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Review Article

Effect of antibiotic prescribing in primary care on antimicrobial resistance: a literature review 2020

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ABSTRACT

Our aim is to review the literature and, where appropriate, investigating subsequent antibiotic resistance in individuals prescribed antibiotics in primary care. Data sources are observational and experimental studies identified through Medline, Embase, and Cochrane searches. Review methods Electronic searches using MeSH terms and text words identified 4373 papers. 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. The observations concluded that individuals prescribed an antibiotic in primary care for a respiratory or urinary infection develop bacterial resistance to that antibiotic.

Keywords: Antibiotics, Resistance, Primary care, Review

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 recognized 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.

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.[2-4]

Much of this use is in the treatment of suspected respiratory infection and levels of prescribing vary widely within and between countries, suggesting that further reductions are possible.[5,6] However, there are many barriers to reducing the inappropriate use of antimicrobials, including: patient and practitioner expectations, lack of patient awareness of the problems

caused by antimicrobial resistance, and a perception in primary care clinicians and patients that antibiotic resistance is only a theoretical or minimal risk.[7-10] 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.[11-13] 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.[14] To reduce prescribing, it may therefore be important to highlight the effect of antimicrobial use on emergent resistance for individuals.[15] 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.[16-19]

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 anybody site; analysed at the level of the individual; and published in any language. We searched the Medline (1955 to May 2019), Embase (1980 to May 2019), 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 Table 1 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. Data extraction and quality assessment Full articles were independently reviewed for quality and data extracted using a purpose-designed form by two reviewers (CC and one other). Disagreements were resolved by discussion with a third author (ADH). Where data extraction was difficult or unclear, the paper’s author was contacted for clarification. The explanatory variables extracted included: study design; description of participants; recruitment location; prescribed antibiotic types; dose and number of courses; and time between antibiotic exposure and measurement of resistance. Time was measured as the exact time at which individuals took antibiotics, or time period during which antibiotic prescribing was recorded, before measurement of resistance.

Table 1: Medline and Embase search strategy.

S. no.	
1	Exp Drug Resistance, Microbial/145030
2	Bacterial resistan$.tw. 7742
3	Antibiotic resistan$.tw. 36098
4	Family practice (no related terms) 1530
5	Antimicrobial resistance (no related terms) 2042
6	Drug resistan$.tw. 77383
7	Primary care (no related terms) 10339
8	Ambulatory care (no related terms) 913
9	Family practice (no related terms) 1530
10	Exp Primary health care/91893
11	Antibiotics (no related terms) 10404
12	2 or 3 or 4 or 6 or 7 232539
13	5 or 8 or 9 or 10 or 11 97137
	Combination of 12 and 13 4373

$ indicates truncation. tw=text word. No related terms specifies search words only.

RESULTS

Study characteristics database searches identified 4373 potential studies of which 3239 were excluded on the basis of title. 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. These consisted of five randomized 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.

Resistance over time in MRSA

The study was found few studies investigating effects on MRSA; three studies in skin samples and one study in nasal samples. Paganini et al examined community acquired MRSA in children.[31] 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% (2 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 al 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).[32]

Baggett et al 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.[33] 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 al examined resistance associated with the use of any antibiotic in the 12 months preceding resistance testing.[34] 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 abrasions 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).

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 to12 months. This residual effect is likely to be an important driver for the high endemic levels of antibiotic resistance in the community.[28] 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 longer 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.[28-30]

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