University of Dundee

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

Neilly, Mark D. J.; Guthrie, Bruce; Hernandez Santiago, Virginia; Vadiveloo, Thenmalar; Donnan, Peter T.; Marwick, Charis A.

Published in:
Journal of Antimicrobial Chemotherapy

DOI:
10.1093/jac/dkx220

Publication date:
2017

Document Version
Peer reviewed version

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

Neilly, Mark D.J.; Guthrie, Bruce; Hernandez Santiago, Virginia; Vadiveloo, Thenmalar; Donnan, Peter; Marwick, Charis

Published in:
Journal of Antimicrobial Chemotherapy

Publication date:
2017

Document Version
Accepted author manuscript

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

Mark D J NEILLY[1], Bruce GUTHRIE[2], Virginia HERNANDEZ SANTIAGO[2], Thenmalar VADIVELOO[3], Peter T DONNAN[3], Charis A MARWICK[2]*

1. Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, UK

2. Population Health Sciences, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee DD2 4BF, UK

3. Dundee Epidemiology and Biostatistics Unit (DEBU), Population Health Sciences, University of Dundee, Mackenzie Building, Kirsty Semple Way, Dundee DD2 4BF, UK

Running title: Antimicrobial use: trends and measures

***Corresponding author e**mail: c.z.marwick@dundee.ac.uk, telephone +44 (0)1382 383800

Main manuscript word count: 3,335

Synopsis

Objective

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

Methods

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

Results

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

Conclusion

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

Introduction

Antimicrobial resistance (AMR) is a global public health threat with antimicrobial use in humans significantly contributing.[1-3] Approximately 80% of UK antimicrobial use is in the community, with up to 50% deemed inappropriate.[1] Associations between primary care prescribing and AMR are well described,[1, 4-7] and multiple initiatives have targeted reductions in this prescribing,[2, 3, 8-10] but UK rates appeared to still be increasing until 2012.[11, 12] This interpretation is based on population-level volumes of antimicrobials dispensed, measured in WHO Collaborating Centre for Drug Statistics Methodology's DDD.[13] DDD is the assumed average maintenance dose per day for an individual drug's main indication in adults rather than the actual daily dose used in practice which has changed over time, as has the mix of antimicrobials used which also affects total DDD.[13]

Increases in total DDD could be due to more people being prescribed, more prescriptions for each person, and/or changes in antimicrobial choice or dose. Therefore, total DDD can change without changes in the proportion of the population exposed. Measures other than total DDD are required to examine antimicrobial use and the impact of antimicrobial stewardship interventions,[14] and changes within specific patient groups and antimicrobials could help explain population changes. In this study, we examined changes in primary care antimicrobial use from 1995 to 2014 in Tayside, Scotland, using patient-level data for all community dispensed antimicrobials across a complete geographical population.

Population and methods

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

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

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

Statistical comparisons between 2014 and 1995 used chi-squared tests for proportions, Student's t-test for means, and Mann –Whitney U test for medians. Statistical tests of trend for total DDD and total prescriptions, both per 1000 population per year, included the continuous data period (2005 to 2014). The large dataset means that statistical tests of significance should be interpreted alongside clinical significance.

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

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

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

Results

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

DDD per 1000 population

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

Prescriptions per 1000 population

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

Proportion prescribed any antimicrobial

The proportion of the population with at least one antimicrobial prescription per year fell overall. There was a reduction from 1995 to 2000, followed by increases between 2005 and 2012, then a reduction to 308 per 1000 population by 2014 (Tables 1 and 2). The biggest reductions were among those <5, who had the highest rate until 2005. Older people had the highest rate since then, but this reduced from 445 to 412 per 1000 population between 2010 and 2014. Among 5-64 year olds, there was a 24% reduction overall (Table 1). Higher proportions of females (11-13% difference) had prescriptions each year but without temporal trend in differences (45% *versus* 33% in 1995; 37% *versus* 25% in 2014). Gender difference was largest among 5-64 year olds (females 13-15% higher each year). Among those <5 more males (1-3% higher each year) had any prescription (Table S2).

