Bedaquiline: what might the future hold?

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Tuberculosis drug development has stagnated for decades, so the recent availability of bedaquiline is welcome. Bedaquiline-containing regimens, now the first-line therapy recommended by WHO, have transformed the treatment of drug-resistant tuberculosis, offering safer and more effective oral treatment options. However, key obstacles need to be overcome to ensure global access and prevent the rapid development of resistance against this promising class of drugs. In this Personal View, building on an international workshop held in 2023, we evaluate the current evidence and suggest possible ways forward, recognising the tension between increasing use and slowing the rise of resistance. We also discuss problems in accessing bedaquiline-containing regimens, the potential widening of their use beyond drug-resistant tuberculosis, and lessons for utilising new drugs as they are developed.

Introduction

Since the 1980s, tuberculosis treatment has relied on a core combination of first-line antibiotics for drug-sensitive tuberculosis, consisting of rifampicin, isoniazid, ethambutol, and pyrazinamide. The emergence of drug-resistant tuberculosis, specifically rifampicin-resistant, multidrug-resistant (MDR), and extensively drug-resistant (XDR) variants,[1] necessitated the development and use of second-line and third-line drugs.[2] In 2022, among the estimated 10·6 million people with tuberculosis, >400 000 had MDR or rifampicin-resistant infections.[1] Drug-resistant tuberculosis has been much more difficult to treat than drug-sensitive tuberculosis, with longer regimens, more side-effects, lower survival rates, and greater costs.

Mycobacterium tuberculosis drug resistance typically arises through sequential mutations in the bacterial genome. In biological terms, the occurrence of drug resistance is almost inevitable, and the development and spread of drug-resistant bacterial strains are exacerbated by numerous logistical and social factors.[3] This situation threatens the ability to effectively treat individuals and the preservation of tuberculosis as a curable disease, particularly considering the paucity of new drugs.

Bedaquiline[4] has been a game changer. In 2012, it became the first new class of drugs for tuberculosis to be approved by the US Food and Drug Administration (FDA) in 40 years.[5] This approval occurred in parallel with the development of other new drugs (pretomanid and delamanid) and the use of linezolid and clofazimine, which altered the tuberculosis-treatment landscape and resulted in the first multidrug combination that differed completely from the standard regimen and could override pre-existing resistance to first-line drugs.[6] Programmatic and trial data prompted WHO to revise its guidance for treating drug-resistant tuberculosis in 2022 to include bedaquiline-containing regimens.[7]

However, this good news is tempered with concerns about the development of bedaquiline resistance, poor access to reliable testing, and limited access to bedaquiline.[8] Tension exists among these factors, in that the more a drug is used, the greater the likelihood of resistance developing and spreading.

In this context, tuberculosis researchers at the Africa Health Research Institute and University College London jointly hosted an online workshop in June, 2023, titled "Bedaquiline and TB: What might the future hold?"[9] The panel comprised ten clinicians, scientists, ethicists, patient advocates, and policy makers with expertise in drug-resistant tuberculosis from seven different countries. They presented and discussed opportunities and concerns regarding the roll-out of bedaquiline for treating active disease. The topics addressed included patient perspective, bedaquiline resistance, clinical practice, clinical trials and future directions, and policies. A video and transcript of the workshop are available.[10,11]

In this Personal View, we summarise and expand upon points raised to contribute to the broader discussion about bedaquiline and other new anti-tuberculosis drugs among stakeholders.

Current knowledge

Introduction of bedaquiline to treat drug-resistant tuberculosis

Just over a decade ago, WHO guidelines for individuals with tuberculosis resistant to isoniazid and rifampicin (MDR tuberculosis) recommended 20–24 months of treatment, frequently requiring more than six drugs, including a fluoroquinolone, 8 months of a daily injectable (amikacin, capreomycin, or kanamycin), ethionamide or prothionamide, cycloserine, clofazimine, para-aminosalicylic acid, and pyrazinamide.[12] Such regimens remain the standard where bedaquiline is unavailable, although MDR tuberculosis-treatment programmes before the introduction of bedaquiline provided only a 56% chance of cure.[13] Adverse events (including sensorineural hearing loss, kidney damage, vomiting, and psychosis) are common,[14] and an individual participant data (IPD) meta-analysis revealed that 23% of patients who started treatment had adverse events leading to cessation of a drug.[15]

The workshop opened with two tuberculosis survivors sharing their experiences of being treated for drug-resistant tuberculosis for 24 or 44 months. Both individuals developed severe side-effects from injectable drugs, highlighting

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the life-changing potential of bedaquiline. One of the stories is shared in panel 1 to illustrate the personal consequences of inadequate options for treating drug-resistant tuberculosis.

