	2.26		
	Contingency Fee 10%	total	1,226.20					

TRAINING	Pilot Training in Arsi		38,662.45					
	N-Pilot Training		7,007.00					
IN-PATIENT COSTS	Per Bed							
	Doctor Costs		950.00					
	Nurses		400.00					
	Technician							
	Overhead/Utilities							
	Building	1930's	???					
OUT-PATIENT COSTS								
	Telephone w/ delivery		300.00					
	Telephone w/o delivery		100.00		0.45	0.45		
	Electricity w/ delivery		1,000.00					
	Electricity w/o delivery		300.00		0.75	0.75		
	Water w/ delivery		200.00					
	Water w/o delivery		100.00		0.45	0.45		
	Building	/health cnt	1, 2 000. 000					
ADMINISTRATION	Coordinator	/month	950.00		1.84	1.84		
	Sister Enesh	/month	710.00		1.37	1.37		
	Dr. Eyob 10% of time	/month	980.00		0.19	0.19		
PHARMACY	Coordinator 10% of time	/mo	980.00		0.19	0.19		
	Pharmacist 1/2 day each 45 days	/mo	600.00		0.3	0.3		
	(stocking and ordering)							
TRAVEL	Fuel/Driver	/week/HC	10.00	insignificant-driver doesn't just do TB				
	(Defaulter cost integrated w/other)							
CVC DIAGNOSIS	Nurse Time	400-500			2.34	2.34		
	Lab Technician	400-500						
	CVC Health Centres	1.5						
	CVC Hospitals	5			50	50		
	Stool/Urine Private	3-7						
TOTAL COST					449.736	553.016		
COST PER CURE					603.756	609.305		
COST PER PATIENT								
COST/DEATH AVERTED								
COST PER HEALTH CNTR								
RETREATMENT								
				H Sensitive (all defaulters)	H Resistant (All Bac. +)			
DRUG COSTS	RIFAMPICIN: 300mg	1.06	@ 90 Days	95.4	95.4			
	ISONIAZID	0.06		5.4	5.4			
	PYRAZINAMIDE	0.78		70.2	70.2			
	ETHAMBUTOL	0.42		37.8	37.8			
	STREPTOMYCIN	1.71		153.9	153.9			
	Syringe and Needle	0.26		23.4	23.4			
	Water for Injection	0.48		43.2	43.2			
	TB450 (Daily for 4 months)		@ 150 Days	5.25				
	R (3 times/week):4(150) mg.	2.12	@ 64 Days		135.68			

	H (3 times/week): 4 (100) &4(300)mg	0.32	@ 64 days		20.48			
	E (3 times/week):4(400)mg.	0.28	@ 64 days		17.92			
LABOUR	Nurse Time	10.22/mo.pat.	@ 90 Days	30.67	30.67			
	Doctor Time			3.24	3.24			
	Health Assistant	6.81/mo. pat.	@ 90 Days	20.44	20.44			
	Lab Technician Screening Cost			33.4	33.4			
	Lab. Tech @ Health Centre			2.82	2.82			
	Pharmacist @ Health Centre			0.3	0.3			
SPUTUM MICROSCOPY	Sputum Costs/Screening			53.49	53.49			
	Gen. Sputum Costs			2.33	2.33			
CVC	CVC Nurse Time			2.34	2.34			
	CVC Screening Cost			50	50			
CRX	CRX Screening Costs			150	150			
	XR Technician Cost			1.88	1.88			
Stationary	Stationary			1.64	1.64			
Coordinators	TB Coordinator			1.84	1.84			
	Coordinator Nurse			1.37	1.37			
	Head of Epidemiology			0.19	0.19			
	Coordinator Pharmacist			0.19	0.19			
	TOTAL			790.69	959.52			
DEATH COSTS	3 birr per day- Find out who died							
	1200 birr/year lost							
	23 died: S.C.C.	1031412		4142.22				
	9 died L.C.C.	403596		4435.12				
	Average Age:27							
	Life Expectancy: 64.37							
	37.37 years of life lost							
	44844 birr lost /patient who died							

APPENDIX C

KEFETEGNE 17

Interviewed: Dr. Ketsela/Nurse Maseret
TB Patients to Date: 134 from 13/3/86-25/12/86 E.C.
NP/P: NP
Laboratory: on-site
Initial Smear: 3 read by 2 technicians depending on who's working (no form of quality control)
Staining method: Ziehl-Neelsen Method/Gram stain
Laboratory Supplies: No problem
Drug Supply: No Problem with supplies but suffered two months ago before drugs were free and patients had to get a letter saying they could get them free of charge.
Source of Drugs: Zone 14 health bureau
Drug Ordering: done in conjunction with pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: complete
Ease of hospitalisation of patients: no problem
Defaulter Follow-up: give person responsible for the patient (i.e. family member) a call, if contacted, get the patient to sign that he will come in.
How are those transferring to rural areas treated: 2 months continuation phase treatment administered.
Case Finding: Most are referred from hospitals or the TB centre
Problems: defaulters often do not give their real address or phone number. Those coming from rural areas for treatment are often quite critical, but having no place to live, they only take two weeks of intensive treatment.
Forms: Tuberculosis register, identity cards, patient cards, smear requests
Syringes: New

