Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

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ABSTRACT

Objective To systematically review the literature and, where appropriate, meta-analyse studies investigating subsequent antibiotic resistance in individuals prescribed antibiotics in primary care.

Design Systematic review with meta-analysis.

Data sources Observational and experimental studies identified through Medline, Embase, and Cochrane searches.

Review methods Electronic searches using MeSH terms and text words identified 4373 papers. Two independent reviewers assessed quality of eligible studies and extracted data. Meta-analyses were conducted for studies presenting similar outcomes.

Results The review included 24 studies; 22 involved patients with symptomatic infection and two involved healthy volunteers; 19 were observational studies (of which two were prospective) and five were randomised trials. In five studies of urinary tract bacteria (14 348 participants), the pooled odds ratio (OR) for resistance was 2.5 (95% confidence interval 2.1 to 2.9) within 2 months of antibiotic treatment and 1.33 (1.2 to 1.5) within 12 months. In seven studies of respiratory tract bacteria (2605 participants), pooled ORs were 2.4 (1.4 to 3.9) and 2.4 (1.3 to 4.5) for the same periods, respectively. Studies reporting the quantity of antibiotic prescribed found that longer duration and multiple courses were associated with higher rates of resistance. Studies comparing the potential for different antibiotics to induce resistance showed no consistent effects. Only one prospective study reported changes in resistance over a long period; pooled ORs fell from 12.2 (6.8 to 22.1) at 1 week to 6.1 (2.8 to 13.4) at 1 month, 3.6 (2.2 to 6.0) at 2 months, and 2.2 (1.3 to 3.6) at 6 months.

Conclusions Individuals prescribed an antibiotic in primary care for a respiratory or urinary infection develop bacterial resistance to that antibiotic. The effect is greatest in the month immediately after treatment but may persist for up to 12 months. This effect not only increases the population carriage of organisms resistant to first line antibiotics, but also creates the conditions for increased use of second line antibiotics in the community.

INTRODUCTION

One of the most pressing problems faced by healthcare services is the increasing prevalence of antimicrobial resistance. Compounded by a diminishing number of new agents entering clinical practice, such resistance is widely recognised as a major threat to public health.1

In general practice, there are concerns that some common infections are becoming increasingly difficult to treat and that illnesses due to antibiotic resistant bacteria may take longer to resolve.2

Some antimicrobial resistance may result from indiscriminate or poor use of antibiotics. In response, initiatives at the local, national, and international levels, are trying to promote “antibiotic stewardship,” with the goal of improving the appropriateness of antimicrobial use. However, such initiatives rely for success on the continuing education of prescribers and patients, which needs to be supported by high quality evidence linking antimicrobial use to the emergence of resistance.

Although many countries have been successful in reducing primary care prescribing of antimicrobials, primary care is still responsible for the majority of antibiotics prescribed to people.3 4 Much of this use is in the treatment of suspected respiratory infection and levels of prescribing vary widely within5 and between countries,6 suggesting that further reductions are possible. However, there are many barriers to reducing the inappropriate use of antimicrobials, including: patient and practitioner expectations,7 lack of patient awareness of the problems caused by antimicrobial resistance,8 and a perception in primary care clinicians and patients that antibiotic resistance is only a theoretical9 or minimal10 risk. Although the reason for such views being held is unclear, it may in part be because some previous studies have only investigated the relation between prescribing and resistance with population level data.11 12 Consequently for clinicians, whose primary concern is the unwell individual, the
impact of antimicrobial use on the prevalence of societal resistance may not be an important consideration. To reduce prescribing, it may therefore be important to highlight the effect of antimicrobial use on emergent resistance for individuals.

To date, a limited number of good quality studies have reported on the relation between prescribing and prevalence of resistance for individuals treated in primary care, and to the best of our knowledge no systematic reviews have been published in this area. We have therefore undertaken a systematic review and meta-analysis of studies where the effect of antimicrobial use on the emergence of resistance has been assessed for individual patients in primary care. We were particularly interested in quantifying the strength and duration of any association as well as identifying which antibiotics were most and least likely to cause resistance.

METHODS

Search strategy
The search strategy was designed to identify observational and experimental studies: conducted in any country; investigating relations between primary care prescribed antibiotics and antimicrobial resistance in bacteria sampled from any body site; analysed at the level of the individual; and published in any language.

