

1 **Has primary care antimicrobial use really been increasing? Comparison of changes in**  
2 **different prescribing measures for a complete geographic population 1995-2014**

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11 **Running title:** Antimicrobial use: trends and measures

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16 **Synopsis**

17 **Objective**

18 To elucidate how population trends in total antimicrobials dispensed in the community translate into  
19 individual exposure.

20 **Methods**

21 Retrospective, population-based observational study of all antimicrobial prescribing in a Scottish region  
22 in financial years 1995, 2000 and 2005-2014. Analysis of temporal changes in all antimicrobials and  
23 specific antimicrobials measured in: WHO DDD per 1000 population; prescriptions per 1000 population;  
24 proportion of population with  $\geq 1$  prescription; mean number of prescriptions per person receiving any;  
25 mean DDD per prescription.

26 **Results**

27 Antimicrobial DDD increased between 1995 and 2014, from 5651 to 6987 per 1000 population  
28 (difference 1336 (95%CI 1309 to 1363)). Prescriptions per 1000 fell (from 821 to 667, difference -154, -  
29 151 to -157), as did the proportion prescribed any antimicrobial (from 39.3% to 30.8% (-8.5, -8.4 to -  
30 8.6)). Rising mean DDD per prescription, from 6.88 in 1995 to 10.47 in 2014 (3.59, 3.55 to 3.63), drove  
31 rising total DDD. In the under-5s, every measure fell over time (68.2% fall in DDD per 1000; 60.7% fall in  
32 prescriptions per1000). Among 5-64 year olds, prescriptions per1000 was lowest in 2014 but among  
33 older people, despite a reduction since 2010, the 2014 rate was still higher than in 2000. Trends in  
34 individual antimicrobials provide some explanation for overall trends.

35 **Conclusion**

36 Rising antimicrobial volumes up to 2011 were mainly due to rising DDD per prescription. Trends in  
37 dispensed drug volumes do not readily translate into information on individual exposure which is more  
38 relevant for adverse consequences including emergence of resistance.

## 39 **Introduction**

40 Antimicrobial resistance (AMR) is a global public health threat with antimicrobial use in humans  
41 significantly contributing.<sup>1-3</sup> Approximately 80% of UK antimicrobial use is in the community, with up to  
42 50% deemed inappropriate.<sup>1</sup> Associations between primary care prescribing and AMR are well  
43 described,<sup>1, 4-7</sup> and multiple initiatives have targeted reductions in this prescribing,<sup>2, 3, 8-10</sup> but UK rates  
44 appeared to still be increasing until 2012.<sup>11, 12</sup> This interpretation is based on population-level volumes of  
45 antimicrobials dispensed, measured in WHO Collaborating Centre for Drug Statistics Methodology's  
46 DDD.<sup>13</sup> DDD is the assumed average maintenance dose per day for an individual drug's main indication  
47 in adults rather than the actual daily dose used in practice which has changed over time, as has the mix  
48 of antimicrobials used which also affects total DDD.<sup>13</sup>  
49 Increases in total DDD could be due to more people being prescribed, more prescriptions for each  
50 person, and/or changes in antimicrobial choice or dose. Therefore, total DDD can change without  
51 changes in the proportion of the population exposed. Measures other than total DDD are required to  
52 examine antimicrobial use and the impact of antimicrobial stewardship interventions,<sup>14</sup> and changes  
53 within specific patient groups and antimicrobials could help explain population changes. In this study,  
54 we examined changes in primary care antimicrobial use from 1995 to 2014 in Tayside, Scotland, using  
55 patient-level data for all community dispensed antimicrobials across a complete geographical  
56 population.

## 57 **Population and methods**

58 The Tayside region of Scotland has a stable population with health care delivered by a single National  
59 Health Service (NHS) organisation. Access to NHS services requires registration with a single general  
60 practice which delivers all primary health care including prescribing.

61 The Health Informatics Centre (HIC),<sup>15</sup> University of Dundee, enables anonymised linkage of health and  
62 demographic data from multiple population datasets in NHS Tayside at the individual patient level, via a  
63 unique identifier (the community health index (CHI) number) used across all healthcare delivery in  
64 Scotland. We linked demographic data on everyone registered with a Tayside general practice to  
65 dispensed primary care prescriptions for oral antimicrobials for financial years 1995, 2000 and 2005-  
66 2014. Annual measurements were in financial years (e.g. 2005 is 1st April 2005 to 31st March 2006) so  
67 each year included a complete winter. HIC provided annual population estimates by age and gender. We  
68 calculated the DDD for each prescription using 2014 values.<sup>13</sup> Data allowing DDD calculation (either/both  
69 of strength or quantity) were missing from 0.8% of prescriptions (highest in earlier years) so we used  
70 multiple imputation to estimate missing DDD values, with age, gender, drug and year of prescription as  
71 predictors. Antimicrobials were grouped into classes as defined in the British National Formulary version  
72 68 chapter 5 (penicillins, tetracyclines, macrolides, sulphonamides and trimethoprim, quinolones,  
73 metronidazole and tinidazole, cephalosporins, other).<sup>16</sup>

74 We calculated antimicrobial DDD and prescriptions dispensed per 1000 population per year, in total, by  
75 class, and by age group (<5 years old; 5-64 years old; >64 years old). We then calculated the proportion  
76 of the population with at least one prescription in each study year, the mean and median number of  
77 prescriptions per patient per year among patients with any antimicrobial prescription in that year, and  
78 the mean and median DDD per prescription in each year, in total and by age group and gender.

