DOI:
10.1093/jac/dkx374

Document Version
Peer reviewed version

Association between prior antibiotic therapy and subsequent risk of community-acquired infections: A Systematic Review

Authors:
Umer Malik*
David Armstrong
Mark Ashworth
Alex Dregan
Veline L'Esperance
Lucy McDonnell
Mariam Molokhia
Patrick White.

All authors affiliated with:
Department of Primary Care and Public Health Sciences
King's College London
Addison House, Guy's Campus, London, SE1 1UL, United Kingdom

Corresponding author:
Dr Umer Malik
Dept of Primary Care & Public Health Sciences
King's College London
Addison House, Guy's Campus, London, SE1 1UL, United Kingdom.
E-mail: umer.malik@kcl.ac.uk
Telephone: +44 (0)2078488679
Fax: +44 (0)207 848 6620

ABSTRACT:

Background: Antibiotic use can have negative unintended consequences including disruption of the human microbiota which is thought to protect against pathogen overgrowth. We conducted a systematic review to assess whether there is an association between exposure to antibiotics and subsequent risk of community-acquired infections.

Methods: We searched MEDLINE, EMBASE and Web of Science for studies published before 30/06/2017 examining the association between antibiotic use and subsequent community-acquired infection. Infections caused by Clostridium difficile and fungal organisms were excluded. Studies focussing exclusively on resistant organism infections were also excluded.

Results: Eighteen of 22,588 retrieved studies met the inclusion criteria. From these, 16 studies reported a statistically significant association between antibiotic exposure and subsequent risk of community-acquired infection. Infections associated with prior antibiotic use included *Campylobacter jejuni* infection (1 study), recurrent furunculosis (1), invasive *Haemophilus influenzae* type b infection (1), infectious mastitis (1), meningitis (1), invasive pneumococcal disease (1), *Staphylococcus aureus* skin infection (1), typhoid fever (2), recurrent boils and abscesses (1), upper respiratory tract infection and urinary tract infection (1), and salmonella infection (5), although in 3 studies on salmonella infection the effect was of marginal statistical significance.

Conclusions: We found an association between prior antibiotic use and subsequent risk of a diverse range of community-acquired infections. Gastrointestinal, and skin and soft tissue infections were most frequently found to be associated with prior antibiotic exposure. Our findings support the hypothesis that antibiotic use may predispose to future infection risk, including infections caused by both antibiotic-resistant and non-resistant organisms.

INTRODUCTION

Antibiotics are an important weapon in our fight against bacterial infections. Antibiotic use is associated with recognised harms and among them is emergence of antibiotic resistant organisms.[1] There is concern that straightforward infections that are currently easy to control may become untreatable in the future. The growing threat of antimicrobial resistance has been declared a global public health crisis.[2] Much attention has been focussed on limiting inappropriate antibiotic usage as a strategy to control drug resistance, particularly in primary care, where 90% of antibiotic prescriptions are issued.[1] Even so, in the UK, most general practices continue to prescribe antibiotics at rates in excess of what is clinically justified.[3]

Antibiotic therapy can have further unintended consequences, other than selection of resistant microorganisms. The human microbiota is a complex community of up to one hundred trillion microorganisms lining hosts' epithelial surfaces exposed to the outside world.[4] The microbiota influences human health through its role in a diverse range of physiological functions,[4] including a protective role in defence against pathogens. The microbiota is thought to contribute to development of the host's immune system and its response to infection.[5] The huge range of organisms in the microbiota, commensals and potential pathogens, compete with each other for attachment sites and nutrients thereby preventing pathogen overgrowth.[6] Exposure to antibiotics can change the composition of the microbiota, reducing microbial diversity and allowing the overgrowth of potentially harmful microorganisms.[6] Short-term antibiotic treatment for *Helicobacter pylori* eradication, for example, reduces microbial diversity in the human throat and gut microbiota which in some cases persists for up to four years.[7]

The question arises whether antibiotics prescribed to treat an acute bacterial infection could paradoxically predispose to future infections due to collateral damage inflicted on the microbiota? *Clostridium difficile* associated diarrhoea is a well-recognised example of an infection resulting from pathogenic colonisation of a microbial community disrupted by recent antibiotic use.[8, 9] Antibiotic

treatment is also associated with increased risk of fungal infection.[10-12] Are there other medium and long-term infection risks associated with antibiotic use unrelated to increased resistance, or infection with *Clostridium difficile* or opportunist fungi? The current systematic review sought evidence of the association between antibiotic use and subsequent risk of infection in the community setting, unrelated to these previously known infection risks.