We searched the MEDLINE (1955 to May 2009), EMBASE (1980 to May 2009), and Cochrane databases using the OVID interrogation software. We also searched for grey literature and unpublished work using the ISI web of knowledge, which identifies journal articles, patents, websites, conference proceedings, and open access material. MeSH terms used included “ambulatory care”, “drug resistance”, “antimicrobial resistance”, and “bacterial resistance”. We combined these terms with selected text word searches that included: “primary care”, “ambulatory care”, “family practice”, and “antibiotics” (see box for full search strategy). Additionally, we screened the reference lists of selected papers and wrote to authors who appeared more than once in our search asking for details of other published and unpublished studies. We performed citation searches of all full text papers.

Study selection
Studies were eligible for inclusion if they investigated and reported quantitative relationships between primary care prescribed antibiotics and subsequent antimicrobial resistance at the level of the individual. Studies were excluded if they were not original research, did not measure antibiotics prescribed in primary care, or were ecological studies.

Two independent reviewers (CC, ADH) screened the title and abstract of papers identified by the electronic searches, completing an inclusion/exclusion form for all papers. We retrieved full copies of included papers, each of which was independently reviewed for eligibility by two authors (CC and either DM, CM, ADH, or AL). Disagreements were resolved by discussion with a third author.
95% confidence intervals (CI) were tabulated by bacterium type and sampling location (for example, *Escherichia coli* from the urinary tract) and by time since exposure to antibiotic. Heterogeneity was measured using the I² statistic and the null hypothesis of no heterogeneity was tested using the Q statistic generated from the χ² test. For analyses in which we found evidence of heterogeneity, a random effects model was used to estimate the pooled OR. Where meta-analyses involved non-randomised studies the unadjusted OR was calculated or used, since unadjusted ORs were available for many more studies than the adjusted OR.

We carried out a meta-analysis of the adjusted results, although we only had sufficient data to do this for the studies examining resistance in urinary tract bacteria at the 0-3 month period. Meta-regression was used to investigate differences in the OR between exposures and resistance across different time periods. The meta-regression analyses could each include several estimates based on overlapping data from the same study; a sensitivity analysis based on the bootstrap method was used to check for overestimation of the precision of estimates. Finally, we produced funnel plots to look at the possibility of small study effects, one cause of which is publication bias. All methods were undertaken according to the MOOSE²⁹ and QUOROM²¹ guidelines for the conduct and reporting of systematic reviews. During the course of the study the PRISMA²² guidelines were developed and we have also adhered to these where relevant.

RESULTS

Study characteristics

Database searches identified 4373 potential studies of which 3239 were excluded on the basis of title (fig 1). Assessment of title and abstract led to the identification of 208 duplicate studies and the exclusion of 728 studies not meeting eligibility criteria. For 514 studies, no primary care prescribing data were presented and 146 of the studies identified were reviews, and not original research. Sixty-eight articles were ecological studies and did not report on resistance individuals. The remaining 198 papers were read in full, and of these 174 were excluded on the basis of not including primary care prescribing data (143), not reporting original research [23], and not reporting sufficient evidence to determine resistance risk [8]. Twenty-four papers were included in the review.

Table 1 summarises the characteristics of the final 24 studies included in the review. These consisted of five randomised controlled trials (RCTs) and 19 observational studies, two of which were prospective, and 17 retrospective controlled observational or case-control studies. These studies investigated effects in 15,505 adults and 12,103 children. Although not an inclusion criterion, all studies were based in countries where antibiotics are available by prescription only.

Twenty-two studies sampled bacteria from patients with symptomatic infection: urinary tract infection (seven studies); respiratory tract infections (seven); otitis media (two); chronic obstructive pulmonary disease (one); meticillin resistant *Staphylococcus aureus* (MRSA) infection (four); and trachoma in children (one). Two studies examined asymptomatic healthy adult volunteers. Studies presented a wide range of antibiotic exposure analyses including those for: macrolides (eight studies); cefalosporins (seven); sulphonamides and trimethoprim (six); cephalosporins (six); tetracyclines (two); quinolones (two); nalidixic acid (one); metronidazole (one); nitrofurantoin (one); “any antibiotic” (seven) given between two and 104 weeks before measurement of antibiotic resistance. Adherence to antibiotic regime was not assessed in most of the studies as they were retrospective and researchers were only able to measure prescribing from patients’ records or questionnaires, though in one of the RCTs adherence was measured by recording medicine bottle weights at various time points throughout the study.