Prescriptions per patient dispensed at least one antimicrobial

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

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

DDD per prescription

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

Median DDD per prescription was 2.50 in all years among those <5, but it increased from 5.25 in 1995 for others to 7.50 among those aged 5-64 years and 8.00 among those >64 by 2014 (Table 1). Among most antimicrobial drug classes mean DDD per prescription increased: penicillins from 5.60 to 8.64; tetracyclines from 12.87 to 18.88; quinolones from 7.15 to 11.23; macrolides 8.51 to 15.44. Cephalosporin mean DDD was more constant (4.54 and4.87) and the mean DDD per sulphonamide/trimethoprim prescription decreased from 7.69 in 1995 to 5.77 in 2014.

Contribution to changes in aggregate measures

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

Trends in individual drugs

Amoxicillin had the highest DDD and prescriptions per 1000 population of any individual drug and both increased until 2011 then fell until 2014 (Figure 4, Table S3). The converging trend lines for DDD and prescriptions per 1000 population reflect the increasing DDD per prescription (Figure 4). Other penicillins (co-amoxiclav, flucloxacillin and penicillin V) also had increasing DDD per prescription, and reducing prescriptions per 1000 population (Figure 4). Drugs targeted by a 2008 Tayside antimicrobial stewardship intervention (ciprofloxacin and co-amoxiclav)[19] had reducing DDD and prescriptions per 1000 population since 2008, while drugs recommended in the intervention guidelines (doxycycline, nitrofurantoin and trimethoprim)[19] had increasing DDD and prescriptions per 1000 population but reducing DDD per prescription (Figure 4). Clarithromycin and erythromycin had high mean DDD per prescription, with small increases over time (Figure 4). Lymecycline and oxytetracycline have very high mean DDD per prescription (>28 at each time point, Figure 4), reflecting long term use for acne, and resulting in disproportionate contributions to total DDD per 1000 population for a relatively small number of patients (Figure 4, Table S3).

Discussion

Summary

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

Strengths and Limitations

We report secular trends across a comprehensive set of antimicrobial prescribing measures using patient-level dispensed prescribing data across a whole geographical population. Most previous reports generally focus on volume (e.g. DDD) and/or prescriptions (or packages) per 1000 population, or patient-level analysis for specific clinical conditions.[20-26] A recent, more comprehensive, study included data across a whole country but without demographic information and included only seven years' data.[14] Our ability to link demographic and detailed prescribing data at patient level, including historically, enabled detailed investigation over a relatively long time period.

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

While we cannot assume similar changes in patient-level prescribing explain trends in DDD elsewhere, the observed reductions in cephalosporin and fluoroquinolone use and increases in tetracycline use are consistent with national guideline changes,[19, 28] and we know that cephalosporins, co-amoxiclav and fluoroquinolones, as a proportion of all community prescriptions, have reduced across Scotland and in England.[12, 29] These intended changes contributed to observed increases in DDD due to promoted drugs such as doxycycline having a relatively low DDD value. Changes in recommended dosing additionally contributed to the observed increased DDD per prescription. Local guideline recommended amoxicillin doses for non-severe community acquired pneumonia increased from 500mg to 1g three times daily in 2009,[28, 30] and the increasing amoxicillin DDD per prescription is consistent with this guideline influencing dosing. Similar trends in dosing impacting on DDD per treatment have occurred elsewhere,[14] indicating our findings will apply more widely.

Comparison with other data

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

Two large European studies analysing antimicrobial prescribing data up to 2007, reported different trends when measuring using DDD *versus* packages per 1000 population,[22, 36] and one reported rising DDD per package (0.04-0.31 DDD increase/package/year), similar to our findings.[22] A Belgian study reported increases in antimicrobial DDD but decreases in antimicrobial packages, treatments and the proportion of people exposed from 2002-2009 using a variety of measure definitions (rates per 1000 population, per 1000 insured patients, per 1000 GP contacts).[14] None of these studies reported prescribing measures by age or gender of patients exposed, or for individual antimicrobial drugs, which we found help explain trends in the overall measures.

