

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.¹¹⁻¹³ 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,¹⁶ and to the best of our knowledge no systematic reviews have been published in this area.¹⁷⁻¹⁹ 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 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.

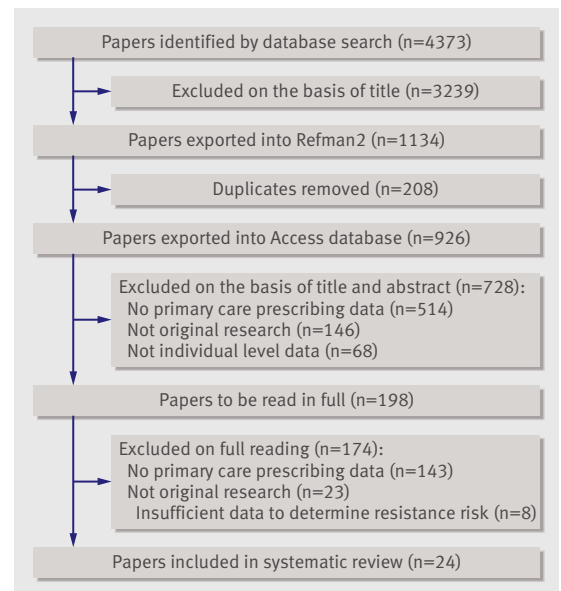


Fig 1 Stages of inclusion/exclusion and evaluation of studies in the systematic review

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.

The outcome data extracted were: bacteria type; sampling location; the antibiotics to which resistance was measured; and the method of measuring resistance.

We agreed that the most important quality criteria for studies quantifying the relation between prescribing and resistance were (1) a reliable measure of antibiotic exposure; (2) a reliable measure of resistance; (3) unbiased control selection; (4) ability to identify incident cases (that is, patients’ bacteria were known to be non-resistant before exposure to antibiotics); (5) adjustment for key confounders such as recent hospitalisation or instrumentation of the urinary tract. Each study was rated according to these criteria and any studies that met fewer than three criteria present were not included in the meta-analyses.

Data synthesis and analysis

All analyses were done using STATA version 10. The outcome measure was the odds ratio (OR) of resistance in participants exposed to antibiotics compared with those who were unexposed. The ORs and associated

MEDLINE and EMBASE search strategy

- 1 exp Drug Resistance, Microbial/145030
- 2 bacterial resistanc\$.tw. 7742
- 3 antibiotic resistanc\$.tw. 36098
- 4 family practice (no related terms) 1530
- 5 antimicrobial resistance (no related terms) 2042
- 6 drug resistanc\$.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

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 I^2 statistic and the null hypothesis of no heterogeneity was tested using the Q statistic generated from the χ^2 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 MOOSE²⁰ 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.^{17-19 23-43} 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);^{17-19 23-25 27} respiratory tract infections (seven);²⁸⁻³⁴ otitis media (two);^{36 42} chronic obstructive pulmonary disease (one);³⁷ meticillin resistant *Staphylococcus aureus* (MRSA) infection (four);³⁸⁻⁴¹ and trachoma in children (one).⁴³ Two studies examined asymptomatic healthy adult volunteers.^{18 35} Studies presented a wide range of antibiotic exposure analyses including those for: macrolides (eight studies);^{19 24 29 31 33-35 37 42 43} penicillins (five);^{17 27 32 34 35} sulphonamides and trimethoprim (six);^{17-19 23-25} cephalosporins (six);^{27 33 34 36 37 42} tetracyclines (two);^{33 37} quinolones (two);^{33 37} nalidixic acid (one);²⁷ metronidazole (one);²⁴ nitrofurantoin (one);²⁷ and “any antibiotic” (seven)^{18 25 30 38-41} 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 RCTs³² 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 study³⁵ met all five criteria. Three studies,²⁵⁻²⁷ 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 study²¹ (table 1). The remaining seven studies reported comparisons between no treatment and prescription of any antibiotic,^{18 25 23} amoxicillin,¹⁹ trimethoprim,^{17 19 24} and ofloxacin²⁵ in relation to resistance to ampicillin,¹⁹ trimethoprim,^{17-19 23-25} sulphonamides,²⁴ or ciprofloxacin.²⁵ Five were of sufficient quality to be included in the meta-analysis.^{17-19 24 23} 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)