Table 2 reports the quality assessment of the studies. Only one study met all five criteria. Three studies, all of urinary tract bacteria, met fewer than three criteria and were excluded from the meta-analyses.

Resistance in urinary bacteria

Of the eight studies investigating effects on urinary bacteria, one was an antibiotic comparison study (table 1). The remaining seven studies reported comparisons between no treatment and prescription of any antibiotic, amoxicillin, trimethoprim, and ofloxacin in relation to resistance to ampicillin, trimethoprim, sulphonamides, or ciprofloxacin. Five were of sufficient quality to be included in the meta-analysis. Estimates from these studies were grouped according to the periods over which exposure was measured and represented on a forest plot (fig 2). This plot shows that at all time
Table 1 | Study characteristics (by reference number)

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<th>Design</th>
<th>n</th>
<th>Participants</th>
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<th>Sample site</th>
<th>Method</th>
<th>AB used</th>
<th>AB to which resistance measured</th>
<th>Time* (months)</th>
<th>Crude or adjusted OR (95% CI), P for primary comparison</th>
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</table>

**Urinary bacteria**

17  O  332 SA MLR Ec U PDT Tr Tr 0-6 1.22 (1.16 to 1.28) P<0.001
19  CC  903 SA GP Ec U PDT Am Am 0-12 1.7 (1.24 to 2.32)
23  CC  3435 SA MLR Ec U PDT AA Tr Tr 0-6 1.36 (1.14 to 1.60)
24  CC  559 SA OP Ec U PDT ST, Q, P, AA ST 0-12 4.1 (2.20 to 7.50) P<0.003
18  O  618 ASA GP or POST Ec U PDT AA Tr, Am 0-12 1.13 (0.79 to 1.63)
19  O  883 SA GP Ec U PDT AA 0-3 2.1 (1.2 to 3.6) P<0.01
21  O  263 SC GP Sp T PDT Am 0-6W 2.11 (1.05 to 4.26)
28  OP  119 SC GP H T MIC Am Am 2 1.9 (1.3 to 2.7) P<0.001
29  CC  145 SA GP Sp T PDT Ma Ma 0-6W 2.15 (0.94 to 4.89)
30  CC  193 SA GP Ec U PDT Su Am, Str, Te, Ch, K, Su, G, Tr, N 0-6 0.26 (0.09 to 0.74)
31  O  263 SC GP Sp T PDT Ma Ma 0-6W 4.19 (1.23 to 14.26)
32  O  737 SC GP Ec U PDT Su Am, Str, Te, Ch, K, Su, G, Tr, N 0-6 2.3 (0.74 to 2.54)
33  O  131 C with MRSA OP Ec U PDT N or Cp N 2-6 W 0.67 (0.30 to 1.6) P=0.01
34  CC  134 SC and ASC PED Sp NP,IC,AN E B P 0-1 –
35  RCT  224 ASA U Sp TON GAP Az Ma 0-6 1.86 (0.9 to 3.75) P<0.01
36  CC  448 C with suspected otitis media DCC Ph NP PDT B, Co, or E P 0-12 8.8 (2.69 to 28.8) P<0.001
37  CC  100 A with COPD OP Hi S PDT P B 0-24 2.15 (0.94 to 4.89)
38  O  167 A with skin infection GP Sa SK PDT AA Me 0-1 2.7 (0.8 to 15.0) P=0.1
39  O  206 A with skin infection MTC Sa SK PDT AA Me 0-12 1.5 (0.6 to 4.0) P<0.01
40  CC  131 C with MRSA positive N samples PED Sa N PDT AA Me 0-12 16.13 (6.38 to 40.76) P<0.001
41  O  840 C with Sa skin infection PED Sa SK PDT AA Me 0-3 0.98 (0.67 to 1.42)
42  RCT  1009 C with acute otitis media PED GN ST PDT Cf or Am or Az CETF, Cp, Am 3-5D P<0.01
43  RCT  121 C with early trachoma PED Ct OC E Az Az 2W P=0.1†

**Respiratory bacteria**

17  O  332 SA MLR Ec U PDT Tr Tr 0-6 1.22 (1.16 to 1.28) P<0.001
18  O  883 SA GP Ec U PDT Am Am 0-12 1.7 (1.24 to 2.32)
23  CC  3435 SA MLR Ec U PDT AA Tr Tr 0-6 1.36 (1.14 to 1.60)
24  CC  559 SA OP Ec U PDT ST, Q, P, AA ST 0-12 4.1 (2.20 to 7.50) P<0.003
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43  RCT  121 C with early trachoma PED Ct OC E Az Az 2W P=0.1†