79 Statistical comparisons between 2014 and 1995 used chi-squared tests for proportions, Student's t-test  
80 for means, and Mann-Whitney U test for medians. Statistical tests of trend for total DDD and total  
81 prescriptions, both per 1000 population per year, included the continuous data period (2005 to 2014).

82 The large dataset means that statistical tests of significance should be interpreted alongside clinical  
83 significance.

84

85 To estimate the extent to which changes in total DDD and total prescriptions, per 1000 population, were  
86 attributable to changes in each contributory measure (patients per 1000 population with any  
87 prescription, mean prescriptions per patient with any, mean DDD per prescription) we calculated the  
88 relative (percentage) change in each measure for each year compared to 1995.

89 To investigate potential reasons behind any changes we first examined seasonal variation in prescribing,  
90 which is attributed to prescribing for respiratory tract infection. Seasonal variation, using DDD, is a  
91 European Surveillance of Antimicrobial Consumption (ESAC) quality indicator.<sup>17, 18</sup> We calculated  
92 prescriptions per 1000 population quarterly by age group and expressed seasonal variation as overuse in  
93 “winter” quarters (October-March) compared to the previous “summer” quarters (April-September) as a  
94 percentage, and compared 2014 to 1995 using chi-squared tests. We then examined trends in  
95 prescribing, from 2005-2014, of twelve commonly prescribed individual antimicrobial drugs (amoxicillin,  
96 ciprofloxacin, clarithromycin, co-amoxiclav, doxycycline, erythromycin, flucloxacillin, lymecycline,  
97 nitrofurantoin, oxytetracycline, penicillin V, trimethoprim).

98 Anonymised record linkage was conducted in accordance with HIC Standard Operating Procedures  
99 (SOP).<sup>15</sup> These are approved by The East of Scotland Research Ethics Service and the NHS Tayside  
100 Caldicott Guardian with agreement that studies adhering to the SOP do not require individual ethical  
101 review. All data were analysed in IBM SPSS statistics v22 in an ISO27001 and Scottish Government  
102 accredited data Safe Haven.

## 103 **Results**

104 In 1995 and 2014 there were 419,447 and 441,298 registered patients, respectively. 49% were male. In  
105 all study years 5% were under 5 years old, but the proportion >64 years increased from 16% to 20%.  
106 2,377,258 antimicrobial DDD were dispensed in 1995, rising to 3,083,451 in 2014, but prescriptions fell  
107 from 345,328 to 294,391, and the proportion of the population exposed fell from 39% to 31%.

### 108 **DDD per 1000 population**

109 Among the whole population, DDD per 1000 population fell between 1995 and 2000 then increased to a  
110 peak at 7092 in 2011 before decreasing to 6987 in 2014 (Table 1, Figure 1). There was a very large (68%)  
111 reduction among those <5 but increases otherwise (Table 1). Change varied by antimicrobial class  
112 (Figure 1), with more than doubling of tetracycline DDD per 1000 population per year between 1995 and  
113 2014 (18% *versus* 31% of total DDD), and increases in all other classes except cephalosporins (7% *versus*  
114 0.5%) and quinolones (4% *versus* 2%) (Figure 1, Table S1).

### 115 **Prescriptions per 1000 population**

116 Antimicrobial prescriptions per 1000 population overall fell between 1995 and 2000 then increased until  
117 2011 before falling to 667 by 2014 (Table 1, Figure 2). There was a large (61%) reduction among those  
118 <5s and a small (2%) increase among those >64 (Table 1). Seasonal variation was greatest among pre-  
119 school children (Figure 3) with 52-69% more prescriptions per 1000 population each winter, except in  
120 2007 (40%) due to low winter prescribing, and no significant difference between 1995 and 2014 (chi<sup>2</sup>  
121 test p=0.92). Seasonal variation in other age groups decreased over time, from 29% among 5-64yr olds  
122 and 25% among those >64 in 1995, to 5% and 6% in 2014, respectively (chi<sup>2</sup> tests p <0.001).  
123 Changes by antimicrobial class were similar to DDD, with reductions in cephalosporins (from 9% to 1% of  
124 prescriptions) and quinolones (4% to 2%), and increases in tetracyclines (10% to 17%) and  
125 sulphonamides/trimethoprim (7% to 12%) (Figure 2, Table S1).

### 126 **Proportion prescribed any antimicrobial**

127 The proportion of the population with at least one antimicrobial prescription per year fell overall. There  
128 was a reduction from 1995 to 2000, followed by increases between 2005 and 2012, then a reduction to  
129 308 per 1000 population by 2014 (Tables 1 and 2). The biggest reductions were among those <5, who  
130 had the highest rate until 2005. Older people had the highest rate since then, but this reduced from 445  
131 to 412 per 1000 population between 2010 and 2014. Among 5-64 year olds, there was a 24% reduction

132 overall (Table 1). Higher proportions of females (11-13% difference) had prescriptions each year but  
133 without temporal trend in differences (45% *versus* 33% in 1995; 37% *versus* 25% in 2014). Gender  
134 difference was largest among 5-64 year olds (females 13-15% higher each year). Among those <5 more  
135 males (1-3% higher each year) had any prescription (Table S2).