Following promising phase 2b clinical-trial results, bedaquiline was first made available through compassionate use or clinical access programmes.[16–18] In March, 2015, the South African National Tuberculosis Programme rolled out a 9-month bedaquiline-containing regimen, specifically targeting people with pre-XDR and XDR tuberculosis who had limited alternative treatment options. By 2018, 20 000 people with MDR, rifampicin-resistant, or XDR tuberculosis had been treated, with an analysis of 1016 people showing a marked reduction in the risk of all-cause mortality when compared with that in individuals receiving the standard of care (MDR or rifampicin-resistant tuberculosis: hazard ratio 0·35, 95% CI 0·28–0·46; XDR: 0·26, 0·18–0·38).[19] In parallel, an IPD meta-analysis of cohorts with MDR tuberculosis from 25 countries showed that recipients of bedaquiline had a 60% lower mortality rate than matched controls.[20]

Further breakthroughs were reported in 2022 on the basis of the results of two trials with bedaquiline-containing regimens. In August, 2022, data from the ZeNix trial demonstrated that 6 months of oral bedaquiline, pretomanid, and linezolid treatment produced favourable outcomes in 91% of study participants with XDR (at that time defined as resistance to rifampicin, a fluoroquinolone, and an aminoglycoside), pre-XDR, or rifampicin-resistant tuberculosis who did not respond to or were unable to tolerate standard regimens,[21] confirming the results of the earlier Nix-TB trial.[22] In December, 2022, data from the TB-PRACTECAL trial showed that 6 months of oral bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) treatment cured 89% of people with rifampicin-resistant tuberculosis, irrespective of their fluoroquinolone-resistance status.[23]

In May, 2022, WHO issued a rapid communication to amend its 2020 drug-resistant tuberculosis-treatment guidelines and endorsed both 6-month and 9-month all-oral bedaquiline-containing regimens for MDR or rifampicin-resistant tuberculosis.[7,24]

Bedaquiline resistance

Bedaquiline is a diarylquinoline that kills *M tuberculosis* by inhibiting the proton pump of the mycobacterial ATP synthase, mainly by binding to the subunit encoded by the *atpE* gene.[25] Resistance-associated genetic variants (RAVs) have been found in the *atpE* gene;[26] these mutations confer medium-level to high-level resistance (eight-fold to 128-fold increase in the minimal inhibitory concentration [MIC])[27] but are rare, as the gene is essential and variants must retain function.

Much more abundant are RAVs in the *Rv0678* gene,[28] which result in low-to-medium resistance (2–16× increase in the MIC)[29] to bedaquiline and another anti-tuberculosis drug (clofazimine). *Rv0678* encodes a transcriptional repressor of the MmpS5–MmpL5 complex, an efflux pump that can remove bedaquiline from cells. Under typical circumstances, the repressor keeps expression of the pump (and therefore bedaquiline efflux) low. When *Rv0678* is inactivated, production of the efflux pump and bedaquiline efflux increase. Therefore, levels of the drug within bacteria fall. Because many different RAVs can cause this loss of function, the *Rv0678* mutation frequency is much greater than the *atpE*-mutation frequency in viable bacteria. Loss-of-function RAVs in *pepQ*, which is possibly related to drug efflux,[30] are also associated with lower bedaquiline resistance (four-fold to eight-fold increase in the MIC).

Clinicians should be mindful of two factors, namely, the poor early bactericidal activity (EBA) of bedaquiline[31] and its extraordinarily long half-life of 164 days,[32] in contrast with first-line drugs that have a half-life of a few hours.[33] Both aspects can theoretically contribute to the development of resistance to bedaquiline or other drugs in the regimen (see Regimen modification below).

Regarding epidemiological factors leading to bedaquiline resistance, most bedaquiline RAVs described above were generated in vitro, and resistance in natural populations was expected to be low to this novel compound. However, when bedaquiline drug-susceptibility testing (DST) was used to screen clinical isolates, resistance was soon detected.

Panel 1: **Tuberculosis survivor story: experiencing extensively drug-resistant tuberculosis**

Phumeza Tisile was a 19-year-old, first-year university student in South Africa in 2010 when she developed symptoms consistent with pulmonary tuberculosis. Following an abnormal chest x-ray, she was started on first-line drugs, which soon proved ineffective, and her disease was eventually re-classified as multidrug-resistant tuberculosis. She began the standard regimen available at the time: 2 years of treatment, with an initial daily phase of more than 20 tablets and parenteral kanamycin (her injectable), but was subsequently diagnosed with pre-extensively drug-resistant (XDR) and then XDR tuberculosis, when she was given a 20% chance of survival. She had to abandon her university studies and had multiple complications from her disease and treatment, including a period when her disease was considered unsurvivable, and she was advised to see a priest.

Kanamycin can have severe side-effects and, in Phumeza's case, it resulted in sudden-onset, irreversible, sensorineural deafness, such that she became reliant on written communication. She said, "My choice was whether I was deaf or I was dead." Eventually, she secured compassionate use of linezolid and achieved cure 44 months after tuberculosis treatment was first initiated. Fortunately, she subsequently received bilateral cochlear implants that partly restored her hearing, and she was able to resume her studies. If she had been provided with a bedaquiline-containing regimen from the outset, she would have had an 80% chance of being cured in 6 months and would have almost certainly been spared hearing loss, with much less disruption to her life and career development.