*Either exact time at which individuals took antibiotics, or time period during which antibiotic prescribing was recorded, before measurement of resistance.
†Insufficient data to calculate OR and/or 95% CI and/or P value.
periods the odds of resistance were greater in patients exposed to these antibiotics than in those who were unexposed and that the strongest association was at 0-1 months, with reduced association at subsequent time points, and a small but important residual association within 12 months. In participants who were unexposed to antibiotics, the pooled odds of resistance varied little between time periods (pooled odds of resistance among unexposed participants was 0.44 at 0-1 month, fig 2). The β coefficient for each month increase in the exposure period was −0.33 (95% CI −0.49 to −0.17, P<0.001) from the meta-regression showing a clear time trend. There was no evidence of within group heterogeneity in the 0-1 and 0-3 month periods, but some evidence of heterogeneity in the 0-6 month and 0-12 month periods. For studies in which adjusted ORs were presented we did a meta-analysis of these results, although we only had sufficient data to do this for the studies examining resistance in urinary tract bacteria at the 0-3 month period. The resulting pooled OR did not differ markedly from the unadjusted or crude OR used in the meta-regression at the same time point (pooled adjusted OR 2.17, 95% CI 1.49 to 3.22), compared with 2.48 (2.06 to 2.98).

**Resistance in respiratory bacteria**

Nine studies examined resistance in respiratory tract bacteria.28-35,37 Since the Malhotra-Kumar35 and Chung studies28 were prospective and measured resistance at specific time points, their data are presented separately from the remaining retrospective studies measuring antibiotic exposure during periods of time. The Sportel study34 measured resistance over a 0-24 month period in a group of patients with chronic obstructive pulmonary disease (in which the lower respiratory tract becomes colonised with different bacteria from those usually resident in the upper respiratory tract)28 so it was not included in the meta-analysis. The remaining seven studies were meta-analysed according to time periods.29-34,36 Figure 3 shows that although there was some evidence of an association between antibiotics and resistance between 0 and 1 month (with an OR of 2.1, 95% CI 1.0 to 4.2), 0 and 2 months (pooled OR 2.4, 95% CI 1.4 to 3.9), and 0 and 12 months (pooled OR 2.4, 95% CI 1.3 to 4.5), intervening periods showed less evidence of such associations, and no association between resistance and time with a β coefficient of −0.01 (95% CI −0.26 to 0.24, P=0.91). We found little within group heterogeneity with the most heterogeneity present in the 0-12 month period with an I² value of 57.3% (P=0.04). Among participants who were unexposed to antibiotics the pooled odds of resistance varied across time periods (fig 3) from 0.08 in the 0-2 month period to 0.51 during the 0-3 month period. Some studies did not report raw data and for these studies the odds of resistance in the control group could not be calculated.

The Chung study28 used minimum inhibitory concentrations of ampicillin as a measure of antibiotic resistance and also presence of the integrative and conjunctive element ICEHin1056 that encodes β-lactamase and circulates among nasopharyngeal *Haemophilus* species. Prescribing amoxicillin to a child in general practice more than tripled the mean inhibitory concentration for ampicillin (9.2 µg/ml compared with 2.7 µg/ml, P=0.005) and doubled the risk of isolation of *Haemophilus* isolates possessing homologues of ICEHin1056 (67%, 42 of 63, compared with 36%, 14 of 39 in patients who were not exposed to antibiotic) with a relative risk of 1.9 (95% CI 1.2 to 2.9) at two weeks post-exposure and 1.0 (0.5 to 1.7) at 12 weeks post-exposure.28

The Malhotra-Kumar study35 was the only randomised controlled trial to examine resistance (associated with azithromycin or clarithromycin) at specific time points. Figure 4 and the meta-analysis of the pooled
OR showed a decaying association with resistance to macrolides at all time points up to 6 months with strong evidence of a time trend ($\beta$ coefficient $-0.25$ (95% CI $-0.39$ to $-0.11$, $p=0.004$).35

Resistance over time in MRSA studies
We found few studies investigating effects on MRSA; three studies in skin samples38 39 41 and one study in nasal samples.40 Paganini et al41 examined community acquired MRSA in children. These isolates were obtained from skin and soft tissue infections, and some invasive infection sites. The study found that 10% (26 of 273) of isolates were resistant to clindamycin as well as meticillin and 1% (two of 272) were resistant to trimethoprim-sulfamethoxazole. Raw data obtained from the authors allowed the calculation of an OR for resistance of 0.98 (95% CI 0.67 to 1.42) suggesting that previous antibiotic use is not an important risk factor for community acquired MRSA isolated from children’s skin infections. However, exposure data for this study relied on parental reports only.