#### 136 **Prescriptions per patient dispensed at least one antimicrobial**

137 In 1995, the 164,864 people in Tayside with at least one antimicrobial prescription had a mean 2.09  
138 prescriptions. Overall, there were clinically small but statistically significant changes over time, with  
139 increases since 2000 resulting in patients with any prescription in 2014 receiving a mean additional 0.08  
140 prescriptions compared to 1995. There were reductions among pre-school children and increases among  
141 older people (Table 1). Females with any prescription had higher mean prescriptions, overall (mean  
142 additional 0.19-0.28 prescriptions per patient per year), among 5-64 year olds (additional 0.20-0.28) and  
143 those over 64 years (additional 0.15-0.36), but among those <5 this was higher for males (additional  
144 0.00-0.12). The gender difference among those >65 increased over time but there were no other  
145 temporal patterns (Table S2).

146 Median prescriptions per patient with any per year was 1.00 except among those >64, and those <5 in  
147 1995 only, with median 2.00 (Table 1).

#### 148 **DDD per prescription**

149 Mean DDD per prescription overall increased by more than half over the study period (Table 1, Table 2).  
150 Among young children it was low (due to paediatric dosing) and decreased by 0.72 (95% CI -0.66 to -  
151 0.80) while it increased among 5-64 year olds by 4.00 (3.95 to 4.06) (Table 1). Males had higher mean  
152 DDD per prescription overall, and the difference increased over time, from 0.69 additional DDD per  
153 prescription in 1995 to 2.28 in 2014. The difference among those <5 decreased with time; males having  
154 an additional 0.23 in 1995 but females having an additional 0.05 by 2014 (Table S2).

155

156 Median DDD per prescription was 2.50 in all years among those <5, but it increased from 5.25 in 1995  
157 for others to 7.50 among those aged 5-64 years and 8.00 among those >64 by 2014 (Table 1).  
158 Among most antimicrobial drug classes mean DDD per prescription increased: penicillins from 5.60 to  
159 8.64; tetracyclines from 12.87 to 18.88; quinolones from 7.15 to 11.23; macrolides 8.51 to 15.44.  
160 Cephalosporin mean DDD was more constant (4.54 and 4.87) and the mean DDD per  
161 sulphonamide/trimethoprim prescription decreased from 7.69 in 1995 to 5.77 in 2014.

## 162 **Contribution to changes in aggregate measures**

163 Total antimicrobial DDD per 1000 population was 24% higher in 2014 than in 1995 despite prescriptions  
164 per 1000 population decreasing by 19% (Table 2). Of potentially contributory measures, the proportion  
165 of the population with any prescription fell continuously and although mean prescriptions per patient  
166 increased until 2011, the changes are numerically small and decreased slightly by 2014 (Table 2).  
167 Changes in this measure only account for 10,455 (3.6%) prescriptions dispensed in 2014. In contrast, the  
168 mean DDD per prescription increased by 52.2% between 1995 and 2014 (Table 2). Had the mean DDD  
169 per prescription not changed, total DDD in 2014 would have been 2,025,410 (rather than the observed  
170 3,083,451), a 19% reduction in DDD per 1000 population from 1995, rather than the observed 24%  
171 increase.

## 172 **Trends in individual drugs**

173 Amoxicillin had the highest DDD and prescriptions per 1000 population of any individual drug and both  
174 increased until 2011 then fell until 2014 (Figure 4, Table S3). The converging trend lines for DDD and  
175 prescriptions per 1000 population reflect the increasing DDD per prescription (Figure 4). Other  
176 penicillins (co-amoxiclav, flucloxacillin and penicillin V) also had increasing DDD per prescription, and  
177 reducing prescriptions per 1000 population (Figure 4). Drugs targeted by a 2008 Tayside antimicrobial  
178 stewardship intervention (ciprofloxacin and co-amoxiclav)<sup>19</sup> had reducing DDD and prescriptions per  
179 1000 population since 2008, while drugs recommended in the intervention guidelines (doxycycline,



180 nitrofurantoin and trimethoprim)<sup>19</sup> had increasing DDD and prescriptions per 1000 population but  
181 reducing DDD per prescription (Figure 4). Clarithromycin and erythromycin had high mean DDD per  
182 prescription, with small increases over time (Figure 4). Lymecycline and oxytetracycline have very high  
183 mean DDD per prescription (>28 at each time point, Figure 4), reflecting long term use for acne, and  
184 resulting in disproportionate contributions to total DDD per 1000 population for a relatively small  
185 number of patients (Figure 4, Table S3).

## 186 **Discussion**

### 187 **Summary**

188 In this large population based study with individual prescribing data we found that antimicrobial use in  
189 DDD increased considerably between 1995 and 2014 in Tayside, despite substantial reductions in  
190 prescriptions per 1000 residents and the proportion of the population exposed. Between 2000 and 2011  
191 there were annual increases in total prescriptions, the proportion of the population exposed, and mean  
192 prescriptions per patient, but total prescriptions and the proportion exposed then fell again and had  
193 returned to the same level as 2000, or lower, by 2014. Among pre-school children (<5 years old)  
194 antimicrobial use by all measures decreased substantially, but among older people (>64 years old) all  
195 measures were the same or higher, except the proportion exposed, which had decreased by 7%.  
196 Seasonal variation, representing prescribing for respiratory tract infection, reduced overall but remained  
197 high among pre-school children. The most significant change in prescribing practice was the large  
198 increase in mean DDD per prescription, which was driven by both increasing doses (e.g. penicillins and  
199 macrolides) and changes in choice of antimicrobial (e.g. greater use of doxycycline).

