Time series analysis of the impact of an intervention in Tayside, Scotland to reduce primary care broad-spectrum antimicrobial use

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Objectives: Concern about Clostridium difficile infection (CDI) and resistance has driven interventions internationally to reduce broad-spectrum antimicrobial use. An intervention combining guidelines, education and feedback was implemented in Tayside, Scotland in 2009 aiming to reduce primary care prescribing of co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin (‘4C antimicrobials’). Our aim was to assess the impact of this real-world intervention on antimicrobial prescribing rates.

Methods: We used interrupted time series with segmented regression analysis to examine associations between the intervention and changes in antimicrobial prescribing (quarterly rates of patients exposed to 4C antimicrobials, non-4C antimicrobials and any antimicrobial in 2005–12).

Results: The intervention was associated with a highly significant and sustained decrease in 4C antimicrobial prescribing, by 33.5% (95% CI –26.1 to –40.9), 42.2% (95% CI –34.2 to –50.2) and 55.5% (95% CI –45.9 to –65.1) at 6, 12 and 24 months after intervention, respectively. The effect was seen across all age groups, with the largest reductions in people aged 65 years and over (58.4% reduction at 24 months, 95% CI –46.7 to –70.1) and care home residents (65.6% reduction at 24 months, 95% CI –51.8 to –79.4). There were balancing increases in doxycycline, nitrofurantoin and trimethoprim prescribing as well as a reduction in macrolide prescribing. Total antimicrobial exposure did not change.

Conclusions: A real-world intervention to reduce primary care prescribing of antimicrobials associated with CDI led to large, sustained reductions in the targeted prescribing, largely due to substitution with guideline-recommended antimicrobials rather than by avoiding antimicrobial use altogether. Further research is needed to examine the impact on antimicrobial resistance.

Keywords: family practice, quality of healthcare, interrupted time series studies

Introduction

Antimicrobials are commonly used in primary care, but are known to be unnecessary or inappropriate in up to 50% of cases, and are associated with a range of risks including the development of antimicrobial resistance and Clostridium difficile infection (CDI). In the USA up to 23 488 deaths annually are estimated to be due to infections by resistant organisms, and 14 000 to CDI. Exposure to antimicrobials is the most modifiable risk factor for the development of CDI, with broad-spectrum cephalosporins, fluoroquinolones and clindamycin the most implicated. Antimicrobial exposure is particularly common in older people and care home residents, with an estimated 70% of care home residents prescribed one or more antimicrobials annually. Despite increasing concerns about adverse effects, antimicrobial use is increasing internationally. In 2010 there were 801
dispensed outpatient antimicrobial prescriptions per 1000 inhabitants in the USA, with broad-spectrum antibiotics being used in up to 60% of cases with acute respiratory tract infections. Penicillins were the most dispensed antibiotic class in 2010, accounting for 30% of total antimicrobial prescribing, followed up by macrolides (26%), cephalosporins (14%) and quinolones (11%). A 14% overall rise in quinolone use was observed between 1999 and 2010, mainly in the outpatient setting, which is particularly concerning, although there is huge prescribing variation across different states. In the same way, outpatient antimicrobial use in Europe has increased since 1997, particularly penicillins and quinolones.

Developing effective interventions to reduce antimicrobial use which can be implemented on a large scale is therefore of considerable importance. There is reasonable systematic review evidence that interventions to reduce antimicrobial prescribing in...
Rising rates of CDI in the mid-2000s in Scotland led to a major policy initiative to reduce CDI. At national level, new performance targets for Scottish Health Boards were implemented in 2009 relating to CDI rates and antimicrobial prescribing in both primary and secondary care [Health Boards are National Health Service (NHS) regional organizations with responsibility for all NHS services in a geographical area]. The overall aim was to reduce the rate of CDI by at least 30% among patients aged 65 years old or over within 2 years, in both hospital and community settings. This was supported by three new national quality indicators of antimicrobial prescribing, with the primary care indicator focused on fluoroquinolone use. These national targets in turn led to local primary care-based interventions within Health Boards, most commonly aiming to reduce use of all of the ‘4C’ antimicrobials associated with particularly high risk of symptomatic CDI. The 4C antimicrobials are co-amoxiclav, ciprofloxacin (which accounts for over 90% of fluoroquinolone prescriptions in primary care in Scotland), cephalosporins and clindamycin.