OBJECTIVES:

To examine whether exposure to antibiotic therapy is associated with subsequent increased risk of community-acquired infections.

METHODS

Procedures used in this review were consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

Protocol and registration:

A review protocol was submitted in advance to PROSPERO which is a database of systematic review protocols (registration ID: CRD42016048521).[14]

Eligibility Criteria:

Our inclusion criteria were: (i) studies, of any design, evaluating risk of community-acquired infection associated with prior antibiotic usage; (ii) human participants, of any age, in the community setting; (iii) studies that assessed risk of infection associated with prior antibiotic exposure compared with the risk of infection without prior antibiotic exposure, in the same period (iv) the endpoint was any community-acquired infection. Our exclusion criteria were; (i) studies focussed on immune-compromised patient groups (e.g. patients with human immunodeficiency virus) as these would not be representative of the general population; (ii) studies focussing on infections that are known to be associated with prior antibiotic exposure including fungal infection[10-12] and *Clostridium difficile* infection;[9] (iii) studies focussing exclusively on infections caused by antibiotic-resistant organisms as

these have been the subject of a previous systematic review.[15] Furthermore, these studies would not provide a true estimate of the overall risk of infection following antibiotic exposure because infections resulting from non-resistant organisms would be excluded; (iv) studies assessing the risk of nosocomial infections because their relationship with prior antibiotic use could be confounded by other factors (e.g. vulnerable patients, infectious contacts, invasive procedures); (v) non-English language articles; (vi) reviews, letters, editorials and case reports; (vii) studies assessing impact of prior antibiotic use on complications resulting from a specific infection (e.g. mortality rate); (viii) studies examining use of antibiotics as a prophylactic measure to prevent a specific infection (e.g. post-operative wound infection) because such studies are not designed to assess the impact of the antibiotic exposure on the subsequent risk of acquiring other unrelated infections.

Search Strategy:

The initial literature search was performed on 29th April 2016. The search was repeated on 30th June 2017 to identify further articles published since the date of the initial search. The databases searched were MEDLINE, EMBASE and Web of Science. No restrictions were imposed on publication period. Search terms included both text words and MESH terms. Detailed search strategies are presented in in the Supplementary Material (**Table S1**). The reference lists of eligible studies and review articles were screened to identify further studies eligible for inclusion.

Study Selection:

Covidence software was used to facilitate screening and selection of studies.[16] The first reviewer (UM) conducted the literature search, removed duplicate articles and screened titles and abstracts with respect to the eligibility criteria. Full text articles of potentially relevant studies were independently assessed for eligibility by two reviewers (UM and PW). Any disagreements were resolved through discussion and consensus.

Data Extraction:

One reviewer (UM) extracted data from the full texts of included studies. Extracted data were summarised in a predesigned format and were cross-checked by a second reviewer (PW). Disagreements were resolved through discussion and consensus.

Data collected included the first author, publication year, country of study, study design, study objectives, participant characteristics, exposure definition (i.e. antibiotic class, length of treatment, time from exposure to infection), exposure interval (length of time prior to the infection during which antibiotic exposure was assessed), exposure ascertainment method, infection type, definition of cases and the comparison group, sample size, main outcome measure and confounding variables. The primary outcome of interest was the odds ratio (OR) for the association of infection with prior antibiotic exposure.

Quality Assessment:

The Newcastle Ottawa Scale (NOS), a tool for assessing the quality of non-randomised studies,[17] was applied independently to each study by two reviewers (UM and PW). Any disagreements were resolved through discussion and consensus.

Each study could be assigned a maximum of nine points; four for the selection domain, two for the comparability domain and three for the exposure domain. Studies assigned NOS scores of ≥7 were considered high-quality, 5-6 were considered moderate quality, and <5 were considered low quality.

Data Synthesis and Analysis

Our research question is broad, aiming to examine the association between past antibiotic consumption and a diverse range of infections, at different body sites, caused by a variety of different microorganisms. Quantitative pooling of results through a meta-analysis was not justified due to the high degree of clinical heterogeneity expected between studies in terms of the infection types being investigated and differences in antibiotic exposures. Any observed association between antibiotic use

and subsequent infection was considered unlikely to be universal for all infection types. We have therefore reported the findings of the systematic review as a narrative (descriptive) synthesis.

RESULTS

Study Selection:

The literature search retrieved 22,582 publications. Six additional publications were identified from the reference list of retrieved articles. After adjusting for duplicates, 21,439 publications remained. After screening by title and abstract, 21,053 publications were excluded. A full text review was conducted of 386 publications, from which 18 met the eligibility criteria and were included in the review.[18-35] Detailed rationale behind the exclusion of studies is presented in **Figure 1**.

