Secular trends of antibacterial prescribing in UK paediatric primary care

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Background: Resistance to antibacterial drugs can be contained by judicious prescribing. In particular, the use of these drugs in children requires ongoing surveillance. While there was a decline in antibacterial prescribing in the UK during the 1990s, recent trends are less well known.

Objectives: To describe antibiotic prescribing patterns and time trends in children in the UK over the last two decades.

Methods: We identified all children ages 0-19 years from 1993 to 2007 and their antibiotic prescriptions from the General Practice Research Database. We used Poisson regression to estimate prescription rates considering the children’s age and gender, calendar year and practice.

Results: The cohort included 1,751,645 children with 5,835,891 antibacterial prescriptions. The average prescription rate was 511 prescriptions per 1000 person-years [95% confidence interval (CI) 509-513]. As of 1995, the rate decreased to 419/1000 person-years (95% CI 411-426) in 2000, then increased to 568/1000 person-years (95% CI 559-577) in 2007. Between 2000 and 2007, rates increased on average by 4.3% (95% CI 3.7-5.0%) annually, amounting to an increase of 40.7% (95% CI 34.5-47.2%) for all children. Rates were generally higher in girls, except for boys <5 years. Broad-spectrum penicillins were most frequently prescribed; their rate increased on average by 4.6% annually (95% CI 4.0-5.3%) after 2000. This trend was similar in most classes of antibacterials.

Conclusions: Antibacterial prescribing to outpatient children in the UK has been steadily increasing since 2000, consistently for boys and girls, across all ages and antibacterial classes.

Keywords: antibacterial drug utilization, General Practice Research Database, children

Introduction

There would be no modern medicine without antibacterial drugs, but the use of antibacterials leads to the development of drug-resistant microorganisms, which in turn represent a serious threat to modern medicine. Balancing benefits and risks of antibacterials, our strategy should be appropriate use, defined by the World Health Organisation (WHO) as ‘the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance’. In practice, however, antibacterials are often prescribed without likely therapeutic effects (e.g. for viral infections). This happens particularly frequently in children in the community. Therefore antibacterial consumption in this specific population requires ongoing surveillance as part of strategies to prevent bacterial resistance.

In the UK, recommendations to reduce antibacterial prescribing in 1998 were preceded by a decline in antibacterial use in the community in adults and children. This decline varied for specific indications and age groups. Subsequent studies have suggested that prescriptions of antibiotics to children in the community may have stabilized after the year 2000. A more recent analysis indicated an increase in outpatient prescribing of antibacterial drugs to children in the UK, with associated specific diagnoses declining and non-specific diagnoses increasing. This change in prescribing has not been assessed for boys and girls or children of different age groups. Trends for classes of antibacterial agents are also unknown.

Thus our objective was to reliably establish the changes in antibacterial prescribing to children in the community in the UK by evaluating patterns of prescribing and time trends for boys and girls in different age groups as well as for different classes of antibacterials.
of antibacterials using the UK General Practice Research Database (GPRD).

Methods

Ethics approval

The study was approved by the Faculty of Medicine of McGill University Institutional Review Board and the independent Scientific Advisory Committee for GPRD studies (Protocol 08_003).

The GPRD

We analysed data from the UK GPRD. This large representative primary care database currently contains about 7% of the UK population, with more than 4 million active patients.13 The database is a prominent tool for population-level research on drugs14,15 and has been previously used to describe antibacterial drug use in the UK.5,7,10,16–18 The database consists of computerized primary care practice records that contain demographic information, diagnostic codes, laboratory data, referral information and drug prescriptions.

Cohort definition

We defined a cohort of children from the GPRD between 1 January 1993 and 31 December 2007. Eligible children had to be between 0 and 19 years of age, with known gender and year of birth, and had to be registered with a general practitioner (GP) for at least 1 day during the study period. Follow-up started on 1 January 1993, the child’s registration date with the general practice or the date the practice started to contribute valid data to the GPRD (up to standard date), whichever was later. Children were only retained in the cohort while the general practice the child was registered with contributed data of sufficient validity to the GPRD. Follow-up ended at the child’s 19th birthday, transfer out of the practice, or the end of the study period on 31 December 2007, whichever was earlier. The last date of data download from practices was on 31 December 2007 or later so that follow-up did not terminate prematurely in any practice due to lack of data.