This study uses dispensed prescribing data from January 2005 to October 2012 to examine the impact of a multifaceted real-world intervention aiming to reduce 4C prescribing on 4C, non-4C and total antimicrobial prescribing for all residents of the Tayside region of Scotland.

### Methods

#### Population studied

The study population was all ~400000 residents of the Tayside region of Scotland registered with an NHS Tayside general practice at any point in the study period (2005–12). General practices are responsible for providing all NHS primary medical care, which is free at the point of use. Demographic and community prescribing data were obtained through the Health Informatics Centre (HIC), University of Dundee, which provides anonymized linked individual patient data from different electronic datasets, including the regional dispensed prescription dataset, demographic data and where the patient lives. Data were extracted for all antimicrobial drugs dispensed from quarter one 2005 to quarter three 2012, and linked to demographic data for the registered population, including whether patients were resident in a care home registered with the Care Inspectorate (the independent regulator of social care and social work services across Scotland, including care homes).

#### Ethics

HIC Standard Operational Procedures have been approved by both the Caldicott Guardian and NHS Tayside Research Ethics Committee and review of individual studies is not required provided that only anonymized

### Table 1. Description of the NHS Tayside intervention for improving high-risk antimicrobial prescribing

<table>
<thead>
<tr>
<th>At Health Board level:</th>
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<tr>
<td>- Practices received a range of educational material</td>
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<td>- A special edition of the Tayside Prescriber newsletter focused on raising awareness about CDI.</td>
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<td>- Easier to use and easier to access primary care antimicrobial guidance (the GP Antibiotic Man, which is a single-page summary with recommended antibiotics, route and dosage for the most common infections seen in primary care).</td>
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<td>- Information from NHS Tayside Health Board about the new antibiotic prescribing guidance and the targets for primary care, as well as advice for managing both proven and suspected C. difficile-associated diarrhoea cases.</td>
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<tr>
<td>- Background information on antimicrobial usage at Board level compared with other NHS Scotland Boards, and on rates of community-acquired CDI.</td>
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<tr>
<td>- Practices received specific feedback on their own use of antimicrobials compared with other named practices in the Community Health Partnership (locality) within the Board.</td>
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<td>- Feedback data informed target setting for each practice, where practices agreed to reduce one or more of the following, with target setting if appropriate: quinolone DDDs per 1000 patients; seasonal variation in quinolone prescribing; the number of telephone antimicrobial prescriptions; the number of quinolone prescriptions for respiratory tract infection; and the number of antimicrobial prescriptions without a documented indication; also finally to increase formulary adherence.</td>
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<tr>
<td>- In order to enable change, the local Antimicrobial Management Team (AMT) gave specific advice to general practices about action at individual prescriber and practice levels to meet targets. Pharmacists employed by the Health Board supported practices in implementing change, themselves supported by the AMT. Practices were provided with a range of patient information leaflets and posters to publicize and explain changes to antimicrobial policy and prescribing to individuals.</td>
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At the practice level, practices were asked to:

- Review the prescribing of antibiotics in the practice through examining the use of 4C (and ideally other) antibiotics, discuss variation within the team and in comparison with other demographically similar practices, and implement change in order to deliver the agreed targets. GPs were encouraged to use this to demonstrate quality improvement activity in their annual appraisal, to provide an individual incentive to engage.
- Discuss and agree a policy for telephone prescribing, including how to explain the correct use of antibiotics to patients and how to manage inappropriate requests for antibiotics.
data are used and HIC Standard Operational Procedures are followed. Data analysis was carried out in the HIC secure Safe Haven.