Study Design and Participant Characteristics:

Tables 1 and 2 summarise the main characteristics of the included studies. 16 studies were case-control studies and two were cohort studies.

The studies involved a total of 349,085 participants. Study sample sizes ranged from 105[24] to 164,461 participants.[34] In 13 studies the hypothesis that antibiotic use would increase subsequent risk of infections was not stated[19-22, 24, 26-28, 30, 32-35] and earlier antibiotic use was one amongst many other variables assessed as potential risk factors for infection.

Exposure assessment and definition:

Six studies ascertained exposure status from recorded prescription data.[18, 19, 23, 29, 31, 34] Ten studies determined exposure status through participant interview or questionnaire.[20-22, 26-28, 30, 32, 33, 35] One study interviewed both participants and their physician,[24] and in one study medication data was obtained from the physician only when the participant was unsure.[25]

Seventeen studies defined exposure as the consumption of any antibiotic medication. One study defined exposure in terms of specific antibiotic classes.[31]

In one study the exposure status was defined as an antibiotic prescription of 6 weeks or more for acne.[31] In the remaining 17 studies, exposure was not defined in terms of the duration of antibiotic course.

The length of time during which antibiotic exposure was assessed prior to the infection (exposure interval) was specified in 14 out of 18 studies.[18-21, 23-30, 33, 34] In these studies, the exposure interval ranged from 2 weeks to 1 year. The median exposure interval was 2.5 months.

Case Definition:

Fourteen studies defined infection on the basis of a positive microbiological specimen.[19-27, 29, 30, 32, 33, 35] Three studies defined infection on the basis of routinely recorded primary care data.[18, 31, 34] One study on recurrent furunculosis did not specify how the cases were defined.[28]

Comparison Group:

In case-control studies the control group consisted of participants who did not have a confirmed history of the infection of interest. In the cohort study on patients with acne, risk of infection was compared between those who were prescribed long-term antibiotics for acne, versus those who were not.[31] In the cohort study on risk of recurrent boil and abscess, antibiotic prescription rates were compared amongst participants who had a repeat consultation for a boil or abscess within 12-months, versus those who did not.[34]

Associations between exposure and outcome:

Positive and significant associations between prior antibiotic use and subsequent risk of infection were reported in 16 out of 18 studies, including one study on *Campylobacter jejuni* infection,[26] one study on recurrent furunculosis,[28] one study on invasive *Haemophilus influenzae* type b infection,[32] one study on infectious mastitis,[35] one study on meningitis,[18] one study on invasive pneumococcal disease,[19] one study on *Staphylococcus aureus* skin infection,[27] two studies on typhoid fever,[30, 33] one study on recurrent boils and abscesses,[34] one study on upper respiratory tract infection and urinary

tract infection,[31] and five studies on salmonella infection.[20, 21, 23, 24, 29] The outcome measure and 95% confidence interval from each study is presented in **Tables 1 and 2**.

Salmonella Infection

Nine out of 18 studies assessed the association between antibiotic use and subsequent risk of salmonella infection.[20-25, 29, 30, 33] As this was the most frequently studied infection the results are described here in further detail. Two out of nine studies focussed exclusively on cases of typhoid fever.[30, 33] Both studies reported a positive and statistically significant association between prior antibiotic use and subsequent risk of typhoid fever. The remaining seven studies assessing the risk of salmonella infection did not restrict the definition of cases to typhoid fever.[20-25, 29] Five out of seven studies reported a positive and significant association between prior antibiotic use and risk of salmonella infection.[20, 21, 23, 24, 29] From these five studies, three studies reported 95% confidence intervals for the OR that included 1.0 at the lower end.[20, 21, 23] In these studies the effect was of marginal statistical significance. We found two negative studies which did not demonstrate a statistically significant association between prior antibiotic use and subsequent risk of salmonella infection.[22, 25]

Timing of antibiotic exposure:

Four studies assessed the effect of timing of antibiotic exposure on subsequent risk of infection.[18, 19, 23, 29] Increased risk of community-acquired infection after antibiotic exposure was documented up to one year in three[18, 23, 29] out of four studies except for one study on pneumococcal disease[19] that showed an increased risk only in the following month.