### 200 **Strengths and Limitations**

201 We report secular trends across a comprehensive set of antimicrobial prescribing measures using  
202 patient-level dispensed prescribing data across a whole geographical population. Most previous reports

203 generally focus on volume (e.g. DDD) and/or prescriptions (or packages) per 1000 population, or  
204 patient-level analysis for specific clinical conditions.<sup>20-26</sup> A recent, more comprehensive, study included  
205 data across a whole country but without demographic information and included only seven years'  
206 data.<sup>14</sup> Our ability to link demographic and detailed prescribing data at patient level, including  
207 historically, enabled detailed investigation over a relatively long time period.

208 The limitations of this study include those common to observational studies using routine data, such as  
209 potentially incomplete data. We addressed missing DDD data using multiple imputation. Consistent with  
210 successful imputation, the mean DDD per prescription was almost identical afterwards. A further  
211 limitation is the lack of prescribing indication data, but coding in GP records is not reliably consistent  
212 between practices or over time. In our analysis of 12 individual drugs, prescriptions per 1000 population  
213 of trimethoprim and nitrofurantoin, both used almost exclusively for urinary tract infections (UTI) in NHS  
214 Tayside, increased after a stewardship intervention which promoted these drugs,<sup>19</sup> then levelled off  
215 since 2011 (Figure 4). The decreasing mean DDD per prescription is consistent with recommended short-  
216 course treatment for uncomplicated UTI.<sup>27</sup> The proportion of nitrofurantoin and trimethoprim  
217 prescriptions for women aged 16 to 64 years for three-days or less ( $\leq 0.6$  grams nitrofurantoin;  $\leq 1.2$   
218 grams trimethoprim), increased from 0.5% to 31.5%, and 13.1% to 59.9%, respectively, between 1995  
219 and 2014. Reductions in trends of amoxicillin and doxycycline prescriptions since 2011/2012, without  
220 increases in other drugs used for respiratory tract infections (Figure 4), suggest reductions in prescribing  
221 for this indication recently.

222 While we cannot assume similar changes in patient-level prescribing explain trends in DDD elsewhere,  
223 the observed reductions in cephalosporin and fluoroquinolone use and increases in tetracycline use are  
224 consistent with national guideline changes,<sup>19, 28</sup> and we know that cephalosporins, co-amoxiclav and  
225 fluoroquinolones, as a proportion of all community prescriptions, have reduced across Scotland and in  
226 England.<sup>12, 29</sup> These intended changes contributed to observed increases in DDD due to promoted drugs

227 such as doxycycline having a relatively low DDD value. Changes in recommended dosing additionally  
228 contributed to the observed increased DDD per prescription. Local guideline recommended amoxicillin  
229 doses for non-severe community acquired pneumonia increased from 500mg to 1g three times daily in  
230 2009,<sup>28,30</sup> and the increasing amoxicillin DDD per prescription is consistent with this guideline  
231 influencing dosing. Similar trends in dosing impacting on DDD per treatment have occurred elsewhere,<sup>14</sup>  
232 indicating our findings will apply more widely.

### 233 **Comparison with other data**

234 The observed increase in total antimicrobial DDD until 2011 is consistent with other reports of primary  
235 care antimicrobial use,<sup>11, 14, 31-34</sup> with many developed countries reporting reductions in the 1990s and  
236 increases between 2000 and 2010.<sup>9, 12, 35, 36</sup> Compared to primary care data from all Scotland and from  
237 England, Tayside had lower DDD per 1000 population in 2010 (Tayside 19.3 DDD per 1000 population  
238 per day, Scotland 20.1, England 20.6) but higher rates than England by 2014 (19.1 *versus* 17.5).<sup>12, 37, 38</sup>  
239 Tayside had a bigger reduction in antimicrobial prescriptions between 2011 and 2014, falling from 2.06  
240 to 1.83 per 1000 population per day, than Scotland (2.14 to 2.05),<sup>12</sup> England (1.92 both years),<sup>39</sup> Wales  
241 (2.32 to 2.30)<sup>40</sup> and Northern Ireland (2.90 to 2.84).<sup>41</sup> National reports have limited adjustment for  
242 population demographics with the exception is the “STAR-PU” (Specific Therapeutic group Age-sex  
243 weightings Related Prescribing Units) English prescribing indicator,<sup>29</sup> which provides useful adjusted  
244 trends over time but limited external comparison.

245 Two large European studies analysing antimicrobial prescribing data up to 2007, reported different  
246 trends when measuring using DDD *versus* packages per 1000 population,<sup>22, 36</sup> and one reported rising  
247 DDD per package (0.04-0.31 DDD increase/package/year), similar to our findings.<sup>22</sup> A Belgian study  
248 reported increases in antimicrobial DDD but decreases in antimicrobial packages, treatments and the  
249 proportion of people exposed from 2002-2009 using a variety of measure definitions (rates per 1000  
250 population, per 1000 insured patients, per 1000 GP contacts).<sup>14</sup> None of these studies reported

251 prescribing measures by age or gender of patients exposed, or for individual antimicrobial drugs, which  
252 we found help explain trends in the overall measures.