Two systematic reviews of baseline and emerging treatment-associated bedaquiline resistance in drug-resistant tuberculosis presumably reflect bedaquiline-naive populations. For example, Mallick and colleagues[34] found resistance, with levels differing depending on whether phenotypic (2·2% bedaquiline-resistant [IQR 1·1–4·6]) or genotypic (4·4% bedaquiline-resistant [IQR 1·8–5·8]) DSTs were used. Perumal and colleagues[35] showed a pooled prevalence of baseline phenotypic bedaquiline resistance of 2·4% (95% CI 1·7–3·5), with substantial heterogeneity, a pooled prevalence of treatment-emergent phenotypic bedaquiline-resistant variants with sequence deviations of 2·1% (95% CI 1·4–3·0), and little heterogeneity. Together, these results represented 21 papers covering tuberculosis from approximately 2008 to 2020 from 23 countries on five continents, albeit not distributed equally.

Two groups studying programmatic data reported higher levels of emerging resistance,[36,37] and showed a striking increase over time in Mozambique, where genotypic resistance rose from 3% in 2016 to 14% in 2021.[36]

Taken together, these findings suggest that bedaquiline resistance is present in most populations, can arise de novo during treatment, can be transmitted, and is increasing in frequency in some settings.

Preventing resistance

Obtaining accurate data

To minimise the development and spread of drug resistance, testing is essential, both at population and individual patient levels. Currently, bedaquiline-resistance testing relies on phenotypic DST or genotypic methods (either whole-genome sequencing [WGS] or targeted amplification/sequencing approaches; no point-of-care methods such as the GeneXpert test are available). Ideally, DST should be undertaken during the drug-development process,[38] but the urgent need for better treatment options meant that DST protocols and reagents for public use were not fully developed before the bedaquiline roll-out.

In principle, DST approaches are straightforward for equipped laboratories. Interim bedaquiline-resistance breakpoints for 7H11 and mycobacterial growth indicator tube (MGIT) methods have been reported,[39] so these approaches can be used and self-validated using either bedaquiline from Johnson & Johnson or (since patent expiry) from commercial suppliers. However, no commercial kits (eg, MGIT drug vials or plates with pre-added drugs for the broth microdilution method) are available. Currently, the European Committee on Antimicrobial Susceptibility Testing reference method (required for calibrating different methods with respect to each other[40]) for bedaquiline is in development, and an amended protocol is not publicly available.

Genotypic testing for bedaquiline resistance is complex,[41] considering that adapting rapid tests for loss-of-function genes is challenging in cases when multiple RAVs might cause resistance; such testing is complicated by the fact that some changes in target genes do not cause resistance, and those that do could have differing MICs and consequently different practical impacts; deep sequencing results might also indicate heteroresistance missed by standard sequencing methods,[42] the significance and interpretation of which is unclear; and access to WGS is variable. In light of these findings, gaining insight into the effects of different RAVs on MICs is important.

In a survey of WHO European region countries conducted in 2023, 84% (37/44) of the respondents had systems to detect bedaquiline resistance.[43] This situation is likely to be worse in other parts of the world where resources and infrastructure are more constrained. In South Africa, the biggest consumer of bedaquiline, phenotypic bedaquiline testing was wisely introduced into the national programme for all pre-XDR isolates. Since April, 2023, all rifampicin-resistant tuberculosis isolates have been tested.

Identifying resistance to first-line drugs is both simpler and more widespread and can be quickly adopted in places where people have access to a bedaquiline-containing regimen. Confirming pre-existing resistance to novel drugs is more challenging. This is a problem that is likely to become more important, highlighting the need to develop guidelines that support countries with different testing capabilities as they introduce novel anti-tuberculosis regimens.

A rapid DST would be useful for evaluating all drugs used to treat tuberculosis. Revisiting rapid, near-patient phenotypic testing similar to the microscopic-observation drug-susceptibility assays[44] might be fruitful, and actively supporting innovation in this area should be encouraged, albeit acknowledging that this will take time.

Regimen modification

Another approach is to modify regimens so that they are less likely to promote bedaquiline resistance and more likely to increase clinician confidence that drug-resistant regimens are sufficiently effective for the full course of therapy.

As some *Rv0678* mutants show lower MICs, resistance can possibly be overcome by increasing the bedaquiline dose. In one case study, a personalised regimen for a highly resistant strain of *M tuberculosis* with low-level bedaquiline resistance included a 50% increased dose of bedaquiline.[45] However, the consequences of drug escalation in terms of safety and toxicity have not been studied, so careful monitoring is required.

A related potential strategy is to reduce the MICs of bacteria with *Rv0678* RAVs by using efflux pump inhibitors. Verapamil and reserpine can reduce the MICs of *Rv0678* mutants,[46] and verapamil was included in the case study reported by Koehler and colleagues.[45] This option is also attractive because *Rv0678* mutations cause low-level resistance against three new drugs with different modes of action (DprE1 inhibitors TBA 3731, BTZ043, and PBTZ169) that are in early-phase clinical trials.[47,48]

Bedaquiline almost did not progress through clinical development beyond phase 2 due to its poor EBA. Initially, no EBA was seen for bedaquiline for 7 days, although it

started to increase thereafter.[31] Therefore, supplementation with additional early-acting drugs during initial treatment would increase the number of effective drugs during this period and thus protect all of the drugs in the regimen from the development of resistance. The importance of protecting fluoroquinolones and other drugs in this way before bedaquiline activity increases has been stressed.[49] Possible approaches might include the use of high-dose isoniazid, carbapenems, and second-line injectables.