Study	Design	n	Participants	Recruitment	Bacteria	Sample site	Method	AB used	AB to which resistance measured	Time* (months)	Crude or adjusted OR (95% CI), P for primary comparison
Urinary bacteria											
17	O	8833	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	Tr	Tr	0-12	2.39 (1.62 to 3.53)
					Ec	U	PDT	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=0.03
					Ec	U	PDT	AA	Tr,Am	0-12	1.13 (0.79 to 1.63)
18	O	618	ASA	GP or POST	Ec	U	PDT	AA	Tr, Am	0-2	1.93 (1.06 to 3.51)
					Ec	U	M	O or Am	Q	0-6	0.26 (0.09 to 0.74)
26	OP	35	SC	GP	Ec	U	PDT	Su	Am, Str, Te, Ch, K, Su, G, Tr, N	NR	0.14 (0.03 to 0.56) P=0.9
27	RCT	131	SA women with recurrent UTI	OP	Ec	U	PDT	N or Cp	N	2-6 W	0.67 (0.30 to 1.6) P=0.01
Respiratory bacteria											
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	2.11 (1.05 to 4.26)
30	CC	412	SA	GP	Hi	S	PDT	AA	Am	0-3	2.1 (1.2 to 36.0) P<0.002
31	O	263	SC	GP	Sp _y	T	PDT	Ma	Ma	0-3	4.19 (1.23 to 14.26)
32	RCT	795	SC	OP	Sp	NP	PDT	Sh Am or StAm	P, Am, Tr-Su	0-2	1.5 (1.2 to 2.8) P=0.001
33	O	737	SC	OP	Sp	NP	E	Cp	P, Ce, E, Tr, Su, To, Cf, Cef, Te	0-4	2.3 (1.04 to 5.1) P<0.05
					Sp	U	PDT	Not Ma	Ma	0-6W	1.27 (0.64 to 2.54)
34	CC	134	SC and ASC	PED	Sp	NP,OC,AN	E	B	P	0-1	-
					Sp	NP,OR,AN	Not B	P	0-1	6.0 (0.06 to 516.4)	
					Sp	NP,OR,AN	B	P	0-6	1.0 (0.003 to 255.6)	
					Sp	NP,OR,AN	Not B	P	0-6	13.7 (0.6 to 311.48)	
35	RCT	224	ASA	U	Sp	TON	GAP	Az	Ma	8D	1.86 (0.9 to 3.75) P<0.05
					Sp	TON	GAP	Cl	Ma	8D	2.47 (1.2 to 5.07)
36	CC	448	C with suspected otitis media	DCC	Pn	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)
					Hi	S	PDT	Cp	B	0-24	4.04 (1.22 to 13.4)
					Hi	S	PDT	Te	B	0-24	2.45 (1.09 to 5.49)
					Hi	S	PDT	Ma	B	0-24	4.04 (1.22 to 13.4)
					Hi	S	PDT	Co	B	0-24	1.94 (0.82 to 4.6)
					Hi	S	PDT	Q	B	0-24	2.13 (0.5 to 9.07)
37	CC	100	A with COPD	OP	Hi	S	PDT	Oth	B	0-24	0.69 (0.29 to 1.61)
					Hi	S	PDT	Oth	B	0-24	0.69 (0.29 to 1.61)
MRSA											
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
					Sa	SK	PDT		Me	0-6	3.1 (1.1 to 8.6) P<0.01
					Sa	SK	PDT		Me	0-12	1.5 (0.6 to 4.0) P<0.4
39	O	206	A with skin infection	MTC	Sa	SK	PDT	AA	Me	0-12	0.147 (0.05 to 0.4) P=0.123
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	CEFT, Cp, Am	3-5D	P<0.01†
43	RCT	121	C with early trachoma	PED	Ct	OC	E	Az	Az	2W	P=0.1†