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

Implications

Our results demonstrate that the main factor influencing total antimicrobial DDD in Tayside is DDD per prescription. Total volume in DDD does not reliably represent actual antimicrobial use so prescriptions/packages per 1000 population and the proportion of the population exposed better evaluate changes over time and the impact of stewardship interventions. What this means for the impact on emerging antimicrobial resistance is not clear, but a recent study modelling relationships between use and resistance found different associations if use was measured in DDD *versus* packages.[21] However, following reductions in antimicrobial use in all age groups between 1995 and 2000, we observed increases in most measures between 2000 and 2011, with the exception of preschool children. In the last few years of observation there were reductions across several measures, but achieving substantial and sustained reductions in the proportion of the population exposed remains challenging for antimicrobial stewardship globally.[9] National and local antimicrobial stewardship activity in Scotland, particularly since the formation of the Scottish Antimicrobial Prescribing Group in 2008, has led to changes in choice of antimicrobial (Figures 1, 2 and 4)[9, 12, 19] but there is less impact on total prescribing within our study timeframe. Older people appear an obvious target group for stewardship due to high rates of exposure and higher risk of adverse events like *Clostridium difficile* infection.[42] However, for lower respiratory tract infections, the number needed to treat to prevent serious complications is lower in older people,[43] making reductions challenging. Prescribing rates are lower among those aged 5-64 years but they received 62% of all antimicrobial prescriptions in Tayside in 2014. They may be a better target for stewardship, with greater scope for change. Recent data from >600 general practices found minor increases in treatable respiratory tract infections associated with large reductions in antimicrobial prescribing, but the authors acknowledged the need for analysis in high-risk subgroups.[44]

Conclusion

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

Acknowledgements

We acknowledge the Health Informatics Centre, University of Dundee, for provision of the linked anonymised dataset.

Funding

This work was supported by a University of Dundee Clinical Academic Track (DCAT) medical student vacation scholarship for Mark DJ Neilly. The funder had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Transparency declaration

None of the authors have any conflict of interest in relation to this work. Outside the submitted work PTD reports grants from Shire Pharmaceuticals, Novo Nordisk, GSK, and is a member of the New Drugs Committee of the Scottish Medicines Consortium.

References

1. Bell B, Schellevis F, Stobberingh E et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* 2014; **14**: 13.
2. Department of Health and Department for Environment Food & Rural Affairs. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. London: United Kingdom Government, 2013.
3. World Health Organisation. Global Action Plan on Antimicrobial Resistance. http://www.who.int/antimicrobial-resistance/global-action-plan/en/.
4. Costelloe C, Williams O, Montgomery A et al. Antibiotic Prescribing in Primary Care and Antimicrobial Resistance in Patients Admitted to Hospital with Urinary Tract Infection: A Controlled Observational Pilot Study. *Antibiotics* 2014; **3**: 29-38.
5. Costelloe C, Metcalfe C, Lovering A et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *Bmj* 2010; **340**: c2096.
6. Duffy MA, Hernandez-Santiago V, Orange G et al. Trimethoprim prescription and subsequent resistance in childhood urinary infection: multilevel modelling analysis. *Brit J Gen Pract* 2013; **63**: e238-e43.
7. Vernaz N, Huttner B, Muscionico D et al. Modelling the impact of antibiotic use on antibiotic-resistant Escherichia coli using population-based data from a large hospital and its surrounding community. *Journal of Antimicrobial Chemotherapy* 2011; **66**: 928-35.
8. Royal College of General Practitioners. TARGET Antibiotics toolkit. http://www.rcgp.org.uk/clinical-and-research/toolkits/target-antibiotics-toolkit.aspx.
9. Scottish Medicines Consortium (SMC); Scottish Antimicrobial Prescribing Group. Primary Care Prescribing Indicators Annual Report 2013-14. Scotland, 2014.
10. National Institute for Health and Care Excellence. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. NICE guideline. United Kingdom, 2015.
11. Hay AD, Costelloe C. Antibiotics for childhood urinary tract infection: can we be smarter? *Brit J Gen Pract* 2013; **63**: 175-6.
12. Scottish Medicines Consortium (SMC); Scottish Antimicrobial Prescribing Group. Antimicrobial Use and Resistance in Humans in 2015. Health Protection Scotland and Information Services Division Scotland, 2016.
13. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2014. http://www.whocc.no/.
14. Coenen S, Gielen B, Blommaert A et al. Appropriate international measures for outpatient antibiotic prescribing and consumption: recommendations from a national data comparison of different measures. *J Antimicrob Chemother* 2014; **69**: 529-34.
15. University of Dundee. Health Informatics Centre. http://medicine.dundee.ac.uk/hic.
16. BMJ Group and the Royal Pharmaceutical Society of Great Britian. *British National Formulary (BNF) 68*, 2014.
17. Adriaenssens N, Coenen S, Versporten A et al. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. *J Antimicrob Chemother* 2011; **66**: vi71-vi7.
18. Coenen S, Ferech M, Haaijer-Ruskamp FM et al. European Surveillance of Antimicrobial Consumption (ESAC): quality indicators for outpatient antibiotic use in Europe. *Qual Saf Health Care* 2007; **16**: 440-5.