**Intervention**
National policy changes led to the implementation of a number of improvement activities in Tayside Health Board (Table 1). These included new primary care antimicrobial prescribing guidelines, written and pharmacist-facilitated educational interventions, and audit and feedback of practice prescribing rates with target setting. There was a small financial incentive to practices to engage through the linking of improvement activity to the medicines’ management domain of the UK pay-for-performance system (the Quality and Outcomes Framework), with the average-size practice eligible for a payment of £390 (US$653/E482) for agreeing to and completing improvement work. Individual GPs were also able to gain continuing professional development credits for involvement. We a priori designated quarter two 2009 as the first timepoint after the intervention since the performance indicators driving board-level improvement activity were applied from 1 April 2009, although the exact date of implementation of different elements of the intervention in 2009 varied somewhat between practices.

**Outcomes**
The primary outcome was the rate per 1000 registered patients dispensed one or more 4C antimicrobial prescriptions (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin) in each quarter between quarter one 2005 and quarter three 2012 inclusive. The secondary outcomes were: (i) the rate per 1000 dispensed one or more of other non-4C antimicrobials per quarter (doxycycline, nitrofurantoin, trimethoprim, macrolides and non-4C penicillins (i.e. excluding co-amoxiclav), selected to explore whether any reduction in 4C use was balanced by increases in other antimicrobials); and (ii) the rate per 1000 dispensed one or more of any antimicrobial per quarter.

**Statistical analysis**
Interrupted time series analysis with segmented regression was used to examine the impact of the intervention, estimating the trend in the proportion of patients dispensed an antimicrobial before the intervention and the changes in trend following the intervention. Analysis was carried out for the whole population, and for the primary outcome separately for three age groups (<5, 5–64 and ≥65 years old), and for people resident in care homes. Time series for each outcome and subgroup were plotted quarterly, giving 17 points before and 14 points after the intervention. We adapted the Cochrane Effective Practice and Organisation of Care (EPOC) method for short time series for our longer time series using a generalized linear model. Preliminary analysis examined for evidence of autocorrelation, and lag terms were fitted when there was significant autocorrelation, which was the only case for nitrofurantoin (lag1) and macrolide (lag2) prescribing. Seasonal variables were fitted in the model if significant seasonality was observed, which was the case for all analyses except 4C prescribing in care homes. Based on model fit, seasonality was accounted for by fitting a variable for ‘quarter’ for any antimicrobial prescribing, doxycycline, trimethoprim, non-4C penicillins and for 4C prescribing in the <5 years old age group. For the analysis of 4C prescribing at all ages and in the two remaining age groups macrolide prescribing across all ages, a variable for ‘season’ representing winter (quarters one and four) or summer (quarters two and three) was fitted. The Akaike Information Criterion was used for choosing the best-fitting model in all cases. Intervention effects were calculated at 6, 12 and 24 months following the intervention, expressed in relative percentage change. The 95% CIs were calculated using the EPOC method. Statistical analysis was carried out in IBM SPSS Statistics v21.0.

**Results**
Data from 408058 registered patients were included, of whom 50.7% were women. The mean age was 47 years (SD 24.2), with 2.3% of the population aged <5 years old and 27.8% of total population 65 years old or older. Of the patients, 11696 (2.9%) were resident in care homes. With regards to deprivation status, measured as quintiles of SIMD (Scottish Index of Multiple Deprivation) score, there was a mixed population with 33.5% living in deprived areas (SIMD 1 and 2) and 49% in affluent areas (SIMD 4 and 5); 27.5% of the total population lived in rural or remote areas.

![Figure 1. Prescribing of: (i) 4C antimicrobials (left-hand scale); and (ii) all antimicrobials (right-hand scale).](image-url)
Figure 2. Prescribing of 4C antimicrobials in care home residents and by age group.