Design: O=observational, OP=observational prospective, CC=case-control, RCT=randomised controlled trial. Participants: A=adults, C=children, SA/SC=symptomatic adults/children, ASA/ASC=asymptomatic adults/children. Recruitment: GP=general practice, POST=post-al recruitment, PED=paediatric clinic, OP=outpatient clinic, DCC=day care centre, MLR=medical lab records (routine laboratory samples linked to regional prescribing database), MTC=military training centre, U=university. Bacteria: Ct=*Chlamydia trachomatis*, Ec=*E. coli*, GN=gram negative, H=*Haemophilus*, Hi=*Haemophilus influenzae*, Pn=pneumococci, Sp=*S. pneumoniae*, Sa=*S. aureus*, Sp_y=*S. pyogenes*. Antibiotics (AB): AA=any antibiotic, Az=azithromycin, Am=amoxicillin, B=β lactam, Ce=ceftriaxone, Cf=cefprozil, Cef=cefalorR, Cp=cephalexin, Cl=clarithromycin, Co=co-trimoxazole, E=erythromycin, G=gentamicin, K=kenamycin, Ma=macrolide, Me=metacillin, N=naladixic acid, O=ofloxacin, P=penicillin, Q=quinolone, ShAm=short course high dose amoxicillin, StAm=standard amoxicillin, Str=streptomycin, Su=sulphonamide, Tr=trimethoprim, Te=tetracycline, Tr=trimethoprim, To=trimethoprim-sulfamethoxazole. Method (of measuring resistance): PDT=paper disk testing, MIC=minimum inhibitory concentration, E=E testing (AB Biodisk, Sweden), GAR=grid agar plate. Sample site: U=urine, T=throat, NP=nasopharyngeal, N=nasal, OC=ocular, ST=stool, SK=skin, S=sputum, TON=tonsil, OR=oral cavity, AN=anterior nares.