253 Between 1994 and 2000, reductions of 45% in the proportion of patients with respiratory tract  
254 infections prescribed antimicrobials, and 27% in total prescriptions per 1000 registered patients, were  
255 reported across 108 UK general practices.<sup>20</sup> Similarly, reductions in total antimicrobial prescriptions and  
256 prescriptions for upper respiratory tract infection, adjusted for patient, practitioner and comorbidity,  
257 per 100 patient encounters, were reported between 1991 and 2003 across 495 Australian GPs.<sup>26</sup> In  
258 contrast, across 570 UK general practices, a 29% increase in the proportion of cough/cold consultations  
259 with an antimicrobial prescription was observed between 1995 and 2011.<sup>24</sup> Consultations coded as  
260 cough/cold increased and the authors attributed between-practice variation to varying concordance  
261 with antimicrobial stewardship,<sup>24</sup> but could be due to coding.

## 262 **Implications**

263 Our results demonstrate that the main factor influencing total antimicrobial DDD in Tayside is DDD per  
264 prescription. Total volume in DDD does not reliably represent actual antimicrobial use so  
265 prescriptions/packages per 1000 population and the proportion of the population exposed better  
266 evaluate changes over time and the impact of stewardship interventions. What this means for the  
267 impact on emerging antimicrobial resistance is not clear, but a recent study modelling relationships  
268 between use and resistance found different associations if use was measured in DDD *versus* packages.<sup>21</sup>  
269 However, following reductions in antimicrobial use in all age groups between 1995 and 2000, we  
270 observed increases in most measures between 2000 and 2011, with the exception of preschool children.  
271 In the last few years of observation there were reductions across several measures, but achieving  
272 substantial and sustained reductions in the proportion of the population exposed remains challenging  
273 for antimicrobial stewardship globally.<sup>9</sup> National and local antimicrobial stewardship activity in Scotland,  
274 particularly since the formation of the Scottish Antimicrobial Prescribing Group in 2008, has led to

275 changes in choice of antimicrobial (Figures 1, 2 and 4)<sup>9, 12, 19</sup> but there is less impact on total prescribing  
276 within our study timeframe. Older people appear an obvious target group for stewardship due to high  
277 rates of exposure and higher risk of adverse events like *Clostridium difficile* infection.<sup>42</sup> However, for  
278 lower respiratory tract infections, the number needed to treat to prevent serious complications is lower  
279 in older people,<sup>43</sup> making reductions challenging. Prescribing rates are lower among those aged 5-64  
280 years but they received 62% of all antimicrobial prescriptions in Tayside in 2014. They may be a better  
281 target for stewardship, with greater scope for change. Recent data from >600 general practices found  
282 minor increases in treatable respiratory tract infections associated with large reductions in antimicrobial  
283 prescribing, but the authors acknowledged the need for analysis in high-risk subgroups.<sup>44</sup>

#### 284 **Conclusion**

285 Our findings highlight the importance of studying trends in antimicrobial use in greater detail than total  
286 volume in DDD. With antimicrobial stewardship focusing on reducing total prescribing, we need to  
287 replicate the large reductions observed in the 1990s, building on the small reductions since 2011, and to  
288 learn from continued reductions among pre-school children. Further research is required to better  
289 understand the relationship between antimicrobial consumption and resistance and the relative  
290 importance of individual and community exposure.

291

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413 **Tables**

414 Table 1. Summary of antimicrobial prescribing measures by year and age group among all patients  
 415 registered with a general practice in the Tayside NHS Health Board region