KEFETEGNE 19

Interviewed: Dr. Mulu
TB Patients to Date: 211 P and ? NP from 13/8/85-3/1/86 E.C.
NP/P: P and NP
Laboratory: on-site
Initial Smear: 3 read by 2 technicians depending on who's working (no form of quality control)
Staining method: solution a and b, 112+/735 with 85 follow-ups
Laboratory Supplies: No problem
Drug Supply: some problems procuring Ethambutol for those with reactions
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: complete
Ease of hospitalisation of patients: no problem
Defaulter Follow-up: give patient (i.e. family member) a call, if contacted, get the patient to sign that he will come in, if cannot get the patient, then contact person responsible.
How are those transferring to rural areas treated: 1 month continuation phase treatment for those moving. If they are in the intensive phase, there is no treatment without an address- if you cannot stay, you get a referral slip and that's the end of it.
Case Finding: Almost all smear negatives and extra-pulmonary cases come from the hospital, some smear positive cases come from the hospital, but many also come from off of the street.

Problems: It is the patients who are smear positive who are the most likely to die. This is probably due to complications from AIDS. Rarely do the smear positive patients die. I find this interesting because it is the smear negative patients who are the most expensive to treat as they often require X-rays both to verify diagnosis and to verify a cure.
Forms: Tuberculosis register, identity cards, patient cards, smear requests
Syringes: Boiled syringes, unless the patients can afford to buy them. Syringes are treated with Savlon and then boiled for 30 minutes or more. There is also a separate boiler just for those patients with tuberculosis. The doctor admitted that some of the syringes are a little dull and difficult to get into the patient sometimes.

KEFETEGNE 13

Interviewed: Dr. Kidist
TB Patients to Date: -
NP/P: Pilot`
Laboratory: on-site
Initial Smear: 3 read by 2 technicians depending on who's working (no form of quality control), after patient appears to be negative, no more smears are done
Staining method: solution a and b
Laboratory Supplies: No problem, except with wire loop and diamond pencil
Drug Supply: always enough drugs
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: not always complete previously, after repeatedly sending patients back for more information, this is less of a problem.
Ease of hospitalisation of patients: there are real problems, patients are not admitted when requested, they say that it is "useless to admit HIV+ patients". Cannot handle critical cases that need to be hospitalised as they have not beds or IV foods.
Defaulter Follow-up: give patient (i.e. family member) a call and tell them to come in, the previous nurse who was trained is now gone, therefore only telephone the patient. If the patient doesn't have a phone, there is no follow-up as there is no car provided to go to the patient's house. Also, patients for fear of not being treated without a phone number, often give a fake one. Chronic patients have developed a hierarchy at this treatment centre and order the new
patients to come for treatment. This is the only other form of follow-up for the patients.
How are those transferring to rural areas treated: 1 month continuation phase treatment for those moving. If they are in the intensive phase, there is no treatment without an address- if you cannot stay, you get a referral slip and that's the end of it.
Case Finding: Almost all cases come from the hospital,
Problems: The nurse that was trained to treat the TB. patients left the centre and now it is very difficult to get nurses to treat the disease. TB. patients are unpopular to treat at the health centre as they can be irritable. Also, nurses are afraid of contamination. Nurses are put on a three month revolving work schedule for treatment of TB. patients which effectively means that nurses must be trained every three months. Smear should have been taken at regular intervals. Pre-pilot times suggest a random taking care of patients, no smear information was recorded nor default, death or record of continuous treatment. Also, treatment occurring in the clinic includes a weird variety of regimens such as SER for one month or RH given for nine months and that's it. Patients are not always weighed.
Forms: Tuberculosis register, identity cards, patient cards, smear requests
Syringes: Syringes are boiled for the patients, but if the patients is suspected of being HIV+, he or she is given disposable syringes.

KAZANCHEZ

Interviewed: Yocabel
TB Patients to Date: 114
NP/P: Non-Pilot
Laboratory: on-site
Initial Smear: 3 read by 2 technicians depending on who's working (no form of quality control), after patient appears to be negative, no more smears are done
Staining method: solution a and b
Laboratory Supplies: No problem
Smear+ Examination: 14/145, 3-5 examinations are done per day, sometimes none.
Drug Supply: it is sometimes difficult to get ethambutol or rifampicin
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: incomplete information sometimes- if this is the case, they just send the patient back for more information
Critical Patients: there is a real problem, some very critical patients arrive at the health
centre from the hospitals often on stretchers and they have to be sent back but the hospitals sometimes will not take them.
Ease of Hospitalisation of Patients: There is a problem
Defaulter Follow-up: telephone the patient and if this does not work, go to the patient's house
How are those transferring to rural areas treated: 1 month continuation phase treatment for those moving. If they are in the intensive phase, there is no treatment without an address- if you cannot stay, you get a referral slip and that's the end of it.
Case Finding: Almost all cases come from the hospital,
Forms: Tuberculosis register, identity cards, patient cards, smear requests Syringes:
Syringes: are boiled but disposable syringes are used for the HIV+ patients. Syringes are used for one week.