The month of birth was known for 99% of all children born in 1993 and for all children born thereafter. Consequently, accurate age information was available for the young children of the cohort, for whom it is most medically relevant, and for older children later in the study period. However, 34% of the children entered the cohort in 1993, and most of them were born prior to 1993. Consequently, for the whole cohort, 32% of children had an unknown month of birth and were assigned 1 July of their year of birth as their birthday. In 10% of children, month of birth was unknown but they registered with their general practice in their year of birth, and the date of registration was taken as their birthday. Month of birth was known in the remaining 58% of children in the cohort.

Determination of antibacterial prescription rates

We identified all antibacterial agents listed in any chapter of the British National Formulary (BNF)19 and retrieved from the prescription database all corresponding prescriptions for all children of the cohort during their follow-up time. We found very few prescription drugs containing antibacterial agents listed in sections of the BNF other than chapter 5.1 (e.g. as preservatives in eye drops) that were likely to have significant systemic antibacterial effects. We therefore subsequently analysed only prescriptions of agents listed in chapter 5.1 of the BNF, excluding antituberculous and antileproic drugs (BNF chapters 5.1.9 and 5.1.10). We also derived the class of a given antibacterial prescription, based on subchapters of BNF chapter 5.1, the titles of which we have used throughout the manuscript to refer to individual antibacterial drug classes. A product containing antibacterial agents from more than one subchapter (e.g. a combination product containing ticarcillin and clavulanic acid) was counted in all antibacterial classes in which it was listed. As an exception and to minimize redundancy, we created a separate class containing nitrofurantoin, methenamine hippurate and fosfomycin, which are antibacterials for urinary tract infections (BNF chapter 5.1.13) that were not listed in other subchapters of BNF chapter 5.1. Thus our antibacterial classes were generally not mutually exclusive and the sum of prescriptions and prescription rates in subclasses is greater than the total number of prescriptions or the overall prescription rate.

For each year of the study period we counted each child’s follow-up time in the following five mutually exclusive and comprehensive age groups: <1 year (from date of birth to the day before their first birthday), 1–4 years, 5–9 years, 10–14 years and 15–18 years. This choice was based on previous studies with similar or identical age bands.20–23 Children changed age groups on the day they completed the year of the upper boundary of the age group they were contributing follow-up time to. Our count of follow-up time included all children irrespective of receiving an antibacterial prescription or not.

We then counted the number of prescriptions for each calendar year of follow-up for each child based on its age group. We summarized all prescriptions to children of the same gender, age group and year of follow-up as well as the corresponding person-time denominator of all children who could have received a prescription for each practice. This allowed us to calculate prescription rates for up to 150 different time-age group-gender strata for each of the 432 contributing practices. We proceeded the same way to obtain rates for the individual antibacterial classes.

Statistical analysis

We used Poisson regression to estimate prescription rates, rate ratios and corresponding confidence intervals (CIs). The Poisson regression models contained the variables children’s age group, gender and calendar year, as well as two-way interactions. The models also incorporated an over-dispersion parameter to account for extra-Poisson variation present in the data. In addition, we used generalized estimation equations (GEEs) to account for clustering by practice with an exchangeable correlation matrix, because we assumed independence of the children within each practice. The correlation coefficient of the most complex GEE Poisson model was 0.57, which indicates that prescription counts for children within practices were strongly correlated. For estimation of the average annual change we included time as a linear predictor in a model restricted to the period from the year 2000 onwards. We assessed goodness of model fit with log-likelihood ratio tests and by assessing reduction in deviance.24 We used SAS 9.1.3 (Cary, NC, USA) for all analyses.

Results

Cohort description

The cohort included 1 751 645 children, of which 863 858 (49.32%) were girls. These children contributed a total of 11 419 335 years of follow-up time with a mean of 6.52 years (SD ± 4.28 years), ranging from 2 days to the complete follow-up time of 15 years. In accordance with their representation in the cohort, girls provided 49.29% of all person-time or 5 628 905 person-years. There were 5 835 891 antibacterial prescriptions written to the children of the cohort during the 15 year study period. Of these prescriptions, 2 959 933 (50.72%) were for girls. Person-time and prescriptions for children of different ages are listed
in Table 1; a breakdown of the number of children, contributed person-time and prescriptions for individual years of the study period is given in Table S1 (available as Supplementary data at JAC Online).