	1995	2000	2005	2010	2014	Difference (95% CI) 2014 vs 1995 and p-value <sup>#</sup>
<b>&lt; 5 years</b>						
Total number of patients <sup>^</sup>	23,054	21,695	19,826	21,266	21,472	
DDD per 1000 patients	6125	2875	2666	2258	1948	-4177 (-4094 to -4260) p<0.001
Prescriptions per 1000 patients	1612	930	898	776	634	-978 (-956 to -1000) p< 0.001
Patients per 1000 with prescription	686	487	477	435	367	-319 (-309 to -329) p< 0.001
Mean prescriptions per patient*	2.44	1.97	1.93	1.83	1.70	-0.74 (-0.79 to -0.69) p<0.001
Median prescriptions per patient*	2.00	1.00	1.00	1.00	1.00	-1.00 p<0.001~
Mean DDD per prescription	3.80	3.09	2.97	2.91	3.08	-0.72 (-0.66 to -0.80) p<0.001
Median DDD per prescription	2.50	2.50	2.50	2.50	2.50	0 p<0.001
<b>5 to 64 years</b>						
Total number of patients <sup>^</sup>	328,048	322,648	318,200	338,033	332,417	
DDD per 1000 patients	5082	4581	5598	6304	6123	1041 (1014 to 1068) p<0.001
Prescriptions per 1000 patients	709	563	633	635	548	-161 (-158 to -164) p<0.001
Patients per 1000 with prescription	362	300	329	322	276	-86 (-84 to -88) p<0.001
Mean prescriptions per patient*	1.96	1.88	1.92	1.98	1.98	0.02 (0.03 to 0.01) p<0.001
Median prescriptions per patient*	1.00	1.00	1.00	1.00	1.00	0 p<0.001~
Mean DDD per prescription	7.17	8.13	8.85	9.92	11.17	4.00 (3.95 to 4.06) p<0.001
Median DDD per prescription	5.25	5.25	7.00	7.00	7.50	2.25 p<0.001
<b>&gt; 64 years</b>						
Total number of patients <sup>^</sup>	68,345	69,443	71,211	78,274	87,408	
DDD per 1000 patients	8336	8183	9617	11,523	11,510	3174 (3075 to 3273) p<0.001
Prescriptions per 1000 patients	1107	1044	1138	1239	1127	20 (9 to 31) p<0.001
Patients per 1000 with prescription	445	414	443	445	412	-33 (-29 to -37) p<0.001
Mean prescriptions per patient*	2.45	2.50	2.54	2.76	2.76	0.28 (0.24 to 0.32) p<0.001
Median prescriptions per patient*	2.00	2.00	2.00	2.00	2.00	0 p<0.001~
Mean DDD per prescription	7.53	7.84	8.45	9.30	10.21	2.68 (2.61 to 2.76)
Median DDD per prescription	5.25	7.00	7.00	7.00	8.00	2.75 p<0.001
<b>All ages</b>						
Total number of patients <sup>^</sup>	419,447	413,786	409,237	437,573	441,298	
DDD per 1000 patients	5651	5094	6153	7037	6987	1336 (1309 to 1363) p<0.001
Prescriptions per 1000 patients	821	663	733	750	667	-154 (-151 to -157) p<0.001
Patients per 1000 with prescription	393	329	356	349	308	-85 (-84 to -86) p<0.001
Mean prescriptions per patient*	2.09	2.02	2.06	2.15	2.17	0.08 (0.06 to 0.09) p<0.001
Median prescriptions per patient*	1.00	1.00	1.00	1.00	1.00	0 p<0.001~
Mean DDD per prescription	6.88	7.68	8.39	9.38	10.47	3.59 (3.55 to 3.63) p<0.001
Median DDD per prescription	5.25	5.25	7.00	7.00	7.50	2.25 p<0.001

416 <sup>^</sup> Total patients registered with general practitioner in the region

417 \* Mean and median prescriptions per patient dispensed at least one antimicrobial

418 ~Although there is no numerical difference there is a statistically significant difference in the distribution

419 # Differences in proportions evaluated using chi-squared, in means using t-test, and in medians using Mann-

420 Whitney U test

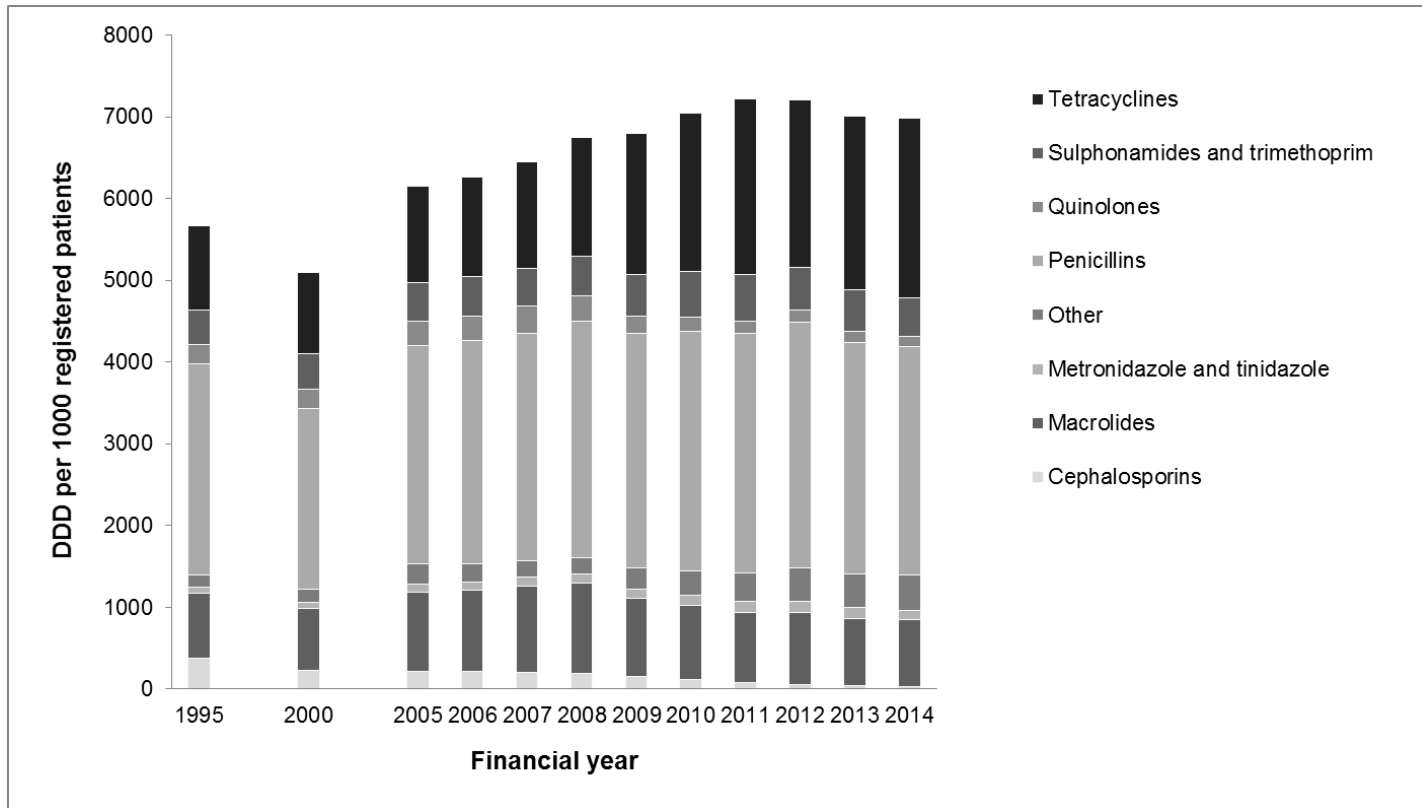
Table 2 Percentage change per year compared to 1995 for each measure of antimicrobial prescribing among all registered patients in Tayside