*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

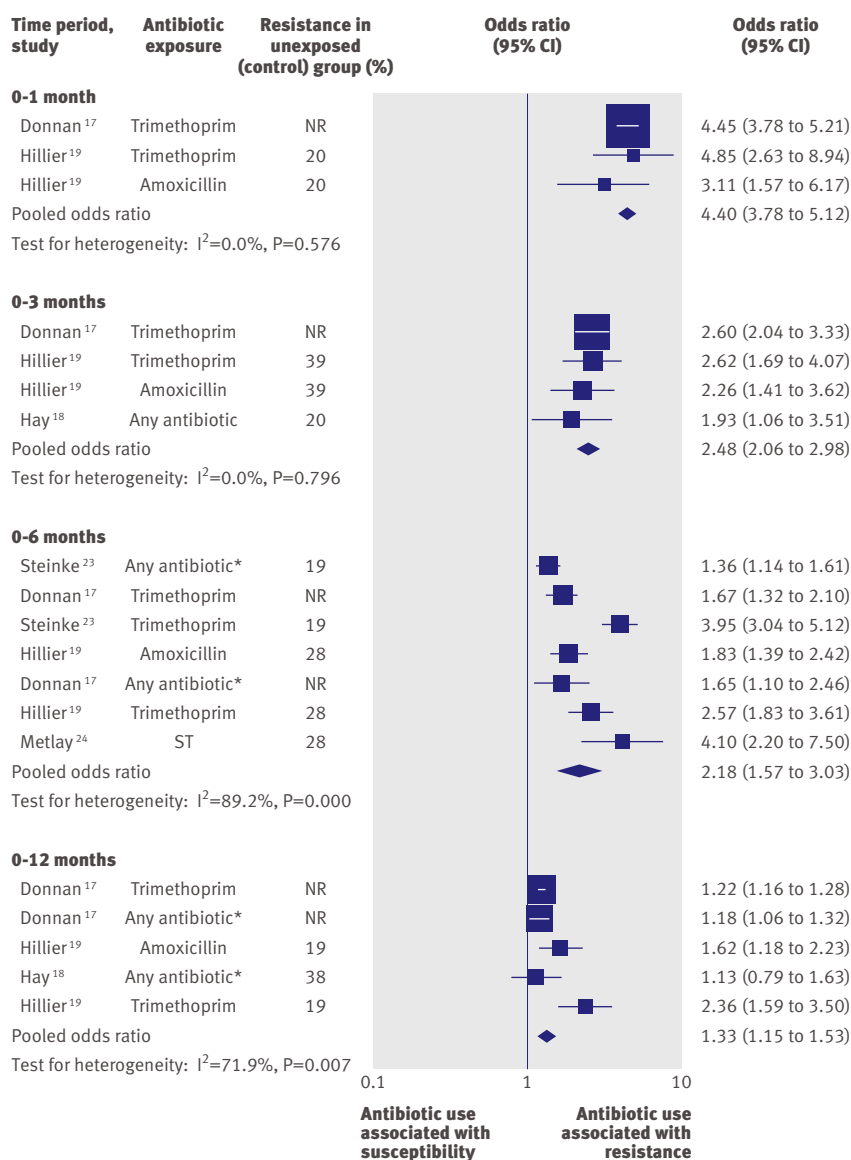
0-6 month and 0-12 month periods. For studies in which adjusted ORs were presented we did a meta-analysis of these results, although we only had sufficient data to do this for the studies examining resistance in urinary tract bacteria at the 0-3 month period. The resulting pooled OR did not differ markedly 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 study³⁷ 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 tract⁴⁴) 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 I^2 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 $\mu\text{g/ml}$ compared with 2.7 $\mu\text{g/ml}$, $P = 0.005$) 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



* Any antibiotic other than trimethoprim. ST=sulfamethoxazole-trimethoprim. NR=not reported

Fig 2 | Forest plot showing individual study and pooled ORs (log scale) for resistance in urinary tract bacteria (*E coli*) and antibiotic exposure. Studies grouped according to time period during which exposure was measured and ordered within each time period by increasing standard error

Table 2 | Study quality (by reference number)

Study	Data on antibiotic exposure complete and accurate?	Resistance well defined?	Resistance threshold described?	Unbiased control selection?	Resistance status known before exposure?	Adjustments for confounders?	Adjusted OR (95% CI)	P
17	Y	Y	N	Y	Unknown	Y	1.22 (1.16 to 1.28)	<0.001
19	Y	Y	Y	Y	Unknown	Y	Not reported	-
23	Y	Y	N	Y	Unknown	Y	4.35 (3.03 to 5.73) 1.32 (1.10 to 1.60)	-
24	Y	Y	Y	Y	Unknown	Y	4.1 (2.2 to 7.5)	0.03
18	Y	Y	Y	Y	Unknown	Y	1.12 (0.77 to 1.65)	-
	Y	Y		Y	Unknown	Y	1.95 (1.08 to 3.49)	-
25	N	Y	Y	NA	Unknown	Y	Ciprofloxacin 20.6 (2.4 to 179.2), ofloxacin 7.6 (2.9 to 19.5)	0.006, 0.0001
26	N	Y	Y	NA	Unknown	Unknown	Not reported	-
27	Y	Y	Y	NA	Y	Unknown	Not reported	-
28	Y	Y	Y	Y	Y	Y	Not reported	-
29	N	Y	Y	Y	Unknown	Y	1.0003 (1.0001 to 1.0004)	<0.0001
30	Y	Y	Y	Y	Unknown	Y	3.4 (1.3 to 9.2)	<0.01
31	Y	Y	Y	Y	Unknown	Y	2.16 (0.55 to 8.45)	0.26
32	Y	Y	Y	Y	Unknown	Y	Not reported	-
33	Y	Y	Y	Y	Unknown	Y	2.7 (1.1 to 6.6)	<0.001
34	Y	Y	Y	Y	Unknown	Unknown	Not reported	-
35	Y	Y	Y	Y	Y	Y	Not reported	-
36	Y	Y	Y	Y	Unknown	Y	Not reported	-
37	Y	Y	Y	Y	Unknown	Y	1.15 (1.04 to 1.28)	<0.01
38	Y	Y	Y	Y	Unknown	Y	Not reported	-
39	Y	Y	Y	Y	Unknown	Y	Not reported	-
40	Y	Y	Y	Y	Unknown	Y	29.37 (10.72 to 80.50)	<0.001
41	N	Y	Y	Y	Unknown	Y	Not reported	-
42	N	Y	Y	No controls	Unknown	No	Not reported	-
43	Y	Y	Not reported	Y	Unknown	Y	Not reported	-