Average prescription rates

The average unadjusted antibacterial prescription rate during the study period was 511/1000 person-years (95% CI 509/1000–513/1000 person-years). The average unadjusted rate in girls was 526 prescriptions/1000 person-years (95% CI 523/1000–529/1000 person-years). The average unadjusted prescription rate was 497/1000 person-years in boys (95% CI 494/1000–500/1000 person-years). After adjustments, the average prescription rate in girls was higher by 6.4% (95% CI 5.4–7.4%) compared with boys.

However, there were strong differences in the average prescription rates for children of different age groups. Children age 1–4 years were the group with the highest prescription rate; they received about twice as many prescriptions per 1000 person-years of follow-up compared with those with the lowest average prescription rate, the group of children age 10–14 years [adjusted rate ratio 2.24 (95% CI 2.16–2.32); Table 1 and Table S2 (available as Supplementary data at JAC Online)].

Prescription rates also differed for boys and girls in the different age groups (Table 1 and Table S2). For children in their first year of life, the difference in antibacterial prescribing for boys and girls was most prominent, with the boys’ adjusted rate exceeding that of the girls by 38.3% (95% CI 33.5–43.3%). Boys age 1–4 years not only received the largest number of prescriptions relative to their contributed time, but their rate also exceeded the rate for girls in the same age group by 8.0% (95% CI 6.9–9.2%). In the age groups representing children 5 years and older the average observed prescription rates were higher for girls than for the corresponding groups of boys. This was particularly marked in girls age 15–18 years whose rates were higher by 28.1% (95% CI 25.5–30.8%) in comparison with boys in the same age group. Consequently, boys in the age group with the highest prescription rate (children age 1–4 years) received more than twice as many prescriptions compared with those with the lowest rate [children age 10–14 years; adjusted rate ratio 2.58 (95% CI 2.47–2.69)]. In girls, this difference was less pronounced [adjusted rate ratio 1.97 (95% CI 1.90–2.04)].

Time trend for all antibacterial drugs

Antibacterial prescription rates varied markedly over the course of the study period (Table 2 and Figure 1). The average observed prescription rate increased from 602 prescriptions/1000 person-years in 1993 to a maximum of 649/1000 person-years in 1995 and then decreased gradually to 419/1000 person-years in 2000, the minimum rate during the study period. Thereafter, prescription rates steadily increased and reached a level of 568 prescriptions/1000 person-years in 2007. After adjustment for demographic differences and practice, this represented an average annual increase of 4.3% (95% CI 3.7–5.0%), amounting to a global increase of 60.7% (95% CI 34.5–47.2%) from 2000 to 2007.

Prescription rates followed similar patterns over time in boys and girls [Table S3 (available as Supplementary data at JAC Online) and Figure 1a]. The maximum and minimum rates were observed in 1995 and 2000, respectively, in both groups. The time trend since 2000 was comparable, with an average adjusted annual increase of 4.0% (95% CI 3.7–5.0%) in boys and 4.7% (95% CI 4.0–5.4%) in girls, resulting in a global increase of 36.0% (95% CI 30.0–42.3%) and 44.9% (95% CI 38.6–51.5%) from 2000 to 2007, for boys and girls, respectively.

Over the course of follow-up, antibacterial prescription rates also varied for the different age groups (Figure 1b), and varied differently for age groups in boys and girls (Figure 2). Generally, concordant with the average rates, the maximum rates in the different age groups were observed in 1995, thereafter rates declined to their minimum in 2000. Antibacterial prescription rates remained relatively stable in older children from 2000 to 2004. The change in prescription rates after the year 2000 was most pronounced in both boys and girls under 5 years of age, whereas prescriptions rates increased the least in the group of children 15–18 years of age (Table 3). These age-specific trends were similar for boys and girls. Due to differences in the time trends for the individual age groups there was a widening difference in maximum and minimum rates of age groups within each gender based on ratios of prescription rates in 2007 compared with 2000. For girls the adjusted rate ratio was 1.97 (95% CI 1.88–2.06) in 2000 and 2.19 (95% CI 2.11–2.26) in 2007, for boys the corresponding rate ratios were 2.56 (95% CI 2.43–2.70) and 2.84 (95% CI 2.72–2.96).