In the case of meningitis,[18] the association between antibiotic exposure and subsequent infection risk remained statistically significant over the 12 months exposure period prior to the infection, although as the interval between exposure and subsequent infection increased, the effect size generally

diminished (0-7 days: OR = 4.23, 95% CI = 3.56–5.04 | 8-30 days: 2.12, 1.86–2.42 | 31-90 days: 1.88, 1.70–2.08 | 91-180 days: 1.74, 1.56–1.94 | 181-365 days: 1.93, 1.76–2.13).

The ORs for the association between antibiotic exposure and risk of pneumococcal disease[19] were reported separately for exposures occurring between 0-30 days, 31-60 days, and 61-90 days before the infection and were 1.9 (95% CI: 1.1–3.2), 1.6 (0.89–3.0), and 1.2 (0.60–2.5), respectively.

Gradel *et al.*[29] reported a higher antibiotic consumption rate amongst cases of salmonella infection, compared with controls, for a one year period prior to infection. The excess antibiotic consumption amongst cases remained constant during the first 30 weeks of the one year exposure period, after which it increased steadily until 2 weeks preceding the infection.

In the study by Neal *et al.*[23] the risk of salmonella infection was greater for antibiotic exposure in the preceding month (1.8, 0.9–3.8) compared with exposure in the past year (1.4, 1.0–2.1).

Three studies assessed antibiotic exposure in the 12 months preceding infection, but excluded exposure occurring within the previous 7 days to account for the possibility of reverse causation. These studies demonstrated an association between previous antibiotic use and recurrent furunculosis (OR: 16.6, 95% CI: 2.2–66.0),[28] non-typhoid salmonella (1.59, 1.43–1.77),[29] and meningitis (2.04, 1.91–2.18).[18]

Number of antibiotic prescriptions:

A dose-response relationship was reported between antibiotic exposure and risk of meningitis.[18] Patients receiving ≥4 antimicrobials in the preceding 12 months had a higher risk of meningitis (2.85, 2.44–3.34) compared to those receiving one antimicrobial prescription (1.74, 1.62–1.88).

The association between invasive pneumococcal disease[19] and antibiotic usage in the preceding 3 months was stronger for patients who had ≥2 antibiotic prescriptions (2.1, 1.2–3.8), compared with those who had a single prescription (1.4, 0.88–2.3).

Quality assessment:

Seven studies were deemed to be of high quality, ten studies of moderate quality and one study of low quality (See Supplementary Material, **Table S2** and **S3**). There was considerable variation between studies in the selection of confounding variables. The most common confounding variables were age, gender and location. Case-control studies scored poorly on method of ascertainment of exposure, mostly relying on written self-reports from participants. Non-response rates were also poorly reported in case-control studies.

DISCUSSION

We have found that previous antibiotic use was associated with 12 different community-acquired infections, including infections of viral and bacterial origin. The associated infections ranged from common ailments such as upper respiratory tract infection (URTI) and infectious diarrhoea, to relatively rare but potentially life-threatening infections such as meningitis. Our findings provide evidence that harms of antibiotic use could extend beyond the widely recognised threat of promotion of drug-resistant organisms, to include an increased subsequent risk of infections caused by a range of microorganisms and at many different anatomical sites.

Prior antibiotic consumption and subsequent infection risk was not the primary research question in most of the included studies. Most studies assessed several potential risk factors for infection, and in these the discovery of an association between antibiotic use and subsequent infection was an unexpected finding. The novelty of this finding was not commented upon by many authors. Despite inclusion as a potential risk factor in several studies, the hypothesis that prior antibiotic therapy could

increase future risk of community-acquired infection has received little attention in published literature.

We did not find evidence of association between prior antibiotic use and subsequent infection in any randomised controlled clinical trials of antibiotics. This was probably for two reasons. Firstly, prior antibiotic use was not an acknowledged confounding factor. Secondly infections occurring at sites different to the target of the intervention would not have been seen as an adverse effect of the use of antibiotics. Recurrence of the target infection would have been interpreted as intervention failure, not an adverse effect of the intervention.

The association between exposure to antibiotics and future infection may be explained by the disruptive effect of antibiotic therapy on the microbiota. Antibiotic-induced alteration of the microbiota could diminish the local suppressive effect of commensal organisms on pathogen overgrowth. There is evidence that the microbiota stimulates host epithelial cells to produce antimicrobial peptides[36] and promotes antimicrobial activity of local immune cells.[5, 37] Furthermore, the gut microbiota may modulate systemic immunity and influence host susceptibility to infections distant from the gut.[38] Experimental studies have shown that microbiota-depleted mice have reduced production of inflammatory cytokines, decreased bactericidal activity of macrophages, reduced production, extravasation and bactericidal activity of neutrophils and impaired antibody response to viral infections.[38]