Campbell et al39 examined community acquired MRSA in skin infections in healthy military trainees. Previous antibiotic use was not associated with MRSA infection (OR 0.7 (95% CI 0.2 to 1.9).

Baggett et al38 investigated a large outbreak of community acquired MRSA in a rural community and found a strong association (OR 3.1, 95% CI 1.1 to 8.6) between this infection and the prescription of any antibiotic in the previous 0-6 months. This association disappeared (1.5, 0.6 to 4.0) when the time period was broadened to include any antibiotic prescription in the preceding 12 months.

Lo et al40 examined resistance associated with the use of any antibiotic in the 12 months preceding resistance testing. This study reported a strong association of OR 16.1 (95% CI 6.4 to 40.8) between previous antibiotic use and nasal colonisation of Panton-Valentine leukocidin positive MRSA in healthy children.

We did a meta-analysis of the three studies investigating MRSA and resistance in bacteria sampled from skin abrasions38 39 41 in which individuals had been exposed to antibiotics in the previous 12 months; the pooled OR for these studies was 1.04, with the confidence interval crossing the null (95% CI 0.47 to 2.29).

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### DISCUSSION

**Principal findings**

Our review identified a number of studies that together provide strong evidence of an association at the individual patient level between the prescribing of antibiotics in primary care and antimicrobial resistance in bacteria at different sites, including the urinary and respiratory tracts and the skin. Effects were strongest in the month directly after prescription but were detectable for up to 12 months. This residual effect is likely to be an important driver for the high endemic levels of antibiotic resistance in the community. Moreover, we found evidence of a dose-response relation for two commonly prescribed first line antibiotics in primary care, amoxicillin and trimethoprim.

**Prescribing time periods**

Most studies that reported resistance in urinary and respiratory bacteria reported the association between resistance and antibiotics prescribed within overlapping time periods. This means that associations with resistance and antibiotics prescribed within overlapping time periods could reflect long or short term relations. However, the prospective studies did not suffer from this methodological weakness and did suggest persistence of resistance over a number of months.

**Effects of antibiotic dose, duration, and number of courses on resistance**

Several studies assessed the relation between resistance and increasing courses of or doses of antibiotic (table 3).

Schräg et al compared the effect of standard dose and duration of amoxicillin with that of high dose and short duration amoxicillin on resistance at 5, 10, and 28 days. They reported some evidence of reduced resistance at 28 days associated with this treatment (OR 0.77, 95% CI 0.06 to 0.97), possibly attributable to better compliance. Hillier et al found greater rates of resistance associated with higher doses of amoxicillin (2.3, 95% CI 1.1 to 4.6) and longer courses of trimethoprim (2.9, 1.4 to 5.8), but no differences associated with different course durations for amoxicillin (1.5, 0.7 to 2.9).

Hillier also found associations between number of courses of amoxicillin (three or more v one; OR 3.9, 95% CI 1.0 to 14.7) and trimethoprim (three or more v one; 3.6, 1.2 to 10.5) and resistance. The Hay study showed no differences in resistance rates with differing numbers of antibiotic courses, but did find an increase of 1% in the odds of resistance for each 200 mg trimethoprim tablet prescribed (OR 1.01, 95% CI 1.01 to 1.02). The same type of association was not found for increasing numbers of 500 mg amoxicillin tablets prescribed.

**Publication bias**

We were able to assess publication bias in the urinary bacteria studies investigating resistance in *E coli* and antibiotic exposure in the previous six months. The funnel plot in fig 5 shows some evidence of positive publication bias. There were too few studies to assess publication bias for respiratory flora.

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**Fig 3** Forest plot showing individual study and pooled ORs (log scale) for resistance in respiratory tract bacteria and previous antibiotic prescribing. Studies grouped according to time period during which exposure was measured and ordered within each time period by increasing standard error.