Figure 3. Prescribing of other antimicrobials (balancing measures) across all ages.
There was an estimated reduction in total antimicrobial prescribing of 3.4% at 24 months (95% CI 1.8% reduction to 1.9% increase).

Table 2. Interrupted time series analysis of changes in antimicrobial prescribing with regards to the NHS Tayside intervention in quarter two 2009

<table>
<thead>
<tr>
<th>Antimicrobial class examined</th>
<th>Trend before the intervention, change per quarter in patients per 1000 dispensed (95% CI)</th>
<th>Change in trend after the intervention, change per quarter in patients per 1000 dispensed (95% CI)</th>
<th>Relative intervention effect at 6 months, percentage difference from pre-intervention trend (95% CI)</th>
<th>Relative intervention effect at 12 months, percentage difference from pre-intervention trend (95% CI)</th>
<th>Relative intervention effect at 24 months, percentage difference from pre-intervention trend (95% CI)</th>
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<tbody>
<tr>
<td>4C antimicrobials</td>
<td></td>
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<tr>
<td>all ages</td>
<td>-0.11 (-0.003 to -0.22)</td>
<td>-0.70 (-0.49 to -0.91)</td>
<td>-33.5 (-26.1 to -40.9)</td>
<td>-42.2 (-34.2 to -50.2)</td>
<td>-55.5 (-45.9 to -65.1)</td>
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<tr>
<td>aged 65 years and over</td>
<td>-0.16 (-0.46 to -0.13)</td>
<td>-1.63 (-1.07 to -2.19)</td>
<td>-35.1 (-25.9 to -44.2)</td>
<td>-44.3 (-34.5 to -54.1)</td>
<td>-58.4 (-46.7 to -70.1)</td>
</tr>
<tr>
<td>aged 5-64 years</td>
<td>-0.14 (-0.07 to -0.21)</td>
<td>-0.83 (-0.29 to -0.57)</td>
<td>-32.1 (-24.9 to -39.2)</td>
<td>-40.3 (-32.6 to -48.1)</td>
<td>-53.4 (-43.9 to -62.9)</td>
</tr>
<tr>
<td>aged under 5 years</td>
<td>-0.19 (-0.06 to -0.32)</td>
<td>-0.29 (-0.04 to -0.53)</td>
<td>-25.5 (-8.3 to -42.8)</td>
<td>-34.8 (-14.8 to -54.7)</td>
<td>-49.0 (-23.7 to -74.3)</td>
</tr>
<tr>
<td>care home residents</td>
<td>-0.62 (-0.26 to -0.98)</td>
<td>-1.91 (-1.21 to -2.60)</td>
<td>-40.1 (-29.2 to -50.9)</td>
<td>-48.2 (-37.0 to -59.3)</td>
<td>-65.6 (-51.8 to -79.4)</td>
</tr>
<tr>
<td>Non-4C antimicrobials</td>
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<tr>
<td>doxycycline</td>
<td>0.97 (0.01-0.18)</td>
<td>0.51 (0.35-0.67)</td>
<td>96.4 (71.9-120.9)</td>
<td>123.9 (97.2-150.6)</td>
<td>151.7 (122.5-180.8)</td>
</tr>
<tr>
<td>nitrofurantoin</td>
<td>0.03 (0.004-0.06)</td>
<td>0.09 (-0.03-0.21)</td>
<td>17.4 (4.09-30.7)</td>
<td>20.9 (4.5-36.5)</td>
<td>23.5 (3.3-43.7)</td>
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<tr>
<td>trimethoprim</td>
<td>0.08 (0.05-0.11)</td>
<td>-0.05 (-0.11-0.004)</td>
<td>7.9 (4.9-11.0)</td>
<td>7.6 (4.3-10.8)</td>
<td>6.1 (2.3-9.8)</td>
</tr>
<tr>
<td>macrolides</td>
<td>0.03 (-0.05-0.12)</td>
<td>-0.47 (-0.69-0.25)</td>
<td>-21.9 (-14.1 to -29.7)</td>
<td>-30.3 (-20.4 to -40.2)</td>
<td>-38.4 (-25.9 to -50.9)</td>
</tr>
<tr>
<td>penicillins (non-4C)</td>
<td>-0.06 (-0.31-0.20)</td>
<td>-0.34 (-0.83-0.15)</td>
<td>1.8 (-3.7-7.4)</td>
<td>1.1 (-5.3-7.6)</td>
<td>-0.96 (-8.6-6.5)</td>
</tr>
<tr>
<td>All antimicrobials</td>
<td>-0.09 (-0.41-0.23)</td>
<td>-0.42 (-1.04-0.19)</td>
<td>-1.1 (-5.1-3.0)</td>
<td>-1.9 (-6.4-2.6)</td>
<td>-3.4 (-8.7-1.9)</td>
</tr>
</tbody>
</table>