19. Hernandez-Santiago V, Marwick CA, Patton A et al. Time series analysis of the impact of an intervention in Tayside, Scotland to reduce primary care broad-spectrum antimicrobial use. *J Antimicrob Chemother* 2015; **70**: 2397-404.

20. Ashworth M, Cox K, Latinovic R et al. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *J Public Health* 2004; **26**: 268-74.

21. Bruyndonckx R, Hens N, Aerts M et al. Exploring the association between resistance and outpatient antibiotic use expressed as DDDs or packages. *J Antimicrob Chemother* 2015; **70**: 1241-4.

22. Bruyndonckx R, Hens N, Aerts M et al. Measuring trends of outpatient antibiotic use in Europe: jointly modelling longitudinal data in defined daily doses and packages. *J Antimicrob Chemother* 2014; **69**: 1981-6.

23. Davey P, Ferech M, Ansari F et al. Outpatient antibiotic use in the four administrations of the UK: cross-sectional and longitudinal analysis. *J Antimicrob Chemother* 2008; **62**: 1441-7.

24. Hawker JI, Smith S, Smith GE et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995–2011: analysis of a large database of primary care consultations. *J Antimicrob Chemother* 2014; **69**: 3423-30.

25. Pan A, Buttazzi R, Marchi M et al. Secular trends in antibiotic consumption in the adult population in Emilia-Romagna, Italy, 2003-2009. *Clin Microbiol Infect* 2011; **17**: 1698-703.

26. Pan Y, Henderson J, Britt H. Antibiotic prescribing in Australian general practice: How has it changed from 1990–91 to 2002–03? *Resp Med* 2006; **100**: 2004-11.

27. Scottish Intercollegiate Guideline Network (SIGN). Management of suspected bacterial urinary tract infection in adults (SIGN 88). 2012.

28. NHS Tayside. Primary Care Adult Empirical Treatment of Infection Guidance. http://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/Antibiotic%20primary%20care%20man.pdf.

29. Public Health England. AMR local indicators. https://fingertips.phe.org.uk/profile/amr-local-indicators

30. British Thoracic Society Community Acquired Pneumonia in Adults Guideline Group. Guidelines for the management of community acquired pneumonia in adults. *Thorax* 2009; **64**: iii1-iii55.

31. Adriaenssens N, Coenen S, Versporten A et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe (1997-2009). *J Antimicrob Chemother* 2011; **66 Suppl 6**: vi3-12.

32. Metz-Gercek S, Maieron A, Strauss R et al. Ten years of antibiotic consumption in ambulatory care: trends in prescribing practice and antibiotic resistance in Austria. *BMC Infect Dis* 2009; **9**: 61.

33. Schneider-Lindner V, Quach C, Hanley JA et al. Secular trends of antibacterial prescribing in UK paediatric primary care. *J Antimicrob Chemother* 2011; **66**: 424-33.

34. Van Boeckel TP, Gandra S, Ashok A et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; **14**: 742-50.

35. Ashiru-Oredope D, Sharland M, Charani E et al. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart—Then Focus. *J Antimicrob Chemother* 2012; **67**: i51-i63.

36. Davey P, Ferech M, Ansari F et al. Outpatient antibiotic use in the four administrations of the UK: cross-sectional and longitudinal analysis. *J Antimicrob Chemother* 2008; **62**: 1441-7.

37. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2014.

38. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2016.