Prescription rates for classes of antibacterial drugs

The total number of prescriptions and prescription rates for the whole study period differed considerably for the antibacterial classes as defined in the BNF (Table S4, available as

### Table 1. Person-time, number of antibacterial prescriptions and prescription rates for outpatient children in the UK GPRD, 1993–2007

<table>
<thead>
<tr>
<th>Age group</th>
<th>Person-time in years</th>
<th>Number of prescriptions</th>
<th>Prescription rate/1000 person-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>658 178</td>
<td>427 954</td>
<td>650 (641–659)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>2 555 396</td>
<td>1 898 204</td>
<td>743 (738–748)</td>
</tr>
<tr>
<td>5–9 years</td>
<td>3 124 191</td>
<td>1 332 013</td>
<td>426 (423–430)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>2 983 593</td>
<td>1 034 199</td>
<td>347 (344–350)</td>
</tr>
<tr>
<td>15–18 years</td>
<td>2 097 977</td>
<td>1 143 521</td>
<td>545 (540–550)</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>336 877</td>
<td>247 879</td>
<td>736 (723–749)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>1 304 345</td>
<td>1 001 554</td>
<td>768 (761–775)</td>
</tr>
<tr>
<td>5–9 years</td>
<td>1 588 579</td>
<td>638 080</td>
<td>402 (397–406)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>1 506 590</td>
<td>477 364</td>
<td>317 (313–321)</td>
</tr>
<tr>
<td>15–18 years</td>
<td>1 054 039</td>
<td>511 008</td>
<td>485 (479–491)</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>321 301</td>
<td>180 075</td>
<td>560 (549–572)</td>
</tr>
<tr>
<td>1–4 years</td>
<td>1 251 051</td>
<td>896 650</td>
<td>717 (710–724)</td>
</tr>
<tr>
<td>5–9 years</td>
<td>1 535 612</td>
<td>693 933</td>
<td>452 (447–457)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>1 477 003</td>
<td>556 835</td>
<td>377 (373–382)</td>
</tr>
<tr>
<td>15–18 years</td>
<td>1 043 938</td>
<td>632 440</td>
<td>606 (599–613)</td>
</tr>
</tbody>
</table>
Table 2. Time trend in antibacterial prescription rates to outpatient children in the UK GPRD, 1993–2007; results from Poisson regression