TEKELEHAMANOT

Interviewed: Nurse Negassa
TB Patients to Date: 294`
NP/P: Pilot
Laboratory: on-site
Initial Smear: three are done and read by one technician
Staining method: solution a and b
Laboratory Supplies: There is a problem getting solution a and b as often they have not been mixed properly and they have expired. They should service at least for a year.
Smear+ Examination: 34/186 100 follow-ups, 5 minutes for solution A and 3 minutes for solution B. It takes 5-10 minutes to read each slide.
Drug Supply: No problem with drugs, those who are on SDR and can afford rifampicin.
are given it.
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: incomplete information sometimes- if this is the case, they just send the patient back for more information

Critical Patients: there is a real problem, some very critical patients arrive at the health centre from the hospitals often on stretchers and hospitals do not want to take them or do not have room. Don't want the TB patients infecting the other patients. TB-HIV cases are seen as hope less and therefore are given little attention.
Ease of Hospitalisation of Patients: There is a problem
Defaulter Follow-up: There are many defaulters, usually they have economic problems. Nurse Negassa goes to the patient's houses to find them. He is exceptional, cares about the patients. The profile of the defaulters are ex-soldiers who are mostly HIV positive. These soldiers served as ton of the main mechanisms for the transmission of AIDS during the Dergue regime due to sex/rape compounded with frequent movement.
Case Finding: Almost all cases come from the hospital.
Syringes: Syringes are boiled, those who can afford to buy syringes do. Syringes can be used in excess of 100 times. The needles gets very dull and become painful to inject. A special problem. (notes: Case of Critical mother-both children of 6 and 7 also got TB. Negassa works entirely on TB with the other nurse.)

ADDIS KETEMA

Interviewed: Dr. Etsegenet (medical director) and Nurse Kassye
TB Patients to Date: 501
NP/P: Non-pilot
Laboratory: on-site
Initial Smear: three are done and read by one technician
Staining method: solution a and b
Laboratory Supplies: No problem
Smear+ Examination: 21+/334 smears 2 minutes for solution A and 2 minutes for solution B. It takes 10 minutes to read each slide.
Drug Supply: No problem with drugs in the past-two months ago- before drugs were free- this was a problem.
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: complete
Critical Patients: very critical patients arrive
Ease of Hospitalisation of Patients: There is a problem
Defaulter Follow-up: Often defaulters give false telephone numbers, it can be very difficult to get them. Often they come from extremely rural areas and live with relatives who claim that they are from Addis. Treatment for those moving to rural areas: 2 months treatment and a transfer letter to the appropriate hospital or health centre
Syringes: Syringes are boiled use disposable syringes for one week. Patients can also buy new syringes.

KEFETEGNE 23

Interviewed: Nurse Fanakebede, Nurse Getalma, HA Temeselew Asefa (spend all of their time working on TB
TB Patients to Date: 306
NP/P: Non-Pilot
Laboratory: on-site

Initial Smear: three are done and read by one technician
Staining method: solution a and b
Laboratory Supplies: No problem
Smear+ Examination: 46+/713 smears 381 follow-ups, 5 minutes for solution A and 3 minutes for solution B. It takes 15-20 minutes to read each slide.
Drug Supply: there are not sufficient supplies for drugs, approximately 120,000 birr per year is allocated for each health centre and out of this must come TB drugs, sometimes there is a problem getting ethambutol or rifampicin, but this is not surprising since this is a non-pilot institution.(from pharmacist)
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: complete
Critical Patients: very critical patients arrive
Ease of Hospitalisation of Patients: Hospitals won;t always admit patients due to lack of space- nurse says that even HIV's must be accepted
Defaulter Follow-up: Patients are given a phone-call and ask them to come in- not problem with patient-compliance.
Treatment for those moving to rural areas: 1-2 months treatment and asked to return after that.
Syringes: They are not getting syringes and have many problems- use a syringe 3-4 times-or for one week. Use old syringes from around the centre-i.e. penicillin injections. Boil, disposable syringes and needles are observed to sometimes get very dull.

KEFETEGNE 18

Interviewed: Nurse Samrawite Bhere Tibebe (spends all her time on TB) also OPD nurse spends afternoons on TB. Dr. Mertework has contracted TB- the doctor who was trained 1-2nd month on TB treatment.
TB Patients to Date: 269
NP/P: Pilot
Laboratory: on-site
Initial Smear: three are done and read by one technician, collects slides for later quality control- students read them
Staining method: solution a and b
Laboratory Supplies: No problem, solution is re-prepared after three months
Smear+ Examination: 68+/535 smears 266 follow-ups, 5 minutes for solution A and 3 minutes for solution B. It takes 30 minutes to read each slide.
Drug Supply: always enough
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing, drugs are ordered every 45 days. Eyob says there is not a 3 month buffer of drugs. Pharmacist takes 1/2 day every 45 days stocking, dispensing the drugs.
Patient Referral Information from hospitals: complete
Critical Patients: very critical patients arrive and are kept at the health centre
Ease of Hospitalisation of Patients: no problem
Defaulter Follow-up: Patients are given a phone-call and if this doesn't work, they go to his house.
Treatment for those moving to rural areas: inject and send away- no medicine is given to them.
Syringes: Boil syringes and use them 5 times