There was a total of 2,464,143 antimicrobial prescriptions dispensed between January 2005 and September 2012. Penicillins were the most commonly prescribed in Tayside between January 2005 and September 2012. trimethoprim (10.4%), followed by tetracyclines (11.3%), in total 4C drugs accounted for 13.8% of all antimicrobials prescribed.
Discussion

There was a large reduction of 55.5% in the proportion of residents dispensed a 4C antimicrobial associated with the implementation of the intervention. Reductions were seen in all age groups but were largest in care home residents and those aged 65 and over, who had the highest pre-intervention use of these drugs and are at the greatest risk of harm from CDI. The wider context of the Tayside intervention was clear national policy requiring all Health Boards across Scotland to act, emphasizing the importance of aligning improvement activity across entire health systems (of note is that similar patterns were seen in other Scottish Health Boards over the same period, although with generally smaller effect sizes). Total antimicrobial use did not significantly change in association with the intervention, reflecting that reduced 4C use was balanced by increases in antimicrobials recommended by local and national policy as first-line for respiratory infection (doxycycline) and urinary tract infection (nitrofurantoin and trimethoprim). The reduction in macrolide use is also consistent with a shift to better adherence to local antimicrobial choice guidelines, as macrolides are now recommended in primary care only for people with acute tonsillitis or epiglottitis with true penicillin allergy (for all other respiratory infections, doxycycline is the recommended antimicrobial in those with penicillin allergy). As well as 4C substitution, reduction in macrolides is likely to account for some of the increase in doxycycline use. Our interpretation is that the intervention largely prompted substitution by more closely following guidelines relating to antimicrobial choice, rather than avoiding antimicrobial prescribing altogether.

The study used 8 years of dispensed prescribing data in a large, complete geographical population to examine the impact of a real-world antimicrobial stewardship intervention using interrupted time series analysis, which is a robust and widely applied design for analysis of real-world interventions. The availability of data aggregated at quarterly time intervals allowed us to control for seasonal variation where appropriate, and being able to distinguish between primary care and secondary care prescribing avoided confounding regarding antimicrobial treatments started within the hospital. Like all observational studies, it is not possible to be certain that there is not some other explanation for the changes seen in prescribing. However, we think this is unlikely given the size of the change observed and there was no other significant primary care antimicrobial stewardship activity in the region in the period examined. It is also not possible to identify which components of this real-world intervention, alone or in combination, were responsible for the observed change in prescribing. Existing evidence shows that interventions are more effective when multifaceted, making it less likely that there is a single ‘magic bullet’ intervention concealed by the inability to examine the impact associated with different components. Like most real-world interventions, particularly those with multiple elements, defining precisely when the intervention was implemented is not straightforward. We a priori selected the second quarter of 2009 as the first timepoint post-intervention, based on the national targets being applied to Health Boards from April 2009. However, Boards had foreknowledge that these targets would be applied, which means that some improvement activity may have preceded this date, and some local interventions happened after April 2009 (e.g. revised primary care antimicrobial guidance was disseminated in June 2009, with practices varying in when they started their own antimicrobial prescribing improvement).