<table>
<thead>
<tr>
<th>Year</th>
<th>Prescription rate/1000 person-years (95% CI)</th>
<th>Unadjusted rate ratio (95% CI) compared with year 2000</th>
<th>Adjusteda rate ratio (95% CI) compared with year 2000</th>
<th>Adjusteda rate ratio (95% CI) compared with preceding year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>602 (591–613)</td>
<td>1.44 (1.40–1.47)</td>
<td>1.40 (1.32–1.49)</td>
<td>1 (reference for 1994 only)</td>
</tr>
<tr>
<td>1994</td>
<td>585 (575–596)</td>
<td>1.40 (1.36–1.43)</td>
<td>1.37 (1.30–1.45)</td>
<td>0.98 (0.96–1.00)</td>
</tr>
<tr>
<td>1995</td>
<td>649 (638–660)</td>
<td>1.55 (1.51–1.59)</td>
<td>1.55 (1.47–1.63)</td>
<td>1.13 (1.10–1.16)</td>
</tr>
<tr>
<td>1996</td>
<td>595 (585–606)</td>
<td>1.42 (1.39–1.46)</td>
<td>1.41 (1.35–1.48)</td>
<td>0.91 (0.89–0.93)</td>
</tr>
<tr>
<td>1997</td>
<td>584 (575–594)</td>
<td>1.39 (1.36–1.43)</td>
<td>1.41 (1.35–1.47)</td>
<td>1.00 (0.98–1.02)</td>
</tr>
<tr>
<td>1998</td>
<td>518 (509–527)</td>
<td>1.24 (1.21–1.27)</td>
<td>1.25 (1.21–1.30)</td>
<td>0.89 (0.87–0.91)</td>
</tr>
<tr>
<td>1999</td>
<td>443 (435–451)</td>
<td>1.06 (1.03–1.08)</td>
<td>1.05 (1.03–1.08)</td>
<td>0.84 (0.82–0.86)</td>
</tr>
<tr>
<td>2000</td>
<td>419 (412–427)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>0.95 (0.93–0.97)</td>
</tr>
<tr>
<td>2001</td>
<td>444 (436–451)</td>
<td>1.06 (1.03–1.09)</td>
<td>1.08 (1.05–1.10)</td>
<td>1.08 (1.05–1.10)</td>
</tr>
<tr>
<td>2002</td>
<td>448 (441–455)</td>
<td>1.07 (1.04–1.10)</td>
<td>1.09 (1.06–1.12)</td>
<td>1.01 (0.99–1.04)</td>
</tr>
<tr>
<td>2003</td>
<td>478 (470–485)</td>
<td>1.14 (1.11–1.17)</td>
<td>1.17 (1.14–1.21)</td>
<td>1.07 (1.06–1.09)</td>
</tr>
<tr>
<td>2004</td>
<td>461 (454–469)</td>
<td>1.10 (1.07–1.13)</td>
<td>1.13 (1.09–1.17)</td>
<td>0.97 (0.95–0.98)</td>
</tr>
<tr>
<td>2005</td>
<td>497 (489–506)</td>
<td>1.19 (1.16–1.22)</td>
<td>1.23 (1.18–1.28)</td>
<td>1.08 (1.07–1.10)</td>
</tr>
<tr>
<td>2006</td>
<td>522 (513–530)</td>
<td>1.24 (1.22–1.28)</td>
<td>1.29 (1.26–1.34)</td>
<td>1.05 (1.04–1.06)</td>
</tr>
<tr>
<td>2007</td>
<td>568 (559–577)</td>
<td>1.36 (1.32–1.39)</td>
<td>1.41 (1.35–1.47)</td>
<td>1.09 (1.08–1.11)</td>
</tr>
</tbody>
</table>

aAdjusted for gender, age groups, gender-age group interactions and practice.

Supplementary data at JAC Online). Broad-spectrum penicillins were, by far, the most heavily prescribed drugs, with 302 prescriptions/1000 person-years, and the prescription rate for this class was similar for boys and girls (306/1000 and 297/1000 person-years, respectively). Antibacterial drugs containing benzylpenicillin and phenoxymethylpenicillin were the second most often prescribed class; prescription rates were less than a quarter of those of the broad-spectrum penicillins and the rate for girls was markedly higher than that for boys. Several antibacterial drugs, such as vancomycin, teicoplanin and linezolid, were rarely prescribed in the outpatient setting of the GPRD. There were no prescriptions for drugs containing noxythiolin, spectinomycin, daptomycin, quinupristin or dalfopristin in the study cohort during the study period. Prescription rates for the different antibacterial drug classes were not consistently lower in boys than in girls. Boys received more prescriptions of broad-spectrum penicillins, macrolides, and penicillinase-resistant penicillins, whereas girls received more prescriptions of benzylpenicillin and phenoxymethylpenicillin, and cephalosporins and other β-lactams. As expected, agents used for the treatment of genitourinary tract infections (nitrofurantoin, methenamine hippurate, fosfomycin, metronidazole and tinidazole, and sulphonamides and trimethoprim) were predominantly prescribed to girls.

Time trends by antibacterial drug class

The time trends were not uniform in all classes of antibiotics (Figure 3). Use of broad-spectrum penicillins in all children decreased drastically in the late 1990s, but increased again in the new millennium, so that the prescription rate in 2007 was higher by 43.4% (95% CI 35.2–52.1%) compared with 2000 (Table 4). On average, prescription rates increased by 4.6% (95% CI 4.0–5.3%) yearly after 2000. Prescription rates changed similarly in most other drug classes, with the exception of prescription rates for quinolones and specific antibacterials for urinary tract infections, which increased by 9.7% (95% CI 6.7–12.7%) and 15.0% (95% CI 11.8–18.2%), respectively, and chloramphenicol, which decreased on average by 23.1% (95% CI –36.8 to –6.4%) per year after 2000.