OR showed a decaying association with resistance to macrolides at all time points up to 6 months with strong evidence of a time trend (β 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 samples^{38,39,41} 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

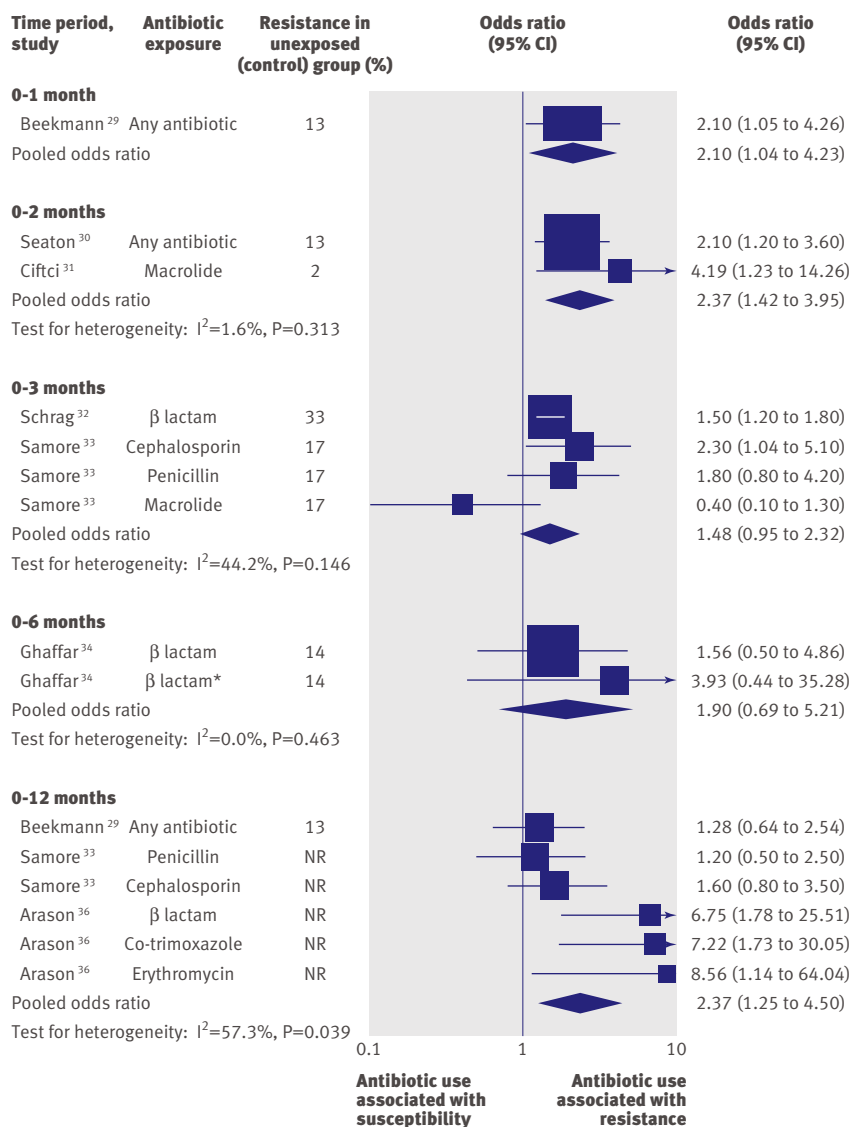
found a strong association (OR 3.1, 95% CI 1.1 to 8.6) between this infection and the prescription of any antibiotic in the previous 0-6 months. This association disappeared (1.5, 0.6 to 4.0) when the time period was broadened to include any antibiotic prescription in the preceding 12 months.