Although injectable drugs are undesirable over long periods, a short course lasting weeks rather than months might be better tolerated and can reduce the bacillary load sufficiently to prevent resistance.[49] This possibility is supported by data from the STREAM trial (stage 2), which achieved a 90% favourable outcome without any acquired bedaquiline resistance using kanamycin for just the first 8 weeks, with low levels (graded 3 or 4 on the Brock scale) of sensorineural hearing loss.[50]

In terms of resistance, the long half-life of bedaquiline should not be an issue if people are cured. People who do not complete treatment, however, will effectively be on bedaquiline monotherapy for a long period as the drug clears, which could lead to further resistance. The long half-life can also be used to rationalise ceasing or reducing the dose in later stages of treatment.

The increasing number of people on bedaquiline regimens who are not getting better necessitates the development of guidance regarding bedaquiline testing and backup regimens. Such guidance might come from WHO with input from national programmes, and future treatment could involve new therapeutics.[51]

Other socioeconomic factors leading to bedaquiline-resistance development

Regarding private health care, the public and private mix for health care, as well as the culture and practice of antibiotic prescriptions, differ substantially between countries. Both factors can influence drug resistance. For example, in India, 60–80% of doctors and patients are in the private sector,[52] and almost half of all people with tuberculosis access care in the private sector.[53] This environment introduces challenges in terms of standardising and ensuring the rational use of anti-tuberculosis medicines.[54,55] Detailed analyses of local situations and solutions[53] are valuable for addressing this issue. Classifying tuberculosis as a notifiable disease, as India did in 2012, is likely to help[56] in settings where this is not current practice. Currently in India, traditional anti-tuberculosis drugs can be purchased over the counter; however, bedaquiline is only available through the government in an effort to protect against its indiscriminate use.

In all countries with a substantial private health-care component, negotiating partnerships between public and private health-care providers will be important for improving stewardship. Importantly, universal DST or genotypic testing should be available in all endemic areas, including those that rely on private health care, so that bedaquiline can be used in a judicious and responsible manner.

Improving adherence and supporting patients during treatment are crucial for successful outcomes. One of the great advantages of bedaquiline regimens over traditional regimens for drug-resistant tuberculosis is that they favour completion due to reduced toxicity and shorter durations and increased cure rates. This is not to diminish the issues associated with treatment in people who often have other health and social complications.

Adopting a patient-centred continuum of care approach[57] in this context means that treatment should be accessible, acceptable, affordable, and appropriate (with a balance of responsibility between patient and health-care services) and as supportive of patient autonomy as possible. Delivering this within high-quality tuberculosis care is resource-heavy and, thus, problematic to implement in areas with the highest needs. Therefore, multi-agency, international strengthening of national tuberculosis programmes might be required.

A simple step for improving adherence might be changing bedaquiline from thrice-weekly to daily dosing, as done in the ZeNix trial.[21]

Bedaquiline accessibility

If bedaquiline-containing regimens are generally better for treating rifampicin-resistant or MDR tuberculosis, then they should normally be the choice for government-provided "free and universal tuberculosis services of high quality".[58] However, bedaquiline access is low due to both limited availability and the cost to national health-care providers.

Access varies widely between nations. One report showed that among 36 countries surveyed, <20% of people likely to have benefited from bedaquiline received it between 2015 and 2017.[59] More recently, in a survey covering 44 WHO European region countries, 42 countries (96%) had access to bedaquiline, but only 24 countries (55%) had access to pretomanid.[43] Hopefully, this issue will be temporary, but it requires attention. These findings also raise the ethical question of how drug suppliers and health-care providers should prioritise drug distribution when availability is limited.[60] In contrast, in South Africa, bedaquiline-containing regimens are the standard of care for treating drug-resistant tuberculosis.[24] These drugs are only withheld when bedaquiline drug resistance has been detected or a clinical contraindication against its use has been identified.

Drug costs remain high, although the cost of bedaquiline has recently decreased due to the agreement between Johnson & Johnson and the Stop TB Global Drug Facility (GDF; Stop TB 2023). Therefore, current costs for treating drug-resistant tuberculosis (which are high in all countries) should be evaluated.[43]

Ethical considerations of bedaquiline use

The ethical principles that pertain to anti-tuberculosis treatment are complicated.[60–62] In line with the stewardship model of decision making in public health, states should balance a duty of care for individuals and their rights

to autonomy to prevent harm to the population. Tuberculosis care and prevention are also guided by principles of social justice and equity.[62] Equity is especially challenging to ascertain on a global scale where resources between countries are unequally distributed. For example, considerable variability has been noted in terms of the access to medicines such as bedaquiline and pretomanid (key elements of the BPaLM regimen for MDR tuberculosis).[43] Access is not necessarily easier in richer countries as the supply of medicines is susceptible to market forces with a lower profit incentive in richer countries where the demand for tuberculosis medicines is often lower.