Discussion

We observed that, on average, one in two children received an antibacterial prescription each year of the study period. While girls generally received more prescriptions than boys, this tendency was not observed for all age groups and classes of antibacterials. Prescription rates changed drastically during the study period. After a decline in the 1990s, with the low of the study period in the year 2000, use of antibacterial drugs in outpatient children in all age groups has increased, leading to prescription rates that were substantially higher in 2007 than in 2000. This increase was most pronounced in boys and girls less than 5 years of age. The global time trend was mainly determined by use of broad-spectrum penicillins, by far the most often prescribed drug class, but the trend was deviant in only a few drug classes, notably quinolones, for which prescription rates increased even more markedly, but which remained relatively infrequently prescribed.

Other studies

Our findings are consistent with previous analyses of antibacterial prescribing to children in UK primary care. A comparatively high rate of antibacterial prescriptions for outpatient children up to 5 years of age, with the boys’ rate exceeding that of the girls and a reversal in older age groups towards more prescriptions for girls in the UK, was observed in the 1990s. We confirm the prescribing trends observed for UK children in the 1990s and beyond. In particular, our data are in close
concordance with a previous analysis indicating a 10% increase in overall antibacterial prescribing to children from 2003 to 2006.12

A similar distribution of paediatric outpatient prescription frequencies for individual classes of antibacterials and changes in the 1990s were established in an earlier study.7 Use of broad-spectrum antibacterials in paediatric outpatients has increased disproportionately in the USA26,27 and the Netherlands,20 with a trend towards use of newer broad-spectrum agents.28 In contrast, we have observed a relatively uniform pattern of falling and rising prescription rates for most antibacterial classes in our cohort from 1993 to 2007. This difference may be due to local resistance patterns or physician preferences. An exception of note is the quinolones, broad-spectrum agents for which we observed a greater increase in comparison with other antibacterial classes. However, their prescribing rate was still comparatively low. This finding is consistent with a recent Europe-wide comparison of antibacterial prescribing to patients of all ages that showed quinolone use was relatively low in the UK.29 We found that paediatric use of sulphonamides and trimethoprim declined drastically before restrictions on combinations from this group became effective in 1995. However, as our classification did not distinguish between individual drugs, we could not reproduce the resulting shift in use within this class.30

Figure 1. Trends in antibacterial prescription rates for outpatient children in the UK GPRD, 1993–2007. (a) Trends for all children, boys and girls. (b) Trends for all children by age groups.
Strengths

This study provides a comprehensive and detailed description of antibacterial prescribing over an extensive study period for boys and girls, age groups and classes of antibacterials, including a statistical analysis of the time trends. It thereby determines the current burden and recent changes in antibacterial exposure in outpatient children in the GPRD. Our use of the GPRD, a large representative database, ensures that our results can be generalized to the whole of the UK.

We included all children registered with practices in the GPRD that could receive antibacterial prescriptions. Consequently, we provide an accurate denominator of the prescription rates. In addition, we analysed each day of follow-up for each child. Thus the person-time contributed by children who had less than a full year of follow-up in a given calendar year because they changed age group or left the cohort was accurately considered. In this way we avoided underestimating prescription rates by wrongly inflating the person-time denominator by including children’s person-time when they could no longer be prescribed antibacterial drugs. This is a weakness of previous studies that are based on counts of children. Moreover, our analysis is based on counts of prescriptions issued to individual children instead of an aggregate numerator of defined daily doses (DDDs). Because DDDs are based on adult doses and

Figure 2. Trends in antibacterial prescription rates for outpatient children in the UK GPRD, 1993–2007. (a) Trends for boys of different age groups. (b) Trends for girls of different age groups.
children are prescribed only a fraction of these based on their weight, DDDs are far less responsive to changes in paediatric prescribing and thus are less suitable for tracking prescription trends in children. By including children’s age and gender we were able to isolate changes in prescription rates that were not caused by differences or changes in demographics of the practices’ populations over the follow-up time. Our adjustments also included GP practice, a known source of variation in prescription rates and a clustering factor. This also accounted for regional differences in antibacterial prescribing. Consequently, our analytic approach minimized common biases in determining time trends.