The Spertel study allowed greater precision and showed that there was no greater association between penicillin use and amoxicillin resistance than cephalosporin use in *Haemophilus influenzae* (OR 0.4, 95% CI 0.1 to 1.4). The Malhotra-Kumar study also reported no difference in macrolide resistance in *Streptococcus pneumoniae* after use of azithromycin or clarithromycin at any previous time, although use of clarithromycin was associated with greater expression of the erm(B) gene, which confers high level macrolide resistance.

To summarise, in comparisons of different antibiotics in the same antibiotic classes for effects on resistance, we found no evidence that one class led to reduced resistance compared with another, although we were unable to adequately address the issue owing to the limited number of studies available.

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### Table: Effects of antibiotic dose, duration, and number of courses on resistance

<table>
<thead>
<tr>
<th>Antibiotic use associated with susceptibility</th>
<th>Odds ratio (95% CI)</th>
<th>Antibiotic use associated with resistance</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>1</td>
<td>10</td>
<td>2.16 (1.05 to 4.26)</td>
</tr>
<tr>
<td>1.0</td>
<td>1</td>
<td>2.37 (1.42 to 3.95)</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>1</td>
<td>2.10 (1.20 to 3.60)</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>1</td>
<td>4.19 (1.23 to 14.26)</td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>1</td>
<td>2.37 (1.42 to 3.95)</td>
<td></td>
</tr>
</tbody>
</table>

*β-lactam plus another antibiotic. NR=not reported
Reverse causality and confounding

If bacterial samples are taken only if the illness does not respond to first line antibiotics (as is standard practice in many parts of the UK) then retrospective case-control analyses will show a spuriously strong association with previous antibiotic prescribing. This bias is avoided if only incident cases are included. For most of the studies reviewed it was not possible to ascertain whether non-incident cases had been excluded. This bias is less likely, although not impossible, in prospective studies than in retrospective ones. However, both of the prospective studies eliminated reverse causality as a possible explanation by collecting baseline resistance data; they showed substantial increases in resistance within days of prescribing and subsequent decay in effects over three months in the Chung study (28) and six months in the Malhotra-Kumar study.  

Other confounding associations, such as the relation between community prescribing and recent hospital admission, could also have introduced bias. However, the studies that attempted to adjust for potential confounders such as age, sex, comorbidities, catheter use, and smoking status seldom demonstrated substantial difference between crude and adjusted estimates of association.

Heterogeneity between studies

The observed differences between studies may well reflect the difficulties of overlapping time periods and confounding, but could also reflect the differences in populations studied (which must have varied in baseline prevalence of antibiotic resistance and transmission potential), the definition of resistance applied, and the different antibiotic-organism relationships studied. Residual heterogeneity was a particular problem in the pooled analyses of urinary bacteria in the 0-6 month and 0-12 month periods and in the analyses of respiratory bacteria in the 0-12 period. As previously noted, this heterogeneity existed despite some evidence of publication bias.

MRSA studies

Hospital MRSA strains are becoming feral, persisting in the community, and non-hospital epidemic strains are being acquired in the community.  

Although two of the studies suggest that the selective pressure produced by antibiotic prescribing in the community may contribute to this problem, the other two showed no effect. The mechanism of MRSA transmission is clearly complex and to explore this issue further, repeated screening of large numbers of individuals (mostly non-carriers) would be necessary over a long period. In the meantime, minimisation of unnecessary community prescribing for skin infections seems a reasonable precautionary principle.

Clinical and research implications

This review provides the evidence needed by clinicians responsible for the prescription of antibiotics in primary care to quantify the link between individual prescribing decisions and the problem of antibiotic resistance. Although the clinical impact of isolating antibiotic resistant bacteria warrants further research in its own right, resistance is not simply a characteristic of the infecting organism. It is also related to the individual’s bacterial gene pool, since resistance carried on plasmids and integrons can be transferred between commensal organisms and potential pathogens. And because both transmission of commensal organisms between individuals and antibiotic prescribing in the
community remain frequent events, even a transient effect of antibiotic use on the carriage of resistant organisms by an individual could have a major impact on the endemic level of resistance in the population. 28

Our findings also provide evidence to support the Standing Medical Advisory Committee report recommendations that the fewest number of antibiotic courses should be prescribed for the shortest period possible. 3 And they draw attention to the increased risk of resistance to commonly used first line antibiotics: if a patient has received one or more courses of such antibiotics in the previous 12 months and further antibiotic treatment is necessary, for a subsequent respiratory or urinary infection, consideration should be given to choosing a different antibiotic. This final implication serves to highlight that the only way to avoid the vicious cycle of resistance leading to the ever greater use of more powerful broad spectrum antibiotics is to avoid their initial use whenever possible.