ENTOTO #1

Interviewed: Nurse Lakew and Nurse Sewagegne
TB Patients to Date: 270
NP/P: Pilot
Laboratory: on-site
Initial Smear: three are done and read by one technician
Staining method: solution a and b
Laboratory Supplies: No problem
Smear+ Examination : 37/402 smears 128 follow-ups, 2-3 minutes for solution A and 4 minutes for solution B. It takes 5 minutes to read each slide.`
Drug Supply: fine
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: complete
Critical Patients: very critical patients arrive and will give them their medicine at home.
Ease of Hospitalisation of Patients: The patient himself is what limits hospitalisation- it is a question of economics- if he or she cannot afford transport to hospital. Also professionals may not be co-operative, there may be not beds and patients may be told to come again after the patient has paid much to travel there and when some come alone without relatives.
Defaulter Follow-up: See below
Syringes: One or two patient bring syringes. Otherwise, they use a drive oven to sterilise syringes.
Notes: The maximum spent with a patient is 10 minutes per day. The doctor spends about a 1/2 day per week or 3-5 days helping during the month. Many of the staff are trained in Cuba from the Dergue regime. Often they will have spent 10 years in Cuba. 500 or so received military scholarships to study there. The medical director showed me the catchment area. 7 bikes are provided by donation from UNICEF. Telephone the Kebele of the defaulter and a representative from the Kebele will go to their house, pick them up on the bicycle and ride the patient to the health centre. It costs 1.6 birr to get to the health centre ad 3 eggs cost 1 birr. Medical director said that she will go herself if she has problem in getting hold of someone at the Kebele. A patient is considered a defaulter (i.e. he/she is chased) if they miss 4-5 days of treatment. One of the things that the medical director has not considered is that not all that many people know how to ride a bicycle.

KOLFE HEALTH CENTRE

Interviewed: Dr. Dejene T/haimanot
TB Patients to Date: 188
NP/P: Non-Pilot
Laboratory: on-site
Initial Smear: three are done and read by one technician
Staining method: solution a and b, used methyline blue before.
Laboratory Supplies: No problem
Smear+ Examination: 45+/357 with 75 follow-ups, 5 minutes sol A, 3-4 for solution B. 20 TB slides per day (6 patients per day come in). Gloves are a problem. Rechecks positive slides- kept in a box- students come and look. No wire loop- use a stick instead. Heat and it dries, stain, blot, then read for 10 minutes per total smear. Must wear a mask to collect sputum samples.
Drug Supply: fine
Source of Drugs: Zone 14 health bureau

Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: inappropriate referrals come from the hospitals- patients started on SCC must can only be given SDR in this non-pilot area. Some patients are sent with a prescription only and no other information. 75% come from hospitals.
Critical Patients: very critical patients arrive and will give them their medicine at home.
Ease of Hospitalisation of Patients: Difficult to hospitalise patients.
Defaulter Follow-up: Call defaulters and send name to Kebele- there is a problem in motivating health workers sometimes. Many come from the South for treatment and are accepted but then leave. The real defaulters are often not the area residents. Also residents often rent and are made to move and do not notify the health centre. Most workers are weavers and low business traders.
Syringes: Boil syringes- all TB drugs are free- 5% bring syringes maybe. Syringes are used 3-5 times before thrown away. After that- the disposable syringes loses its elasticity and the needle gets dull. Want to use re-usable syringes.

SHEROMEDA HEALTH CENTRE

Interviewed: Nurse Tesfaye Geleta and Dr. Assefu
TB Patients to Date: 417
NP/P: Pilot
Laboratory: on-site
Initial Smear: three are done and read by one technician
Staining method: solution a and b, used methyline blue before.
Laboratory Supplies: sometimes need more solution
Smear+ Examination: 136+/421, with 126 follow-ups. takes 15-20 minutes for the entire reading process. Read 8-12 slides per day, 3-5 minutes solution A, 5-10 minutes +solution B. Positive slides are rechecked `
Drug Supply: fine
Source of Drugs: Zone 14 health bureau
Drug Ordering: done by pharmacist analysis of last quarter report, drug needs are increasing
Patient Referral Information from hospitals: complete
Critical Patients: maybe 1-2 per month
Ease of Hospitalisation of Patients: Admission is a problem, hospitals won't take patients.
Defaulter Follow-up: contact person is called and contact at home through Kebele.
For those leaving for rural areas: Use referral slip and give 2 months treatment if on the continuous phase
Syringes: Most (80%) cannot afford to buy syringes- boil syringes. Use re-usable 100 times and disposable 4-5 times. Nurses give 70 injection per day.`
Occupations: local traders, wazaders (day labourer)