**Limitations**

Our study has some limitations. We could not consider antibacterial drugs received in hospitals, emergency rooms, outpatient specialty clinics or from other sources because the GPRD captures only prescriptions written by the GP. Therefore the number of antibacterial courses prescribed to children is larger...
Trends of UK paediatric outpatient antibacterial prescribing

Table 4. Time trends in antibacterial drug prescriptions by antibacterial drug class for outpatient children in the UK GPRD

<table>
<thead>
<tr>
<th>Antibacterial drug class by BNF chapter</th>
<th>Prescription rate/1000 person-years in 2000</th>
<th>Prescription rate/1000 person-years in 2007</th>
<th>Adjusted(^a) ratio of prescription rates in 2007 compared with 2000</th>
<th>Adjusted(^a) annual change 2000–2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad-spectrum penicillins</td>
<td>231.468</td>
<td>308.013</td>
<td>1.43 (1.35–1.52)</td>
<td>4.6% (4.0–5.3%)</td>
</tr>
<tr>
<td>Benzylpenicillin and phenoxymethylpenicillin</td>
<td>55.305</td>
<td>76.403</td>
<td>1.38 (1.31–1.46)</td>
<td>4.1% (3.4–4.8%)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>55.234</td>
<td>71.798</td>
<td>1.34 (1.27–1.42)</td>
<td>3.7% (2.7–4.8%)</td>
</tr>
<tr>
<td>Penicillin-lactam-resistant penicillins</td>
<td>44.256</td>
<td>62.423</td>
<td>1.42 (1.34–1.50)</td>
<td>4.8% (4.2–5.6%)</td>
</tr>
<tr>
<td>Cephalosporins and other β-lactams</td>
<td>28.229</td>
<td>37.698</td>
<td>1.47 (1.33–1.63)</td>
<td>5.0% (3.7–6.3%)</td>
</tr>
<tr>
<td>Sulphonamides and trimethoprim</td>
<td>24.969</td>
<td>34.285</td>
<td>1.41 (1.34–1.49)</td>
<td>4.9% (4.0–5.8%)</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>27.193</td>
<td>40.921</td>
<td>1.22 (1.16–1.29)</td>
<td>2.6% (1.9–3.4%)</td>
</tr>
<tr>
<td>Metronidazole and tinidazole</td>
<td>2.273</td>
<td>3.154</td>
<td>1.17 (1.06–1.29)</td>
<td>3.7% (2.2–5.2%)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>1.962</td>
<td>3.996</td>
<td>1.87 (1.51–2.31)</td>
<td>9.7% (6.7–12.7%)</td>
</tr>
<tr>
<td>Nitrofurantoin methenamine</td>
<td>0.721</td>
<td>1.920</td>
<td>2.59 (2.07–3.23)</td>
<td>15.0% (11.8–18.2%)</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>0.944</td>
<td>1.235</td>
<td>1.27 (0.97–1.68)</td>
<td>3.5% (0.1–7.0%)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>0.188</td>
<td>0.204</td>
<td>1.01 (0.61–1.68)</td>
<td>3.1% (–1.7 to 8.3%)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.032</td>
<td>0.068</td>
<td>1.96 (0.86–4.47)</td>
<td>3.5% (–5.3 to 13.2%)</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>0.057</td>
<td>0.076</td>
<td>1.34 (0.73–2.46)</td>
<td>1.3% (–6.6 to 9.8%)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.013</td>
<td>0.003</td>
<td>0.20 (0.04–1.01)</td>
<td>–23.1% (–36.8 to –6.4%)</td>
</tr>
</tbody>
</table>

Prescriptions of mecillinams, vancomycin and teicoplanin, linezolid and antipseudomonal penicillins were too infrequent for reliable estimation of time trends.

\(^a\)Adjusted for gender, age groups, gender-age group interactions and practice.

\(^b\)Drugs from chapter 'Urinary tract infections' not listed elsewhere in the BNF.

Table 4 shows the time trends in antibacterial drug prescriptions by antibacterial drug class for outpatient children in the UK GPRD. The table includes pharmacy prescriptions to outpatient children in the UK since the year 2000. We focused our time trend analyses on the time after this point because previous studies suggested—and our raw data confirmed—that the study period consisted of a phase of decline followed by a phase of rising antibacterial prescription rates. A more detailed analysis of the later phase appeared most relevant for an assessment of contemporary trends.