The availability of tools for detecting resistance is similarly heterogeneous, which raises an important question as to whether such tools should be mandated for drug development. The increasing prevalence of bedaquiline resistance brings into focus the balance between restricting its use (to reduce the prevalence of new resistance, thus protecting its use into the future) and enabling its use in reducing tuberculosis-associated morbidity and mortality.[63,64]

Currently, <5% of people affected by tuberculosis use bedaquiline, but the potential exists for this to be considerably increased. The TRUNCATE-TB trial showed that 2 months of treatment with bedaquiline, linezolid, ethambutol, and pyrazinamide (with follow-up and treatment of persistent clinical disease and relapse) was not inferior to 6-month therapy for people with drug-sensitive tuberculosis.[65] Bedaquiline may also be an effective treatment for tuberculosis contacts, and there is a call to use it for non-tuberculous mycobacteria (NTM) disease, which is often more difficult to treat than drug-resistant tuberculosis.[66] Alongside the cost and risk of resistance associated with greater drug use, the main objections to extending the use of bedaquiline to NTM are its low evidence of activity and the negative health consequences in a population of individuals generally older than those with tuberculosis and with comorbidities that predispose them to developing NTM disease. These considerations should be balanced against the risk of hearing loss associated with the protracted use of aminoglycosides. Importantly, concomitant use of bedaquiline and rifamycins is not recommended owing to their interactions.[67]

These specific issues reveal a broader need to ensure that governments and the private sector (including pharmaceutical companies) contribute to equity in tuberculosis care and prevention through their own policies and practices. A socially just response to tuberculosis in general (specifically the use of bedaquiline) requires multilateral, global cooperation and the balancing of many, often competing, interests.

Beyond bedaquiline: the roles of the pharmaceutical industry and drug-approval processes

Constant tension exists between incentivising drug development with intellectual property rights and ensuring

Panel 2: **Main conclusions**

- The ability to detect bedaquiline resistance, both phenotypically and genotypically, wherever bedaquiline is used, is a priority.
- Bedaquiline resistance is present at low levels where it has been tested, but evidence indicates that resistance is rising sharply in some populations where bedaquiline is being used.
- Most resistance is attributable to loss-of-function mutations that increase bacterial drug efflux and have low minimal inhibitory concentrations (MICs). Resistance conferring high MICs due to alterations in the drug target, ATP synthase, is less frequent. The association between different resistance-associated genetic variants and MICs needs to be better documented.
- The emergence of resistance might be mitigated through adjustments to the regimens to protect other drugs during the early phases, when bedaquiline is not effective, and to overcome low-level bedaquiline resistance.
- Health systems should mitigate the risk of non-standard treatments, especially in settings where people with tuberculosis are managed by private practitioners.
- Supporting people with tuberculosis through their treatment with a patient-centred continuum of care is likely to help to mitigate the development of resistance by improving adherence among people who do not adhere to their prescribed treatments (which might effectively become monotherapy due to bedaquiline's long half-life).
- Drug-resistant tuberculosis constitutes only 5% of new tuberculosis cases, and arguments will be made for using bedaquiline to treat other groups, including close contacts of people with drug-resistant tuberculosis, drug-sensitive tuberculosis, and non-tuberculous mycobacteria infections. Treating such groups should be openly discussed and evaluated.
- Access is currently limited by both availability and cost.
- New drugs will not emerge without their development by the pharmaceutical industry. Despite accelerated processes, the development and approval of bedaquiline took too long. The lengthy approval process needs to be addressed, in part by encouraging innovation. In particular, a validated surrogate endpoint for treating tuberculosis would be a major advancement.
- Current diagnostic and therapeutic tools against tuberculosis are inadequate for eradicating tuberculosis during the timescale of current WHO targets. The five-fold increase in overall global investments to US$35 billion annually by 2030, as promised by the 2023 UN High-Level Meeting,[76] could substantially accelerate the elimination of tuberculosis and should be effectively implemented.
- The bedaquiline workshop showed the value of dialogue between diverse partners who all have the common goal of eliminating tuberculosis. Continued and improved cooperation between all stakeholders will facilitate the achievement of shared objectives and will ultimately improve the lives of those affected by tuberculosis.

access to those drugs. No advances in novel drug development could happen without pharmaceutical companies, so incentivising them is essential. Bedaquiline took 20 years to move from being a molecule of interest to part of a WHO-recommended regimen,[68] and the 20-year primary patent expired in July, 2023. A combination of factors, including activist pressure, patent court rejection, and negotiations with Stop TB's GDF for a licence to supply quality-assured generic bedaquiline to most low-income and middle-income countries, has led Johnson & Johnson to not seek a secondary patent.[69]

The 20-year development process for bedaquiline included an 8-year approval process, and pretomanid approval took 19 years. In contrast, four new HIV and hepatitis C virus (HCV) medications were approved in 1·6–4·7 years.[70] The drug-approval process for tuberculosis took longer despite accelerated processes used by the FDA and European Medicines Agency, using drug-resistant tuberculosis as a target population (which required smaller trials) and involving fewer phase 2 and phase 3 trials than those used to evaluate the HIV and HCV drugs. One of the major reasons for the long development times was the absence of a validated surrogate endpoint for tuberculosis. One step towards such an endpoint is represented by the recent publication of target-product profiles for such tests.[71]

Inadequate investment in tuberculosis research and development was also identified as being important. Positive steps towards investment include the establishment of large, well-funded trial platforms and the recent (non-binding) UN High-Level Meeting (UNHLM) political declaration to "commit to mobilise adequate, predictable and sustainable financing for tuberculosis research and innovation especially to high-burden countries towards reaching US$5 billion a year by 2027" (paragraph 68).[72]

One way that the pharmaceutical industry could substantially help to protect against drug resistance would be to produce the formulations, protocols, and resources needed for phenotypic testing (as mentioned in Obtaining accurate data) much earlier in the drug development process.[73] Could such an approach potentially become a regulatory requirement before a drug is approved? A more feasible strategy would be to establish at least a mechanism for population-level or epidemiological surveillance of resistance and the provision of a roadmap for increasing the availability of DST methods. Having the conversation, publicly identifying points of difficulty, and establishing a timeline would help to combat drug resistance.