If alteration of the microbiota was responsible for the increased infection risk following antibiotic therapy it might be expected that the risk of infection would return to baseline as the microbiota recovered to its pre-treatment state. Four studies analysed variation in the strength of association between prior antibiotic therapy and subsequent infection in relation to the timing of antibiotic exposure.[18, 19, 23, 29] In three out of four studies there was a trend for weakening of the association between prior antibiotic therapy and subsequent infection as the interval between antibiotic use and diagnosis of infection increased.[18, 19, 29] In the case of pneumococcal disease the observed association

between antibiotic exposure and risk of infection weakened to the extent that the association failed to reach statistical significance for distant exposures which occurred more than 30 days prior to the infection.[19] Together these findings support the hypothesis that transient alteration of the microbiota may be responsible for mediating an increased infection risk following antibiotic exposure. One study on salmonella infection was an exception since it did not demonstrate a weakening of the association between antibiotic exposure and subsequent infection as the interval between antibiotic exposure and diagnosis of infection increased.[23]

The risk of meningitis and invasive pneumococcal disease was found to increase with increasing number of antibiotics to which the patient was exposed prior to the diagnosis of infection.[18, 19] Repeated exposure to antibiotics within the exposure interval would be expected to delay the recovery of the microbiota to its pre-treatment state. This further strengthens the suspicion that antibiotic-induced alteration of the microbiota may be responsible for increased infection risk following antibiotic therapy.

On the other hand the observed association between previous antibiotic exposure and subsequent infection could reflect excessive prior antibiotic consumption amongst persons with increased susceptibility to infections that was independent of the effect of antibiotic therapy on the microbiota. This susceptibility to infections could have been inherited or acquired. If this was the case, frequent antibiotic consumption above a specific threshold would be a clinically valuable marker in identifying a subset of patients that warranted further investigation for a previously unrecognised immune vulnerability.

A further explanation for the observed association may lie in the variation between patients of the threshold for seeking a medical consultation for symptoms. Patients with frequent healthcare-seeking behaviour may be more likely to be diagnosed with infections, and to be prescribed antibiotics. One study controlled for frequency of medical care in their analysis and found an increased risk of URTI in patients exposed to long-term antibiotics for acne, even after adjusting for consultation frequency.[31]

Limitations and Future work:

To our knowledge, this is the first systematic review to demonstrate the association between prior antibiotic therapy and subsequent risk of community-acquired infections, other than infections caused by antibiotic resistant-organisms, fungal organisms and Clostridium difficile.

The association between antibiotic use and subsequent risk of infection should be interpreted with caution. The observational nature of the included studies means it is not possible to establish causality. Most studies did not exclude antibiotic exposure occurring in the days leading up to the infection hence reverse causation should be considered as an alternative explanation for the observed association. Antibiotic exposure could have occurred as a result of prodromal symptoms of the infection under study, rather than being a distant exposure due to an unrelated illness which then increased susceptibility to the current infection.

A further limitation is the possibility of confounding by indication resulting from underlying host susceptibility to infection, as described earlier. This may be addressed by designing studies which take this into account or adjust for infection susceptibility.

The use of retrospective self-reports of antibiotic exposure in some studies is likely to have introduced recall bias. There was insufficient data on adherence to the prescribed course of antibiotics which could have resulted in misclassification of exposure status.

Most studies did not include sufficient prescribing details to establish whether there was a dose-response relationship between antibiotic usage and subsequent infection, nor whether the relationship was stronger with broad spectrum antibiotics, a finding which might have provided more support for the hypothesis of collateral microbiota damage.

The studies on salmonella infection provided inconclusive evidence on whether there was an association between infection and prior antibiotic therapy. This warrants further investigation,

possibly through a meta-analysis which could provide a more precise estimate of the overall effect size.

A further limitation of our review was the exclusion of non-English language papers and those that met the inclusion criteria but the full text article was irretrievable.

CONCLUSION

Prior antibiotic therapy was associated with a diverse range of community-acquired infections. This included infections caused by antibiotic-resistant and non-resistant organisms. The association between antibiotic exposure and subsequent infection became weaker with increasing time from antibiotic exposure. The risk of infection increased with increasing number of antibiotics to which the patients were exposed. Whilst antibiotic therapy is often necessary for the treatment of bacterial infections, our findings highlight the continued need to limit inappropriate antibiotic prescriptions in primary care, both to reduce the consequences of bacterial resistance and possibly also to reduce the risk of future infections. The observed association may help clinicians in dissuading their patients from insisting on an antibiotic prescription when deemed not to be clinically indicated. New research may help discover whether other infection types, not examined by the studies included in our review, are also associated with prior antibiotic therapy. Further studies are also required to examine the mechanisms underlying the observed association, particularly whether this association could be mediated through antibiotic-induced collateral damage to the microbiota.