Interpretation

We provide robust evidence for a substantial increase in antibacterial prescriptions to outpatient children in the UK since the year 2000. We focused our time trend analyses on the time after this point because previous studies suggested—and our raw data confirmed—that the study period consisted of a phase of decline followed by a phase of rising antibacterial prescription rates. A more detailed analysis of the later phase appeared most relevant for an assessment of contemporary trends.
While prescription rates are the appropriate measure for changes in antibacterial use, we also observed that the proportion of children in the cohort receiving antibacterial prescriptions varied in concordance with the rates (data not shown). This means that the observed trends were caused, at least partially, by more or fewer children being prescribed antibacterials rather than the same fraction of children from the cohort receiving more or fewer prescriptions over time. Taken together with the rather uniform trends across antibacterial classes, we can infer that time trends may partly be a consequence of fluctuations in the threshold of GPs to prescribe antibacterials for any indication.

We observed a widening difference in total prescriptions for individual age groups with a predominant increase in young children. This is largely reflecting the changes in the prescribing of broad-spectrum penicillins (e.g. amoxicillin, ampicillin, or combinations of antibacterials containing these agents). Drugs from this class are often prescribed for respiratory tract infections and acute otitis media, conditions for which antibacterials could be avoided or delayed. As stated previously, causes of the increase in antibacterial prescribing cannot be deduced from this study. However, we can conclude that the general time trend is strongly determined by prescribing to young children and that a reduction in prescribing, particularly of broad-spectrum penicillins, in this population segment would most effectively lower the total burden of antibacterial exposure in outpatient children.

Socio-cultural causes may be a driving force for the observed changes in antibacterial prescribing in children in the UK, and also for the increase recently observed elsewhere in primary care in the EU. Such causes have been proposed in explaining large differences in overall antibacterial use in Europe. Accordingly, Hofstede’s cultural dimensions Power Distance and Uncertainty Avoidance were correlated with overall antibacterial prescription levels in a European cross-national comparison. Changes on a socio-cultural level could thus lead to changes in antibacterial prescribing. These are mediated by changes in the physician-patient or, relevant for this study, physician-parent interaction. It is conceivable that GPs increasingly lack time to discuss unnecessary prescriptions and prescribe antibacterials based on perceived parental expectations. This is consistent with our observation of an increase in prescribing of all classes of antibacterials and thus likely regardless of indication. At the same time GPs may face increasing pressure to prescribe antibacterials for example because a rising proportion of children attend day care institutions where they often get infections. Our results also support this reasoning because prescribing increased most markedly in pre-school children and an increasing proportion of children received antibacterial prescriptions. Consequently, interventions targeting the physician-parent interaction, such as providing parents with take-home information material, may be an effective strategy to reverse the unfavourable prescription trends observed in our study.

This study contributes to ongoing surveillance of antibacterial use as a cornerstone in the fight against resistance development and supports initiatives such as the Antibiotic Resistance and Pre-scribing in European Children (ARPEC) network. Our findings indicate that the reductions in antibacterial prescribing achieved in the 1990s were not sustained, which is worrisome because the total amount of antibacterial use has been recognized as a key factor in the development of antibacterial resistance. Our results also point to an increase in the use of quinolones, which should be monitored, as it may be both a cause and consequence of antibacterial resistance. In addition, according to its product licence, use in children is restricted, and safety data on children for this antibacterial class are still limited.

The reasons for this turn of the tide in antibacterial prescribing to children in recent years should be investigated in future studies. Are GPs less aware of current guidelines? Are guidelines impractical? Are parents increasingly asking for antibacterials?

Conclusions
Antibacterial prescribing to children in the UK has substantially increased across age groups and classes of antibacterials in recent years, with rates for 2007 being comparable to those of the late 1990s. While not adjusted for variation in incidence of infections or prevalence of comorbid conditions, this might indicate a shift in prescribing patterns towards increasingly ignoring the threat of antibacterial resistance. Although unnecessary prescriptions may be more common in other age groups, modifying the burden of antibacterial exposure, particularly the use of broad-spectrum penicillins, in young boys and girls will have the greatest impact on global antibacterial exposure in children. Causes for the observed time trends need further investigation in the UK, and similar trends may emerge in other countries.

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Transparency declarations
None to declare.

Supplementary data
Tables S1–S4 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References
Trends of UK paediatric outpatient antibacterial prescribing