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 Pantone-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^{38,39,41} 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).

Comparisons between antibiotics

Many of the studies included in the review looked at head to head comparisons between antibiotics, although their statistical power was often limited. For example, the Ghaffar study³⁴ examined resistance to penicillin in *Streptococcus pneumoniae* following use of β lactam drugs or β lactam in combination with another antibiotic class but the 95% confidence intervals around the estimated OR varied from 0.1 to 516.



* β lactam plus another antibiotic. NR=not reported

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 Sportel study³⁷ allowed greater precision and showed that there was no greater association between penicillin use and ampicillin resistance than cephalosporin use in *Haemophilus influenzae* (OR 0.4, 95% CI 0.1 to 1.4). The Malhotra-Kumar study³⁵ 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.

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). Schrag et al³² 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 al¹⁹ found greater rates of resistance associated with higher doses of amoxicillin (OR 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.¹⁹ The Hay study¹⁸ 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.

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.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 35}

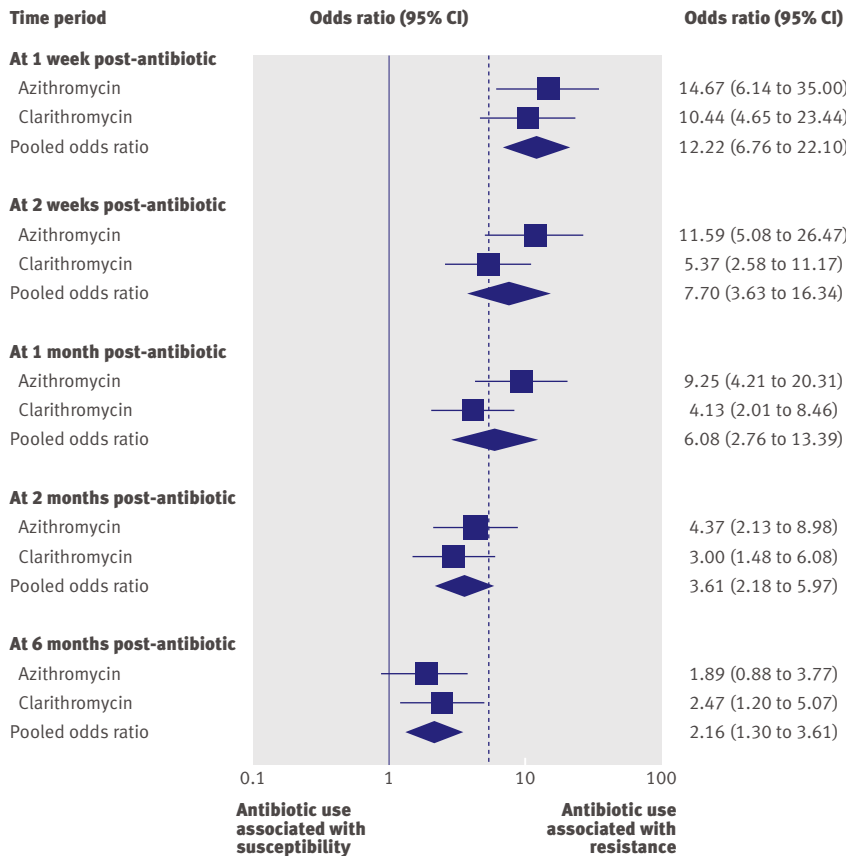


Fig 4 | Forest plot showing individual analytic and pooled ORs (log scale) for resistance in respiratory tract streptococci of healthy volunteers from the Malhotra-Kumar study³⁵ and previous antibiotic prescribing