39. The Health & Social Care Information Centre: Social Care Statistics.

40. Welsh Antimicrobial Resistance Programme: Surveillance Unit.
41. Health and Social Care Business Services Organisation. Northern Ireland.
42. Marwick CA, Yu N, Lockhart MC et al. Community-associated Clostridium difficile infection among older people in Tayside, Scotland is associated with antibiotic exposure and care home residence: cohort study with nested case-control. *J Antimicrob Chemother* 2013; **68**: 2927-33.
43. Petersen I, Johnson AM, Islam A et al. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *Bmj* 2007; **335**: 982.
44. Gulliford MC, Moore MV, Little P et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. *Bmj* 2016; **354**: i3410.

Tables

Table 1. Summary of antimicrobial prescribing measures by year and age group among all patients 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[#]
< 5 years						
Total number of patients^	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
5 to 64 years						
Total number of patients^	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
> 64 years						
Total number of patients^	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
All ages						
Total number of patients^	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

^ Total patients registered with general practitioner in the region

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

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

Differences in proportions evaluated using chi-squared, in means using t-test, and in medians using Mann-Whitney U test

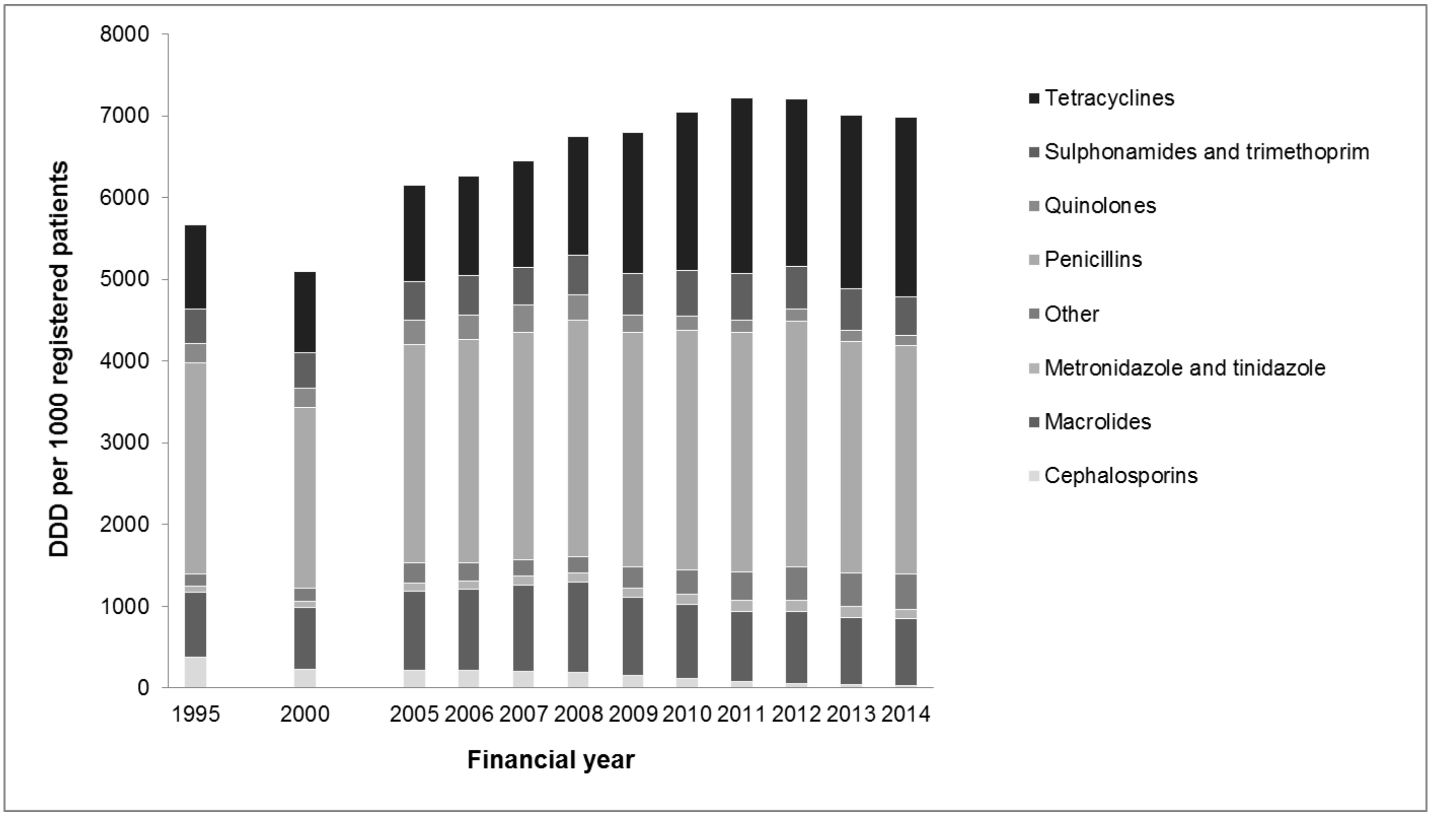
Table 2 Percentage change per year compared to 1995 for each measure of antimicrobial prescribing among all registered patients in Tayside