ACKNOWLEDGEMENTS

Conferences where work has previously been presented:

1. The Society for Academic Primary Care, London Annual Scientific Meeting
   Cambridge, United Kingdom
   January 2016
   Abstract Number: 81

2. Society of Academic Primary Care (SAPC), 45th Annual Scientific Meeting
   Dublin, Republic of Ireland
   July 2016
   Talk Code: EP3A.06

3. 19th International Conference on Human Microbiome
   Singapore
   March 2017
   Paper Code: 17SG030091

FUNDING

No specific funding was sought for this study. The study was conducted as part of our routine work.

TRANSPARENCY DECLARATION

The authors do not have a commercial or other association that might pose a conflict of interest.

UM, DA, MA, LMcD and PW conceived the study. UM carried out the literature search, and extracted the data. UM and PW independently selected eligible articles from potentially suitable articles identified. PW cross-checked extracted data. UM wrote the final manuscript. DA, MA, AD, LMcD, VL,

MM, UM and PW contributed to the interpretation, and revised the final manuscript. PW is guarantor for the study.

REFERENCES

1. Llor C, Bjerrum L. Antimicrobial resistance: Risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf.* 2014; **5:** 229-41.

2. World Health Organization. The evolving threat of antimicrobial resistance - options for action. 2012. http://www.who.int/patientsafety/implementation/amr/publication/en/.

3. Gulliford MC, Dregan A, Moore MV et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: Survey of 568 UK general practices. *BMJ Open.* 2014; **4:** e006245,2014-006245.

4. Ursell LK, Metcalf JL, Parfrey LW et al. Defining the human microbiome. *Nutr Rev.* 2012; **70 Suppl 1:** S38-44.

5. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. *Trends Immunol.* 2012; **33:** 459-66.

6. Levy J. The effects of antibiotic use on gastrointestinal function. *Am J Gastroenterol.* 2000; **95:** S8-10.

7. Jakobsson HE, Jernberg C, Andersson AF et al. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS One.* 2010; **5:** e9836.

8. Chang JY, Antonopoulos DA, Kalra A et al. Decreased diversity of the fecal microbiome in recurrent clostridium difficile-associated diarrhea. *J Infect Dis.* 2008; **197:** 435-8.

9. Brown KA, Khanafer N, Daneman N et al. Meta-analysis of antibiotics and the risk of community-associated clostridium difficile infection. *Antimicrob Agents Chemother.* 2013; **57:** 2326-32.

10. Xu J, Schwartz K, Bartoces M et al. Effect of antibiotics on vulvovaginal candidiasis: A MetroNet study. *J Am Board Fam Med.* 2008; **21:** 261-8.

11. Spinillo A, Capuzzo E, Acciano S et al. Effect of antibiotic use on the prevalence of symptomatic vulvovaginal candidiasis. *Am J Obstet Gynecol.* 1999; **180:** 14-7.

12. MacDonald TM, Beardon PH, McGilchrist MM et al. The risks of symptomatic vaginal candidiasis after oral antibiotic therapy. *Q J Med.* 1993; **86:** 419-24.

13. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Bmj.* 2009; **339:** b2535.

14. Malik U, Armstrong D, Ashworth M et al. Association between antibiotic use and subsequent risk of community-acquired infections: A systematic review. PROSPERO: International prospective register of systematic reviews. 2016. CRD42016048521. http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016048521.

15. Costelloe C, Metcalfe C, Lovering A et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. *Bmj.* 2010; **340:** c2096.

16. Covidence - accelerate your systematic review. 2016. https://www.covidence.org/.

17. Wells GA, Shea B, O'Connell D et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

18. Armstrong D, Ashworth M, Dregan A et al. The relationship between prior antimicrobial prescription and meningitis: A case-control study. *Br J Gen Pract.* 2016; **66:** e228-33.

19. Chun CS, Weinmann S, Riedlinger K et al. Passive cigarette smoke exposure and other risk factors for invasive pneumococcal disease in children: A case-control study. *Perm J.* 2015; **19:** 38-43.

20. Doorduyn Y, Van Den Brandhof WE, Van Duynhoven YT et al. Risk factors for salmonella enteritidis and typhimurium (DT104 and non-DT104) infections in the netherlands: Predominant roles for raw eggs in enteritidis and sandboxes in typhimurium infections. *Epidemiol Infect.* 2006; **134:** 617-26.