Measure of community antimicrobial prescribing	Value in reference year 1995	Relative (%) change from 1995 value*										
		2000	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Patients per 1000 with any prescription (A)	393	-16.3	-9.3	-10.2	-11.0	-9.3	-11.9	-11.2	-12.4	-15.5	-19.6	-21.6
Mean prescriptions per patient with any (B)	2.09	-3.3	-1.4	-1.0	1.0	1.4	2.9	2.9	4.8	4.6	4.6	3.8
Mean DDD per prescription (C)	6.88	11.6	21.9	24.2	26.8	29.6	32.6	36.3	39.2	44.0	47.2	52.2
Prescriptions per 1000 patients (A x B)	821	-19.1	-10.6	-11.0	-10.2	-8.0	-9.4	-8.6	-8.2	-12.9	-15.8	-18.8
DDD per 1000 patients (A x B x C)	5651	-9.7	8.9	10.5	13.9	19.2	20.2	24.6	27.8	27.5	24.0	23.6

\*Positive values are increases, negative values are decreases

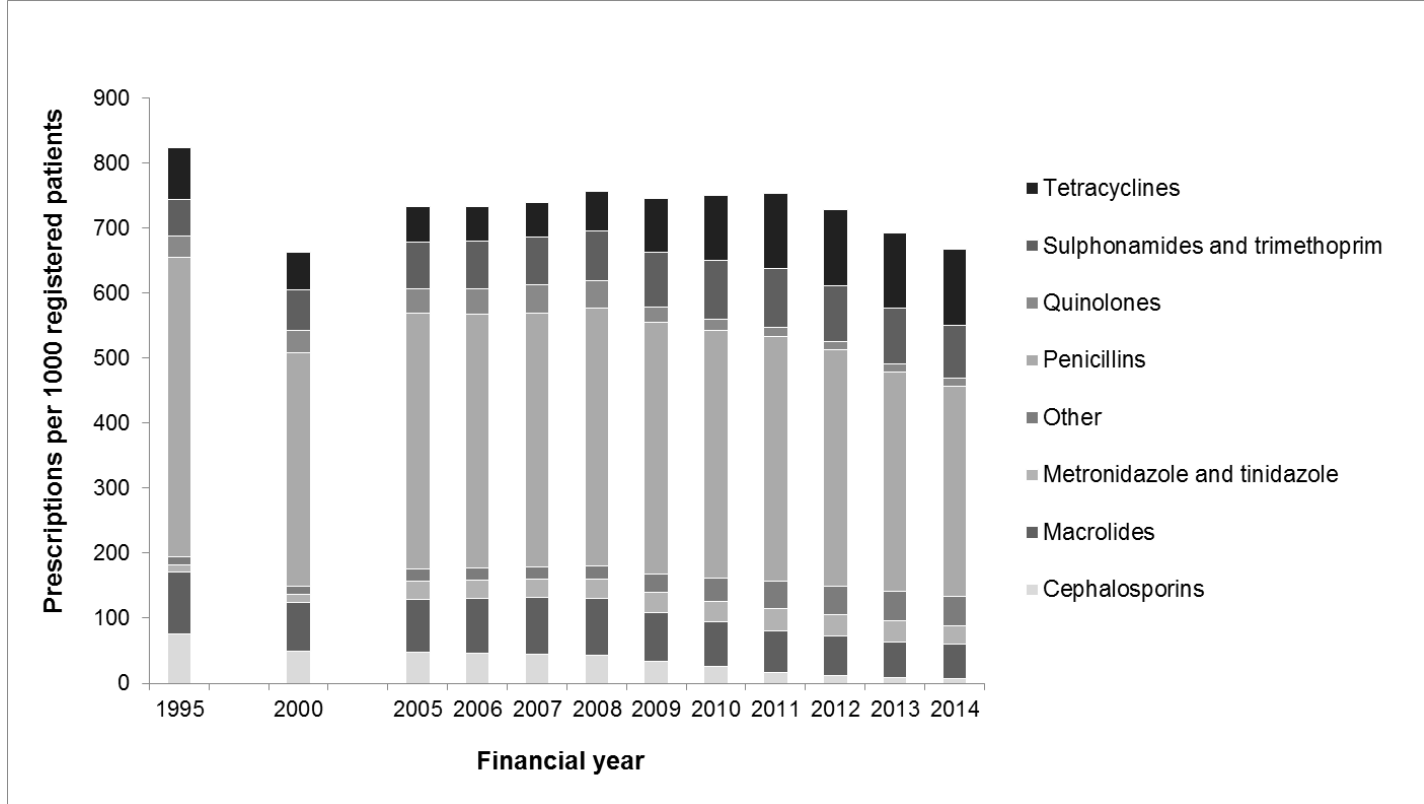
## Figures

Figure 1 Total WHO DDD of antimicrobials dispensed per 1000 registered patients in Tayside per financial year (April to March)