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

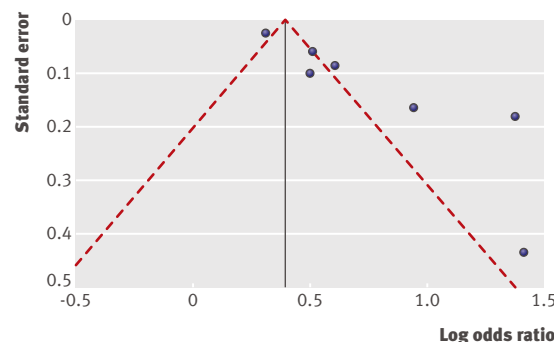


Fig 5 | Funnel plot with pseudo 95% confidence limits for studies investigating the relation between resistance in urinary bacteria and antibiotic use in the previous six months

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.³⁵ 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.⁴⁵ 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

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

Study	High dose/ concentration	Standard dose and duration	Antibiotic to which resistance was measured	Time*	OR (95% CI)
Schrag 2001 ³²	High dose amoxicillin 90 mg/kg for 5 days	Normal dose amoxicillin 40 mg/kg per day for 10 days	Penicillin	5 days	0.9 (0.6 to 1.2)
				10 days	1.16 (0.88 to 1.53)
				28 days	0.77 (0.06 to 0.97)
Hillier 2007 ¹⁹	High dose amoxicillin 500 mg Amoxicillin >7 days	Normal dose amoxicillin 250 mg Amoxicillin <7 days	Ampicillin	0-12 months	2.26 (1.13 to 4.55)
				0-12 months	1.50 (0.76 to 2.92)
				0-12 months	2.89 (1.44 to 5.78)
Hillier 2007 ¹⁹	2 courses amoxicillin 3 courses amoxicillin	1 course amoxicillin 1 course amoxicillin	Ampicillin	0-12 months	1.58 (0.77 to 3.27)
				0-12 months	3.95 (1.06 to 14.72)
				0-12 months	0.98 (0.39 to 2.49)
Hay 2005 ¹⁸	2 courses any antibiotic 3 courses any antibiotic	1 course any antibiotic 1 course any antibiotic	Trimethoprim	0-12 months	3.62 (1.25 to 10.48)
				0-12 months	1.18 (0.53 to 2.37)
				0-12 months	0.4 (0.12 to 1.31)
Hay 2005 ¹⁸	4 courses any antibiotic Increasing dose of trimethoprim by 200 mg	1 course any antibiotic Normal dose of trimethoprim	Trimethoprim	0-12 months	2.77 (0.94 to 8.15)
				0-12 months	1.01 (1.01 to 1.02)
				0-12 months	1.00 (0.99 to 1.01)
	Increasing dose of β lactam by 500 mg	Normal dose of β lactam	Amoxicillin	0-12 months	1.00 (0.99 to 1.01)

*Either exact time at which individuals took antibiotics, or time period during which antibiotic prescribing was recorded, before measurement of resistance.

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.

Contributors: CC performed the searches. CC and ADH identified eligible studies. All authors appraised study quality and extracted data. CC and CM transformed data and performed the meta-analyses. CC and ADH drafted first sections of the text. All authors contributed to the final draft. ADH and CC are the guarantors. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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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

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.

Ethical approval: Not required.

Data sharing: No additional data available.

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