21. Delarocque-Astagneau E, Bouillant C, Vaillant V et al. Risk factors for the occurrence of sporadic salmonella enterica serotype typhimurium infections in children in france: A national case-control study. *Clin Infect Dis.* 2000; **31:** 488-92.

22. Kass PH, Farver TB, Beaumont JJ et al. Disease determinants of sporadic salmonellosis in four northern california counties. A case-control study of older children and adults. *Ann Epidemiol.* 1992; **2:** 683-96.

23. Neal KR, Briji SO, Slack RC et al. Recent treatment with H2 antagonists and antibiotics and gastric surgery as risk factors for salmonella infection. *Bmj.* 1994; **308:** 176.

24. Pavia AT, Shipman LD, Wells JG et al. Epidemiologic evidence that prior antimicrobial exposure decreases resistance to infection by antimicrobial-sensitive salmonella. *J Infect Dis.* 1990; **161:** 255-60.

25. Banatvala N, Cramp A, Jones IR et al. Salmonellosis in north thames (east), UK: Associated risk factors. *Epidemiol Infect.* 1999; **122:** 201-7.

26. Effler P, Ieong MC, Kimura A et al. Sporadic campylobacter jejuni infections in hawaii: Associations with prior antibiotic use and commercially prepared chicken. *J Infect Dis.* 2001; **183:** 1152-5.

27. Early GJ, Seifried SE. Risk factors for community-associated staphylococcus aureus skin infection in children of maui. *Hawaii J Med Public Health.* 2012; **71:** 218-23.

28. El-Gilany AH, Fathy H. Risk factors of recurrent furunculosis. *Dermatol Online J.* 2009; **15:** 16.

29. Gradel KO, Dethlefsen C, Ejlertsen T et al. Increased prescription rate of antibiotics prior to non-typhoid salmonella infections: A one-year nested case-control study. *Scand J Infect Dis.* 2008; **40:** 635-41.

30. Luby SP, Faizan MK, Fisher-Hoch SP et al. Risk factors for typhoid fever in an endemic setting, karachi, pakistan. *Epidemiol Infect.* 1998; **120:** 129-38.

31. Margolis DJ, Bowe WP, Hoffstad O et al. Antibiotic treatment of acne may be associated with upper respiratory tract infections. *Arch Dermatol.* 2005; **141:** 1132-6.

32. McVernon J, Andrews N, Slack M et al. Host and environmental factors associated with hib in england, 1998-2002. *Arch Dis Child.* 2008; **93:** 670-5.

33. Srikantiah P, Vafokulov S, Luby SP et al. Epidemiology and risk factors for endemic typhoid fever in uzbekistan. *Trop Med Int Health.* 2007; **12:** 838-47.

34. Shallcross LJ, Hayward AC, Johnson AM et al. Incidence and recurrence of boils and abscesses within the first year: A cohort study in UK primary care. *Br J Gen Pract.* 2015; **65:** e668-76.