Test for trend from 2005-2014:  $\beta = 109.99$  ( $R^2 = 0.764$ ,  $p = 0.001$ )

Figure 2 Total prescriptions dispensed per 1000 registered patients in Tayside per financial year (April to March)



Test for trend from 2005-2014:  $\beta = -5.75$  ( $R^2 = 0.366$ ,  $p = 0.064$ )

Figure 3 Quarterly prescriptions per 1000 registered patients in Tayside by age group in financial years (April to March) 2005-14

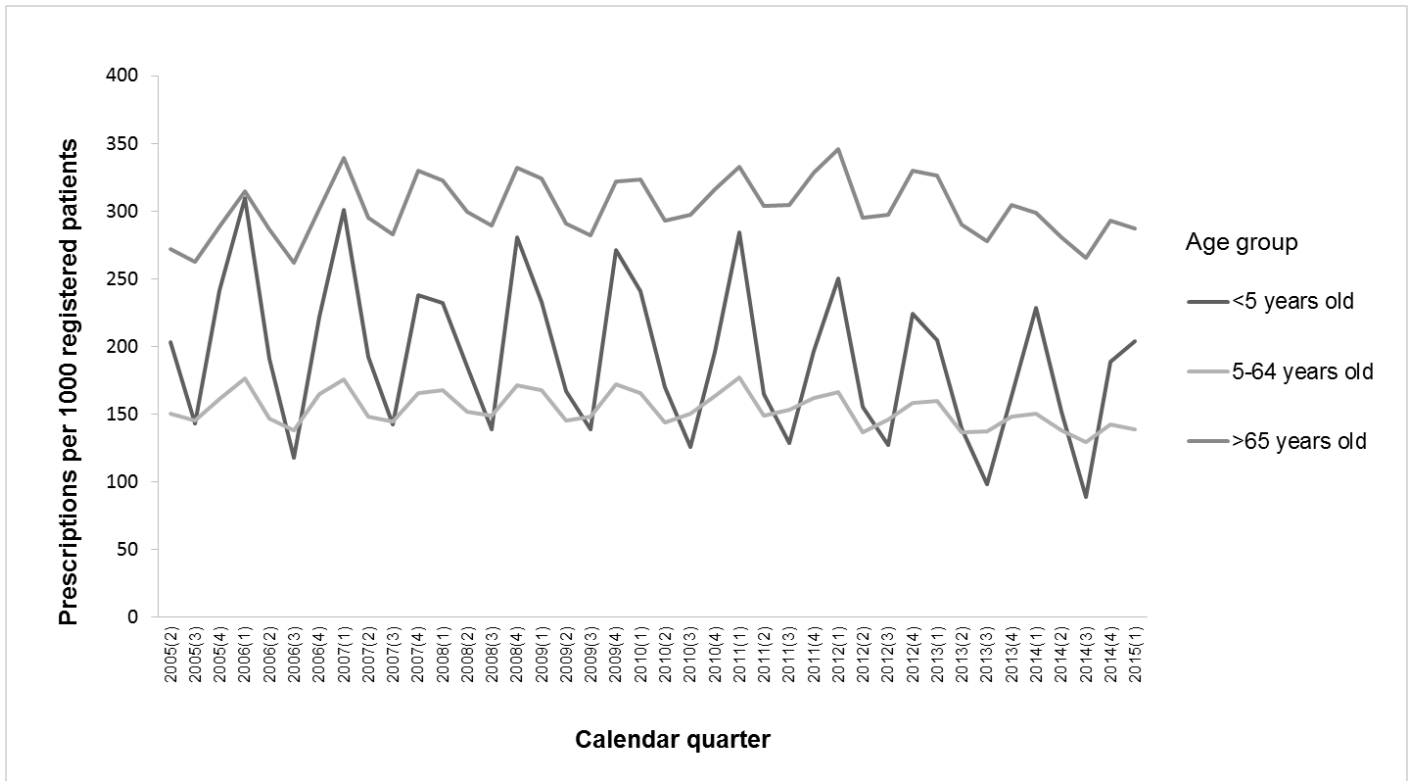


Figure 4 Trends in use of twelve individual antimicrobial drugs commonly used in primary care in Tayside, from 2005 to 2014, with use measured in DDD per 1000 population (dashed lines, left y axes), prescriptions per 1000 population (solid lines, right y axes) and mean DDD per prescription (text below x axes). Each graph is plotted on the same scale for ease of comparison.