APPENDIX D

አንዳንድ ጠቃሚ ምክሮች ፤

1. የነቀርሳ በሽታ በሕክምና ይድናል ፤
2. ከበሽታዎ ሙሉ ለሙሉ እንዲፈወሱ የሚሰጥዎትን መድኃኒት ያለማቋረጥ መውሰድና በቀጠሮዎ ቀን በጤና ድርጅቱ መገኘትዎ የግድ አስፈላጊ ነው ።
3. መዳንዎ በምርመራ ከመረጋገጡ በፊት ጊዜያዊ የጤንነት ስሜት ስለተሰማዎ ብቻ ሕክምናዎን ማቋረጥ ለከፋና በቀላሉ ለማይድን በሽታ ያጋልጥዎታል ።
4. ይህ የመታወቂያ ወረቀት ቢጠፋ በሌላ ሊተካልዎ ይችላል ፤
5. ከቤተሰብዎ ወይም ከጓደኞችዎ መሐከል የጠና (የቆየ) ሳል ያለበት ሰው ቢኖር እኛ ዘንድ መጥቶ እንዲመረመር ይምከሩ ፤

ንግድ ማተሚያ ቤት 41002/85

በጤና ጥበቃ ሚኒስቴር

ብሔራዊ የነቀርሳ መቆጣጠሪያ ፕሮግራም

የነቀርሳ ፡ ሕመምተኛ መታወቂያ ፡ ካርድ ።

Identity Card for Tuberculosis Patients

ስም .....

ዕድሜ ..... ጾታ .....

አድራሻ ፡ ክፍለ ሀገር.....

አውራጃ ..... ከፍተኛ.....

ቀበሌ/ገበሬ ማኅበር .....

የቤት ቁጥር .....

የጤና ድርጅቱ ስም .....

NATIONAL TUBERCULOSIS [illegible]AMME

TB 08

QUARTERLY REPORT ON THE RESULTS OF TREATMENT OF PUL[illegible]RY TUBERCULOSIS PATIENTS REGISTERED 12-15 MONTHS E[illegible]ER

Name of district _____ District No _____

Name of District Tuberculosis coordinator _____

Patients registered during

☐ Quarter of 19

Date of completion of this form

_____ 19 _____

Signature:

Total No of Pulmonary patients registered during the above quarter			Regimen	(1) Cured (smear-negative)	(2) Treatment completed (no smear results)	(3) Died	(4) Failure (smear positive)	(5) Defulted (smear-negative)	(6) Transferred to another distirct	Total number evaluated (sum of columns 1 to 6)
New Cases										
M	F	T	1 New cases							
			1.1 Smear-positive							
			1.2 Smear-Negative							
Relapses										
M	F	T	2 Retreatment							
			2.1 Relapses							
			2.2 Others							
			Total							

. Of those _____(number) were excluded from avaluation of chemotherapy for the following reasons: _____

_____

MA [illegible] LIST [illegible]

TB 07

Quarterly report on new cases and replases of tuberculosis	Patients registered during ☐ quarter of ☐

Name of District Tuberculosis-coordinator: ___

Date of completion of this form : _____

Signature : _____

Name of district:
District No

PULMONARY TUBERCULOSIS SMEAR - POSITIVE					SMEAR - NEGATIVE (3)		EXTERA.-PULMONARY TB. (4)		TOTAL (5)		
NEW CASES (1)			RELAPSES (2)								
Males	Females	Total	M	F	M	F	M	F	Male	Females	Total

SMEAR - POSITIVE NEW CASES : from column (1) above

Age - group (years)														TOTAL		
0 - 14		15 - 24		25 - 34		35 - 44		45 - 54		55 - 64		65(more)				
M	F	M	F	M	F	M	F	M	F	M	F	M	F	MALES	FEMALES	TOTAL

TB LABORATORY FORM

REQUEST FOR SPUTUM EXAMINATION

Name Treatment Unit _____ Date _____

Name of patient : _____ Age ____ Sex M ☐ F ☐

Address (in full) : _____ District : _____

Disease classification : Pulmonary ☐ Extra-pulmonary ☐ Site _____

Reason for Examination: Diagnosis ☐ Follow-up of Chemotherapy ☐

Pervious Lab. Serial No _____

Patient's District TB No _____ Signature of Examiner: _____

RESULTS (To be completed in Laboratory)

Lab. Serial No _____

(a) Visual appearnace of sputum:

Muco-purulent ☐ Blood-stained ☐ saliva ☐

(b) Microscopy

Date	Speciment	Results	Positive (grading)			
			+++	++	+	Scanty(*
1			☐	☐	☐	☐
2			☐	☐	☐	☐
3			☐	☐	☐	☐

* Write Neg. or pos.

Date _____ Examined by (Signature): & _____

TUBER CULOSIS REFFERAL / TRANSFER FORM

Name of Health unit _____ Distric _____ Code No. _____

To: _____

Name of patient _____ Age _____ Sex _____

Adress _____ H. ___ K. ___ House No. _____ Farm Ass.