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

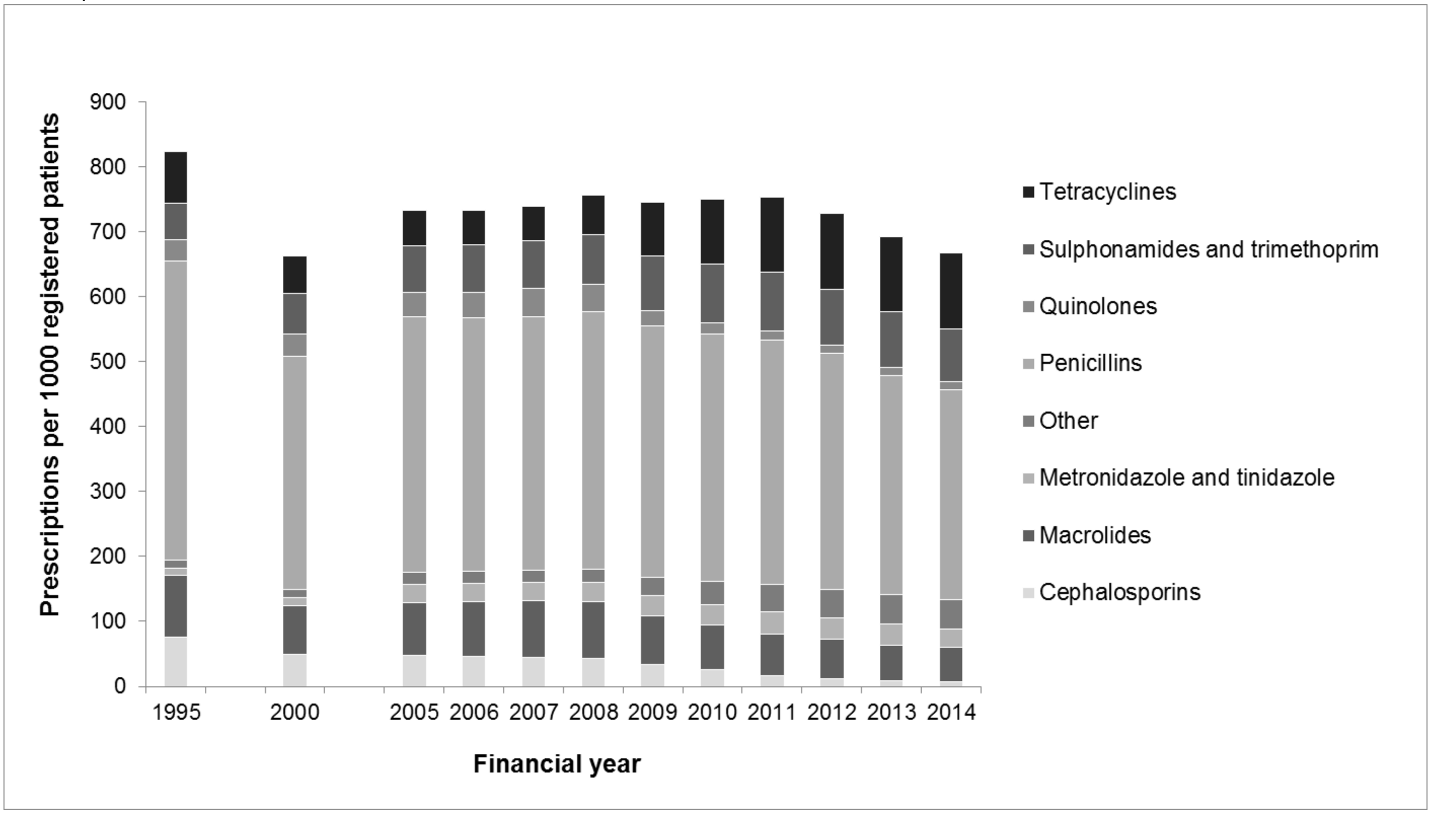
Figures

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: β= 109.99 ($R2$ = 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: β = -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