The main research implication is the need to strengthen the current evidence base, which is heavily reliant on observational studies, with more clinical trials. We believe that the opportunity to assess the effects of antibiotics on antimicrobial resistance should be considered whenever a placebo or “no treatment” controlled trial is being designed. Further research is also needed to assess relations between antibiotics prescribed in primary care and more serious infections that require secondary care treatment, as well as to further clarify the effects of interactions between antibiotic dose, duration, and adherence on resistance.

In conclusion, we have summarised and synthesised evidence from around the world that primary care antibiotics make an important contribution to the problem of antimicrobial resistance. Primary care clinicians and patients may wish to consider this evidence when discussing the benefits and risks of prescribing and consuming antibiotics.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Worldwide, primary care is responsible for the majority of antibiotic use by human beings

Although many countries have reduced prescribing rates, substantial variations remain between countries

Many clinicians and patients do not see antibiotic resistance as a reason to refrain from antibiotic use

**WHAT THIS STUDY ADDS**

Antibiotics prescribed to an individual in primary care were consistently found to be associated with resistance of urinary and respiratory bacteria to those antibiotics in that individual

Antibiotics prescribed in primary care may impact on bacterial resistance in a patient for up to 12 months

The greater the number or duration of antibiotic courses prescribed in the previous 12 months, the greater the likelihood that resistant bacteria would be isolated from that patient

**Table 3** Relations between antibiotic dose and resistance (by reference number)

<table>
<thead>
<tr>
<th>Study</th>
<th>High dose/Standard dose and concentration</th>
<th>Antibiotic to which resistance was measured</th>
<th>Time*</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrag 2001 12</td>
<td>High dose amoxicillin 90 mg/kg for 5 days</td>
<td>Normal dose amoxicillin 40 mg/kg per day for 10 days</td>
<td>Penicillin</td>
<td>5 days</td>
</tr>
<tr>
<td>Hillier 2007 19</td>
<td>High dose amoxicillin 500 mg Amoxicillin &gt;7 days Amoxicillin &lt;7 days</td>
<td>Normal dose amoxicillin 250 mg Trimethoprim &gt;7 days Trimethoprim &lt;7 days</td>
<td>Ampicillin</td>
<td>0-12 months</td>
</tr>
<tr>
<td>Hillier 2007 19</td>
<td>2 courses amoxicillin 3 courses amoxicillin 2 courses trimethoprim 3 courses trimethoprim</td>
<td>1 course amoxicillin 1 course amoxicillin 1 course trimethoprim 1 course trimethoprim</td>
<td>Trimethoprim</td>
<td>0-12 months</td>
</tr>
<tr>
<td>Hay 2005 18</td>
<td>2 courses any antibiotic 3 courses any antibiotic 4 courses any antibiotic</td>
<td>1 course any antibiotic 1 course any antibiotic 1 course any antibiotic</td>
<td>Trimethoprim</td>
<td>0-12 months</td>
</tr>
<tr>
<td>Increasing dose of trimethoprim by 200 mg</td>
<td>Normal dose of trimethoprim</td>
<td>Trimethoprim</td>
<td>0-12 months</td>
<td>2.26 (1.13 to 4.55)</td>
</tr>
<tr>
<td>Increasing dose of β-lactam by 500 mg</td>
<td>Normal dose of β-lactam</td>
<td>Amoxicillin</td>
<td>0-12 months</td>
<td>1.00 (0.99 to 1.01)</td>
</tr>
</tbody>
</table>

*Either exact time at which individuals took antibiotics, or time period during which antibiotic prescribing was recorded, before measurement of resistance.
decision to submit the article for publication. The researchers were independent of the funder.

**Competing interests:** All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) CC, ADH, DM, AL, and CM have support from the Universities of Bristol and Oxford for the submitted work; (2) None of the authors has relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) None of the authors’ spouses, partners, or children have any financial relationships that may be relevant to the submitted work; and (4) None of the authors has any non-financial interests that may be relevant to the submitted work.

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