District TB No. _____

Disease classification Sputum _____ _____

Result Grading

Date done _____

P _____ X-ray finding _____

_____

EP _____

Site _____ Date done _____

_____

Patient category

New case ——
——

(Smear positive seriously ill
smear negative of EP)

New case ——
——

(Smear Negative or EP)

Re treatment ——
——

Regimen category

1. ☐ Date treatment started _____

2. ☐ _____

3. ☐ _____

Reason for transfer (referral _____

_____

_____

Recommendation _____

_____

_____

Date _____ Name & Title _____ Signature _____

_____

REFERRAL / TRANSFER FEEDBACK

FROM _____ District _____ Code No. _____

To _____

Patient's Name _____ Age _____ Sex _____

District TB No _____ Date patient Reported _____

A Transfer accepted ☐ Reason for referral investigated ☐

Findings: _____

_____

Recommendation _____

_____

Date _____ Name & Title _____ Signature _____

NATIONAL TUBERCULOSIS PROGRAMME

TUBERCULOSIS TREATMENT CARD

District TB No.: _____

Card No. _____

Patient Registration No. _____

Name: _____

Address (in full) : Town _____ Higher _____ Kebele _____ House No. _____

Farmers Ass. _____ Awraja _____ Administrative region _____

Sex: M ☐ F ☐ Age: _____ BCG: no scar ☐ scar seen ☐ scar dubious ☐

TYPE OF PATIENT

Pulmonary ☐ Extra-pulmonary ☐

New ☐ Relapse ☐

Transfer in ☐ Other (specify) ☐

Treatment after default ☐

REMARKS and Clinical Notes _____

1. INITIAL INTENSIVE PHASE

Prescribed regimen and dosages*

New case ☐ (Standard) — S TH

New case ☐ (short-course) — S R H Z

Retreatment ☐ — S RH Z E

(S for 2 months only)

MONTH	Results of sputum examination					WEIGHT (kg)
	Local lab.		Reference lab. *			
	Date	Smear	Smear	Cult.	Sens.	
0						
2						
5						
8						
≥ 12						

* for patients on short-course chemotherapy only

S : streptomycin, TH: thiazina, RH: rifampicin and isoniazid
Z : pirazinamide, E: ethambutol
* Indicate daily number of tablets and dosage of S (grams)

MONTH \ DAY*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

* Tick appropriate box after the drugs have been administered

Please turn over for continuation phase

COMMERCIAL PRINTING PRESS

TUBERCULOSIS CENTER
CLINICAL RECORD SHEET

X-RAY NUMBER

St. Mary Printers

PERSONAL DETAILS

NAME:	H. K. House No.	TOWN/VILLAGE	AGE:		SEX:	MALE ☐ FEMALE ☐
ADDRESS:		OCCUPATION				DISTRICT
DOCTOR:						

SOURCE OF REFERRAL	OWN INITIATIVE	HEALTH CENTER	HOSPITAL	DOCTOR	CLINIC	GROUP EXAMINATION	CONTACT	OTHER ORGANIZATION
	☐	☐	☐	☐	☐	☐	☐	☐

INITIAL FINDINGS

DATE	MANTOUX RESULT		BACTERIOLOGICAL RESULT		PREVIOUS B. C. G.		WEIGHT
	1st TEST	2nd TEST	SPUTUM	CULTURE	YES	NO	

SYMPTOMS

LOSS OF WEIGHT ☐
FEVER ☐
COUGH ☐
EXPECTORATION ☐
HAEMOPTYSIS ☐
OTHER SYMPTOMS:
ESTIMATE DATE OF ONSET.

TYPE OF PATIENT

PULMONARY

NEW ☐
TRANSFER IN ☐
TREATMENT AFTER DEFAULT ☐

EXTRA-PULMONARY

RELAPSE ☐
OTHER (SPECIFY) ☐

FOR PATIENTS TO BE HOSPITALIZED			REMARKS
ADMITTED	DISCHARGED		

APPENDIX E

Distribution of life expectancies calculated from model life table west data taken from data in C. J. L. Murray (1994)

Number of data points is: $i = 0..17$

Life expectancies at birth from Murray are: **femaleexatbirth** = 82.5 **maleexatbirth** = 80

Data from Murray follows:-

age	**femaleexpectancy**	**maleexpectancy**
0	82.5	80.00
1	81.84	79.36
5	77.95	75.38
10	72.99	70.4
15	68.02	65.41
20	63.08	60.44
25	58.17	55.47
30	53.27	50.51
35	48.38	45.56
40	43.53	40.64
45	38.72	35.77
50	33.99	30.99
55	29.37	26.32
60	24.83	21.81
65	20.44	17.50
70	16.20	13.58
75	12.28	10.17
80	8.9	7.45

The ages are "normalised" to the life expectancy at birth (i.e. divided by life expectancy at birth) so,

$$\textbf{femaleagefrac} = \frac{\textbf{age}}{\textbf{femaleexatbirth}} \qquad \textbf{maleagefrac} = \frac{\textbf{age}}{\textbf{maleexatbirth}}$$

The fractional ages from Murray therefore become:

femaleagefrac =

	0
0	0
1	0.012
2	0.061
3	0.121
4	0.182
5	0.242
6	0.303
7	0.364
8	0.424
9	0.485
10	0.545
11	0.606
12	0.667
13	0.727
14	0.788
15	0.848
16	0.909
17	0.97

maleagefrac =

	0
0	0
1	0.013
2	0.063
3	0.125
4	0.188
5	0.25
6	0.313
7	0.375
8	0.438
9	0.5
10	0.563
11	0.625
12	0.688
13	0.75
14	0.813
15	0.875
16	0.938
17	1