Although we focused on bedaquiline in this Personal View, tuberculosis treatment should always be considered in terms of regimens rather than drugs. Developing drug combinations that protect the more efficacious drugs, have multiple mechanisms of action, and matched pharmacokinetics is also important. Such advances will become increasingly important as the regimens become less effective.

Search strategy and selection criteria

We searched PubMed for articles published in English that contained both "tuberculosis" and "bedaquiline" in the title or abstract. When evaluating studies reporting bedaquiline resistance in humans, we included both available systematic reviews and relevant studies published thereafter. The final references were selected on the basis of relevance to the scope of this review.

Conclusions

The introduction of bedaquiline-containing regimens is genuinely good news that has already saved many thousands of lives, and our discussion recognises that fact. Bedaquiline-containing regimens are likely to become first-choice treatments for bedaquiline-sensitive drug-resistant tuberculosis, with improved activity and fewer side-effects than other options.

We have briefly summarised and expanded upon issues raised within the workshop and other sources.[73–75] The timing of this article is also important, with the recent UNHLM expressing strong but non-binding political support, including greatly increased funding. We have summarised our main conclusions in panel 2.

This Personal View represents expert opinion, further informed by a literature review. It might not include pertinent but currently unpublished data unknown to the authors. Some sections are limited to overviews rather than in-depth analyses, given the extensive scope of the article.

Contributors

HE, ML, JLP, ESS, NGS, and CDT contributed to conceptualisation. ML, JLP, ESS, and NGS contributed to writing the original draft. All authors contributed to the review and editing of the manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication.

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References

1 WHO. Global tuberculosis report 2023. Nov 7, 2023. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023 (accessed Dec 1, 2023).

2 Tiberi S, Scardigli A, Centis R, et al. Classifying new anti-tuberculosis drugs: rationale and future perspectives. *Int J Infect Dis* 2017; **56:** 181–84.

3 Liebenberg D, Gordhan BG, Kana BD. Drug resistant tuberculosis: implications for transmission, diagnosis, and disease management. *Front Cell Infect Microbiol* 2022; **12:** 943545.

4 Khoshnood S, Goudarzi M, Taki E, et al. Bedaquiline: current status and future perspectives. *J Glob Antimicrob Resist* 2021; **25:** 48–59.

5 Mahajan R. Bedaquiline: first FDA-approved tuberculosis drug in 40 years. *Int J Appl Basic Med Res* 2013; **3:** 1–2.

6 Nasto B. Not-for-profit to launch antibiotic against drug-resistant tuberculosis. *Nat Biotechnol* 2019; published online Nov 15. https://doi.org/10.1038/d41587-019-00034-3.

7 WHO. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. https://www.who.int/southeastasia/publications/i/item/WHO-UCN-TB-2022-2 (accessed Dec 4, 2023).

8 Lessem E, Cox H, Daniels C, et al. Access to new medications for the treatment of drug-resistant tuberculosis: patient, provider and community perspectives. *Int J Infect Dis* 2015; **32:** 56–60.

9 UCL-TB. Bedaquiline and TB: what might the future hold? 2023. https://www.ucl.ac.uk/tb/bedaquiline-and-tb-what-might-future-hold (accessed Nov 15, 2023).

10 UCL-TB. Bedaquiline: what might the future hold? 2023. https://www.youtube.com/watch?v=vQJolt6ebkc (accessed Nov 15, 2023).

11 UCL-TB. Bedaquiline and tuberculosis workshop 30 June 2023 full transcript 09 Oct 2023. https://rdr.ucl.ac.uk/articles/dataset/Bedaquiline_and_tuberculosis_workshop_30_June_2023_full_transcript_09oct2023/24866250/1 (accessed Oct 10, 2023).

12 Falzon D, Jaramillo E, Schünemann HJ, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; **38:** 516–28.

13 WHO. Global tuberculosis report 2019. Oct 15, 2019. https://www.who.int/publications/i/item/9789241565714 (accessed Dec 4, 2023).

14 Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019; **380:** 1201–13.

15 Lan Z, Ahmad N, Baghaei P, et al. Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2020; **8:** 383–94.

16 Conradie F, Meintjes G, Hughes J, et al. Clinical access to bedaquiline programme for the treatment of drug-resistant tuberculosis. *S Afr Med J* 2014; **104:** 164–66.

17 Guglielmetti L, Le Dû D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; **60:** 188–94.

18 WHO. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Feb 16, 2013. https://www.who.int/publications/i/item/9789241505482 (accessed Dec 4, 2023).

19 Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018; **6:** 699–706.

20 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja SD, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018; **392:** 821–34.

21 Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; **387:** 810–23.

22 Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; **382:** 893–902.

23 Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022; **387:** 2331–43.