Previously, the impact of interventions aimed at reducing antimicrobial prescribing has been mostly evaluated in the hospital setting, where intervention impact is typically small to moderate at best. In the last decade there has been increasing research interest in this topic in primary care. Professionally targeted educational interventions combined with audit and feedback have been shown to lead to modest decreases (4%–15% depending on the study) in broad-spectrum antimicrobial prescribing in US paediatric clinics. In UK general practice, a multifaceted educational intervention reduced total antimicrobial use by 4.2% compared with usual care and an intervention to get primary care physicians to use patient education leaflets as part of a strategy to avoid prescribing for respiratory tract infections in children halved antimicrobial use without increasing rapid reconsultation. A high-cost national campaign in France was associated with a 26.5% reduction in antimicrobial use, predominately due to declining use in younger children. A low-cost multifaceted local campaign targeting both the public and prescribers led to a 4.3% reduction in total antibiotic prescribing in one Italian region compared with a control region, although the time series examined is quite short with only 5 months post-intervention data available, meaning that sustainability could not be examined. In Belgium, multifaceted interventions that included both national and local interventions aimed at both professionals and the public were associated with a 36% reduction in total outpatient antimicrobial use between 1997 and 2007, with a subsequent decrease in streptococcal resistance.

In comparison, our study showed a very large but very rapid change in the targeted 4C prescribing only. This study shows that multifaceted interventions targeting practices or clinical teams can be highly effective in reducing broad-spectrum antimicrobial use in primary care. We believe this was at least partly because there was both a strong commitment to reducing this prescribing in national policy and by local senior management, and a clearly expressed rationale for the change in terms of reducing rates of CDI by only using 4C antimicrobials when clearly clinically indicated. It is not possible to say which components of the intervention are more important, but all will be feasible in most healthcare systems, and policymakers should consider using multiple intervention components appropriate to their context to reduce antimicrobial prescribing.

The large reduction in 4C broad-spectrum antimicrobial prescribing found in this study is important, and likely contributed to the large reduction in CDI in Tayside over the same period, from 2009 onwards (although this cannot be simply attributed to changes in primary care antimicrobial use, since other interventions took place at the same time, including changes to hospital antimicrobial use and better infection control). Reducing broad-spectrum antimicrobial use in the community will be helpful in minimizing resistance in people with severe community-acquired sepsis, but reductions in total antimicrobial use are required in the long run to minimize antimicrobial resistance, and further research is needed to understand how large and sustained reductions in total antimicrobial use can best be achieved in everyday practice. The large changes in prescribing observed also create an opportunity to examine the extent to which rates of antimicrobial resistance will change, and to further explore the relationship between resistance and both individual and community antimicrobial exposure, which is the focus of our future work.
Acknowledgements

We thank the NHS Tayside Primary Care Antimicrobial Management team, in particular Hazel Steele and Kirsteen Hill for providing detailed information about the local intervention, and the HIC, University of Dundee, for providing the population data.

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Data sharing: no additional data available.

Transparency declarations

None to declare.

The lead author and manuscript guarantor (V. H.-S.) affirms that the manuscript is an honest, accurate and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author contributions

B. G., P. T. D., P. G. D. and V. H.-S. designed the study. V. H.-S. did the main analysis (with supervision from B. G. and C. A. M.). V. H.-S. wrote the first draft of the manuscript. A. P. and P. T. D. contributed to the statistical analysis. All authors contributed to writing and shaping the final paper. V. H.-S. is the guarantor.

References

21 Norwegian Knowledge Centre for the Health Services, Oslo. EPOC Resources for Review Authors, 2013. http://epocoslo.cochrane.org/eopc-specific-resources-review-authors.
28 Hogberg L, Oke T, Geel P et al. Reduction in outpatient antibiotic sales for pre-school children: interrupted time series analysis of weekly antibiotic