Similarly, the life expectancies for each age are "normalised" to the life expectancy at birth i.e.

$$\mathbf{femaleexfrac} = \frac{\mathbf{femaleexpectancy}}{\mathbf{femaleexatbirth}} \qquad \mathbf{maleexfrac} = \frac{\mathbf{maleexpectancy}}{\mathbf{maleexatbirth}}$$

femaleexfrac =

	0
0	1
1	0.992
2	0.945
3	0.885
4	0.824
5	0.765
6	0.705
7	0.646
8	0.586
9	0.528
10	0.469
11	0.412
12	0.356
13	0.301
14	0.248
15	0.196
16	0.149
17	0.108

maleexfrac =

	0
0	1
1	0.992
2	0.942
3	0.88
4	0.818
5	0.755
6	0.693
7	0.631
8	0.57
9	0.508
10	0.447
11	0.387
12	0.329
13	0.273
14	0.219
15	0.17
16	0.127
17	0.093

Ethiopian life expectancies at birth are: **femaleethiopianexatbirth** = 53 **maleethiopianexatbirth** = 53

The age data from Murray can then be converted into "equivalent" Ethiopian ages by multiplying by the "normalised" age data, above, by the Ethiopian life expectancy at birth, ie:

femaleethiopianage = **femaleagefrac** · **femaleethiopianexatbirth**
maleethiopianage = **maleagefrac** · **maleethiopianexatbirth**

This gives:

femaleethiopianage =

	0
0	0
1	0.642
2	3.212
3	6.424
4	9.636
5	12.848
6	16.061
7	19.273
8	22.485
9	25.697
10	28.909
11	32.121
12	35.333
13	38.545
14	41.758
15	44.97
16	48.182
17	51.394

maleethiopianage =

	0
0	0
1	0.663
2	3.313
3	6.625
4	9.938
5	13.25
6	16.563
7	19.875
8	23.188
9	26.5
10	29.813
11	33.125
12	36.438
13	39.75
14	43.063
15	46.375
16	49.688
17	53

Similarly, the life expectancy data from Murray can then be converted into "equivalent" Ethiopian life expectancies by multiplying by the "normalised" life expectancy data, above, by the Ethiopian life expectancy at birth, ie:

femaleethiopianex = **femaleexfrac femaleethiopianexatbirth**
maleethiopianex = **maleexfrac maleethiopianexatbirth**

This gives

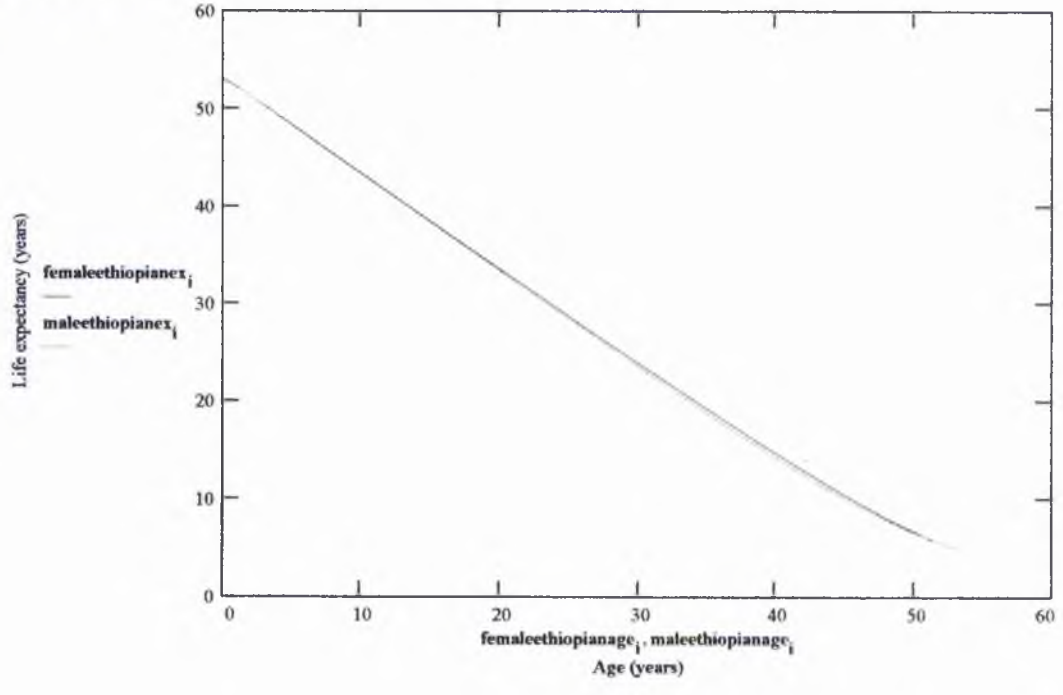
femaleethiopianex =

	0
0	53
1	52.576
2	50.077
3	46.891
4	43.698
5	40.524
6	37.37
7	34.222
8	31.08
9	27.965
10	24.875
11	21.836
12	18.868
13	15.951
14	13.131
15	10.407
16	7.889
17	5.718

maleethiopianex =

	0
0	53
1	52.576
2	49.939
3	46.64
4	43.334
5	40.041
6	36.749
7	33.463
8	30.183
9	26.924
10	23.698
11	20.531
12	17.437
13	14.449
14	11.594
15	8.997
16	6.738
17	4.936