24 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. June 15, 2020. https://www.who.int/publications/i/item/9789240007048 (accessed Dec 5, 2023).

25 Sarathy JP, Gruber G, Dick T. Re-understanding the mechanisms of action of the anti-mycobacterial drug bedaquiline. *Antibiotics (Basel)* 2019; **8:** 261.

26 Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 2005; **307:** 223–27.

27 Huitric E, Verhasselt P, Koul A, Andries K, Hoffner S, Andersson DI. Rates and mechanisms of resistance development in *Mycobacterium tuberculosis* to a novel diarylquinoline ATP synthase inhibitor. *Antimicrob Agents Chemother* 2010; **54:** 1022–28.

28 Hartkoorn RC, Uplekar S, Cole ST. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2014; **58:** 2979–81.

29 Kadura S, King N, Nakhoul M, et al. Systematic review of mutations associated with resistance to the new and repurposed *Mycobacterium tuberculosis* drugs bedaquiline, clofazimine, linezolid, delamanid and pretomanid. *J Antimicrob Chemother* 2020; **75:** 2031–43.

30 Almeida D, Ioerger T, Tyagi S, et al. Mutations in *pepQ* confer low-level resistance to bedaquiline and clofazimine in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2016; **60:** 4590–99.

31 Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; **380:** 986–93.

32 Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother* 2012; **56:** 3271–76.

33 Burhan E, Ruesen C, Ruslami R, et al. Isoniazid, rifampin, and pyrazinamide plasma concentrations in relation to treatment response in Indonesian pulmonary tuberculosis patients. *Antimicrob Agents Chemother* 2013; **57:** 3614–19.

34 Mallick JS, Nair P, Abbew ET, Van Deun A, Decroo T. Acquired bedaquiline resistance during the treatment of drug-resistant tuberculosis: a systematic review. *JAC Antimicrob Resist* 2022; **4:** dlac029.

35 Perumal R, Bionghi N, Nimmo C, et al. Baseline and treatment-emergent bedaquiline resistance in drug-resistant tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2023; **62:** 2300639.

36 Barilar I, Fernando T, Utpatel C, et al. Emergence of bedaquiline-resistant tuberculosis and of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* strains with *rpoB* Ile491Phe mutation not detected by Xpert MTB/RIF in Mozambique: a retrospective observational study. *Lancet Infect Dis* 2024; **24:** 297–307.

37 Derendinger B, Dippenaar A, de Vos M, et al. Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study. *Lancet Microbe* 2023; **4:** e972–82.

38 Georghiou SB, de Vos M, Velen K, et al. Designing molecular diagnostics for current tuberculosis drug regimens. *Emerg Microbes Infect* 2023; **12:** 2178243.

39 WHO. Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Mar 21, 2018. https://www.who.int/publications/i/item/WHO-CDS-TB-2018.5 (accessed Dec 5, 2023).

40 Schön T, Köser CU, Werngren J, et al. What is the role of the EUCAST reference method for MIC testing of the *Mycobacterium tuberculosis* complex? *Clin Microbiol Infect* 2020; **26:** 1453–55.

41 Nimmo C, Millard J, van Dorp L, et al. Population-level emergence of bedaquiline and clofazimine resistance-associated variants among patients with drug-resistant tuberculosis in southern Africa: a phenotypic and phylogenetic analysis. *Lancet Microbe* 2020; **1:** e165–74.

42 Operario DJ, Koeppel AF, Turner SD, et al. Prevalence and extent of heteroresistance by next generation sequencing of multidrug-resistant tuberculosis. *PLoS One* 2017; **12:** e0176522.

43 Günther G, Guglielmetti L, Kherabi Y, Duarte R, Lange C, Tuberculosis Network European Trials group. Availability of drugs and resistance testing for bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaL(M)) regimen for rifampicin-resistant tuberculosis in Europe. *Clin Microbiol Infect* 2024; published online March 13. https://doi.org/10.1016/j.cmi.2024.03.009.

44 Lopez-Garnier S, Sheen P, Zimic M. Automatic diagnostics of tuberculosis using convolutional neural networks analysis of MODS digital images. *PLoS One* 2019; **14:** e0212094.

45 Koehler N, Andres S, Merker M, et al. Pretomanid-resistant tuberculosis. *J Infect* 2023; **86:** 520–24.

46 Andries K, Villellas C, Coeck N, et al. Acquired resistance of *Mycobacterium tuberculosis* to bedaquiline. *PLoS One* 2014; **9:** e102135.

47 Almeida DV, Converse PJ, Nuermberger EL. Mutations in *Rv0678* reduce susceptibility of *Mycobacterium tuberculosis* to the DprE1 inhibitor TBA-7371. *Antimicrob Agents Chemother* 2023; **67:** e0005223.

48 Poulton NC, Azadian ZA, DeJesus MA, Rock JM. Mutations in rv0678 confer low-level resistance to benzothiazinone DprE1 inhibitors in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2022; **66:** e0090422.

49 Tahseen S, Van Deun A, de Jong BC, Decroo T. Second-line injectable drugs for rifampicin-resistant tuberculosis: better the devil we know? *J Antimicrob Chemother* 2021; **76:** 831–35.

50 Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet* 2022; **400:** 1858–68.