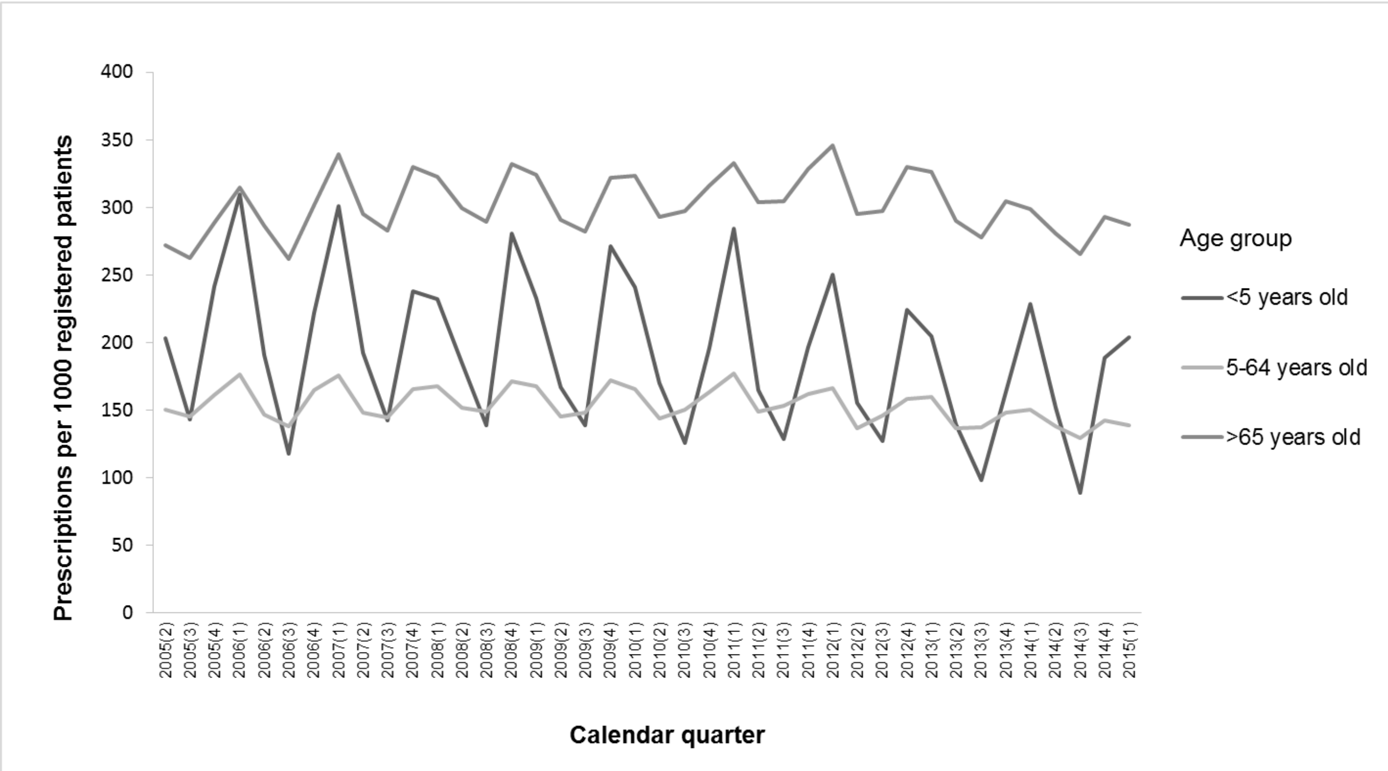


Figure 4 Trends in use of twelve individual antimicrobial drugs commonly used in primary care in Tayside, from 2005 to 2014, with use measured in DDD per 1000 population (dashed lines, left y axes), prescriptions per 1000 population (solid lines, right y axes) and mean DDD per prescription (text below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