The calculated Ethiopian life expectancy data are shown as a function of calculated Ethiopian age graphically below



To give intermediate values for the data (i.e. a life expectancy for each year of age), curves were fitted to the data using parabolic spline fits:

$vsfemale := pspline(femaleethiopianage, femaleethiopianex)$

$vsmale := pspline(maleethiopianage, maleethiopianex)$

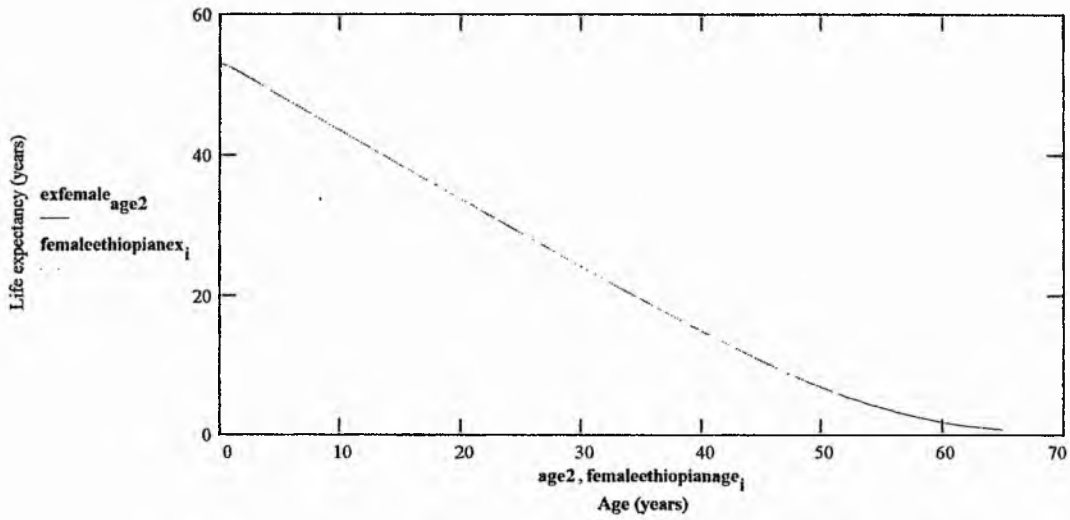
In order to obtain life expectancies for patients older than the life expectancy at birth, the data was then interpolated for ages up to 65 years old

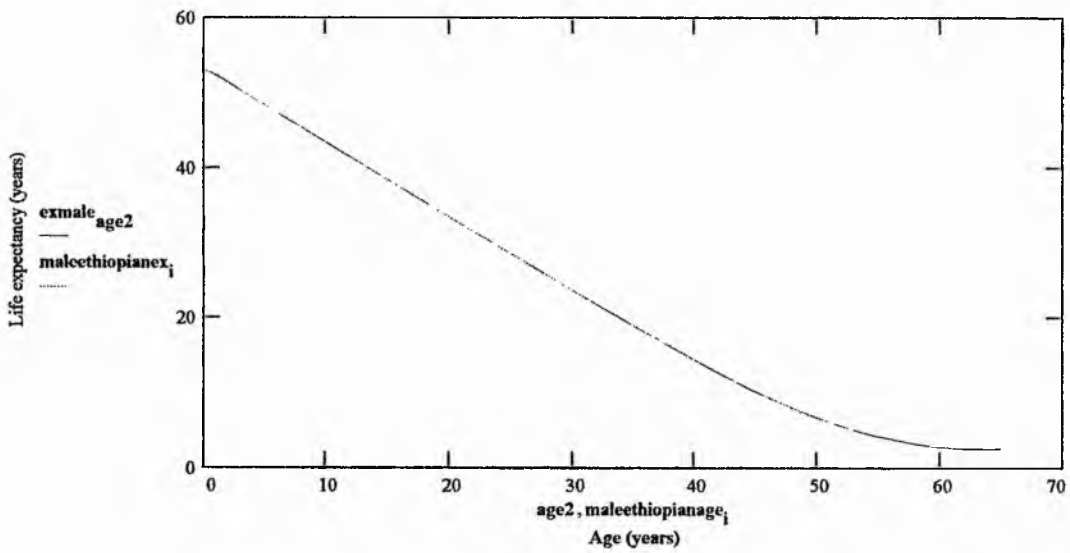
$age2 := 0..65$

$exfemale_{age2} := interp(vsfemale, femaleethiopianage, femaleethiopianex, age2)$

$exmale_{age2} := interp(vsmale, maleethiopianage, maleethiopianex, age2)$

The interpolated data, together with the fitted data are plotted below





Data is then output to files

$WRITEPRN(femex) := exfemale$ $WRITEPRN(maleex) := exmale$ $WRITEPRN(ages) := age2$

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