51 Stop TB Partnership. Clinical pipeline. 2024. https://www.newtbdrugs.org/pipeline/clinical (accessed Jan 12, 2024).

52 Statista. Breakdown of hospital services in India in financial year 2020, by public and private sector. 2021. https://www.statista.com/statistics/1252917/india-breakdown-of-hospital-services-by-public-and-private/ (accessed Nov 26, 2023).

53 Suseela RP, Shannawaz M. Engaging the private health service delivery sector for TB care in India-miles to go! *Trop Med Infect Dis* 2023; **8:** 265.

54 Achanta S, Jaju J, Kumar AMV, et al. Tuberculosis management practices by private practitioners in Andhra Pradesh, India. *PLoS One* 2013; **8:** e71119.

55 Udwadia ZF, Pinto LM, Uplekar MW. Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades? *PLoS One* 2010; **5:** e12023.

56 Shrivastava SR, Shrivastava PS, Ramasamy J. Notification of tuberculosis cases in India: moving ahead in revised National Tuberculosis Control Program. *Infect Ecol Epidemiol* 2013; **3**.

57 O'Donnell MR, Daftary A, Frick M, et al. Re-inventing adherence: toward a patient-centered model of care for drug-resistant tuberculosis and HIV. *Int J Tuberc Lung Dis* 2016; **20:** 430–34.

58 WHO. Ethics in programmatic management of MDR-TB. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization, 2014:249–54.

59 Cox V, Brigden G, Crespo RH, et al. Global programmatic use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2018; **22:** 407–12.

60 Rosoff PM. Unpredictable drug shortages: an ethical framework for short-term rationing in hospitals. *Am J Bioeth* 2012; **12:** 1–9.

61 Jaramillo E, Kuesel AC, Reis A. Ethics and human rights must drive our response to the TB epidemic. *Int J Tuberc Lung Dis* 2020; **24:** 1–2.

62 WHO. Ethics guidance for the implementation of the end TB strategy. 2017. https://iris.who.int/bitstream/handle/10665/254820/9789241512114-eng.pdf?sequence=1 (accessed Dec 5, 2023).

63 Kunkel A, Cobelens FG, Cohen T. Tradeoffs in introduction policies for the anti-tuberculosis drug bedaquiline: a model-based analysis. *PLoS Med* 2016; **13:** e1002142.

64 Littmann J, Viens AM. The ethical significance of antimicrobial resistance. *Public Health Ethics* 2015; **8:** 209–24.

65 Paton NI, Cousins C, Suresh C, et al. Treatment strategy for rifampin-susceptible tuberculosis. Reply. *N Engl J Med* 2023; **388:** 873–87.

66 Zhou Y, Mu W, Zhang J, Wen SW, Pakhale S. Global prevalence of non-tuberculous mycobacteria in adults with non-cystic fibrosis bronchiectasis 2006–2021: a systematic review and meta-analysis. *BMJ Open* 2022; **12:** e055672.

67 Svensson EM, Murray S, Karlsson MO, Dooley KE. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *J Antimicrob Chemother* 2015; **70:** 1106–14.

68 Zhu H, Zhou X, Zhuang Z, Li L, Bi J, Mi K. Advances of new drugs bedaquiline and delamanid in the treatment of multi-drug resistant tuberculosis in children. *Front Cell Infect Microbiol* 2023; **13:** 1183597.

69 Johnson & Johnson. Johnson & Johnson confirms intent not to enforce patents for SIRTURO® (bedaquiline) for the treatment of multidrug-resistant tuberculosis in 134 low- and middle-income countries. Sept 29, 2023. https://www.jnj.com/johnson-johnson-confirms-intent-not-to-enforce-patents-for-sirturo-bedaquiline-for-the-treatment-of-multidrug-resistant-tuberculosis-in-134-low-and-middle-income-countries (accessed Nov 25, 2023).

70 LaHood A, Rahman R, McKenna L, Frick M, Mitnick CD. Comparing timelines and evidence available to support new TB, HIV, and HCV drug approvals: the same, only different. *PLoS One* 2022; **17:** e0271102.

71 Gupta-Wright A, den Boon S, MacLean EL, et al. Target product profiles: tests for tuberculosis treatment monitoring and optimization. *Bull World Health Organ* 2023; **101:** 730–37.

72 United Nations. Political declaration of the high-level meeting on the fight against tuberculosis: resolution / adopted by the General Assembly. 2023. https://digitallibrary.un.org/record/4025280?ln=en&v=pdf (accessed Jan 8, 2024).

73 Lange C, Vasiliu A, Mandalakas AM. Emerging bedaquiline-resistant tuberculosis. *Lancet Microbe* 2023; **4:** e964–65.

74 Chiang CY, Trébucq A, Piubello A, Rieder HL, Schwoebel V, Van Deun A. The looming threat of bedaquiline resistance in tuberculosis. *Eur Respir J* 2020; **55:** 2000718.

75 Guglielmetti L, Varaine F. The coming-of-age of bedaquiline: a tale with an open ending. *Eur Respir J* 2021; **57:** 2100066.

76 Stop TB Partnership. UN High-Level Meeting on TB. 2023. https://www.stoptb.org/advocate-to-endtb/united-nations-high-level-meeting-tb (accessed June 17, 2024).