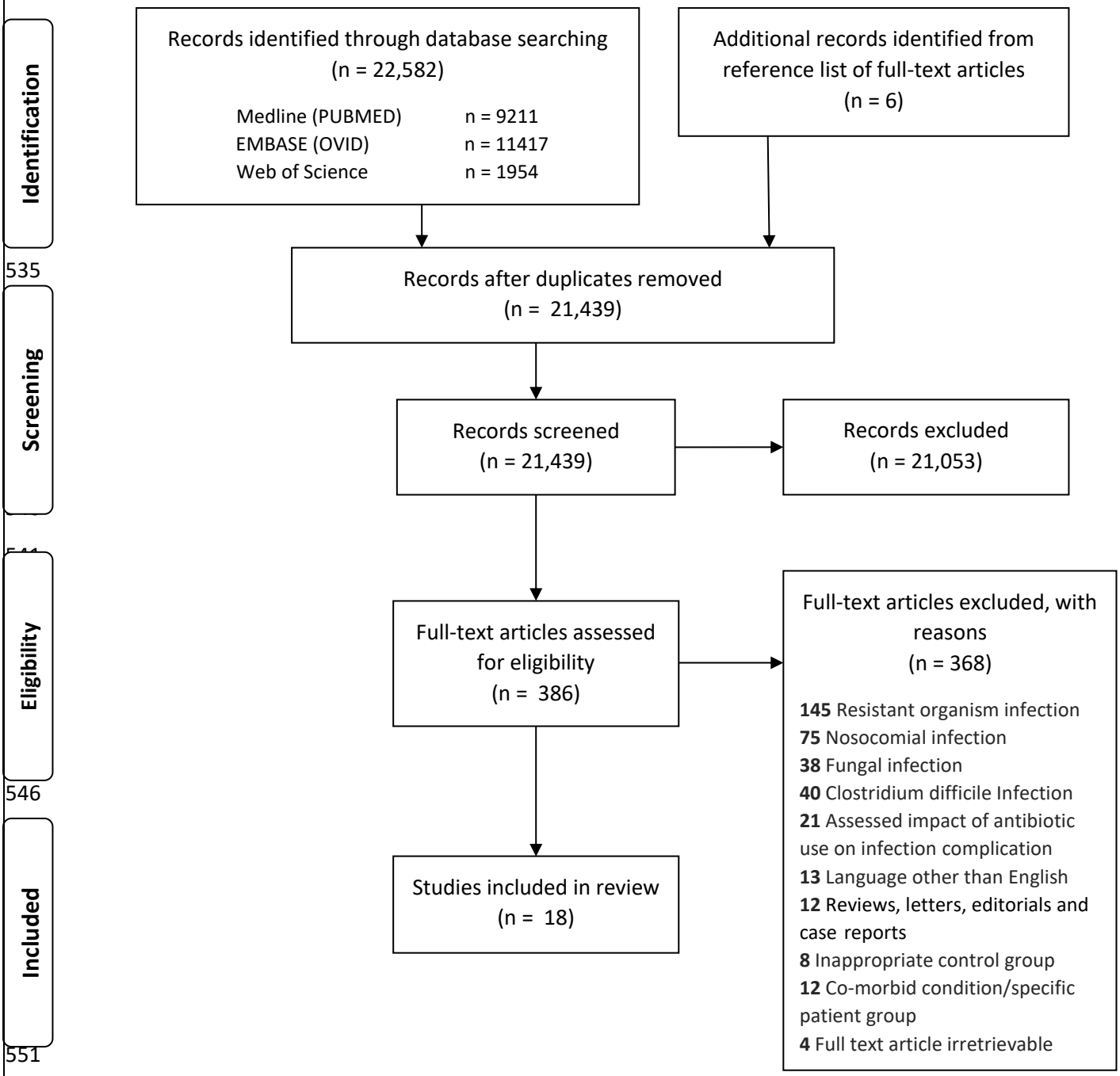
35. Mediano P, Fernandez L, Rodriguez JM et al. Case-control study of risk factors for infectious mastitis in spanish breastfeeding women. *BMC Pregnancy Childbirth.* 2014; **14:** 195,2393-14-195.

36. Gallo RL, Hooper LV. Epithelial antimicrobial defence of the skin and intestine. *Nat Rev Immunol.* 2012; **12:** 503-16.

37. Ivanov II, Atarashi K, Manel N et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell.* 2009; **139:** 485-98.

38. Brown RL, Clarke TB. The regulation of host defences to infection by the microbiota. *Immunology.* 2017; **150:** 1-6.

Figure 1: PRISMA Flow Chart



556 **Table 1: Data Extraction Table for Case-Control Studies (in alphabetical order of infection studied)**

First Author	Publication year; Country	Infection studied	Antibiotic; Exposure Interval	Case definition	Comparison group	Sample size	Fully adjusted outcome (95% CI)	Confounders variables adjusted for
Effler[26]	2001; USA	*Campylobacter Jejuni*	Any; 28 days.	Lab confirmed. Age: not available.	Age and telephone exchange matched.	211 cases 211 controls	OR 3.3 (1.1–9.6)	Consumption of various food items, acid suppressing drugs and contact with live chicken.
El-Gilany[28]	2009; Egypt	Furunculosis (recurrent)	Any; 1 year.	Clinic attendants with ≥3 attacks of boils within the previous 12 months. All ages.	Attendants of the same clinic diagnosed with furunculosis for the first time.	74 cases 74 controls.	OR 16.6 (2.2–66.0)	Family history, diabetes mellitus, anaemia, previous hospitalisation, personal hygiene, skin diseases and number of lesions.
McVernon[32]	2008; UK	*Haemophilus influenzae* type b (invasive)	Frequency of previous antibiotic use	Lab confirmed cases. Age: 5 years to 9 year and 11 months.	Matched by date of birth and region.	136 cases 295 controls	Frequent use: OR 1.51 (1.06–2.13)	Sex, prematurity, breast fed, past illness, family demographic factors, bedroom sharing, smoking, central heating, home ownership, vaccination status.
Mediano[35]	2014; Spain	Mastitis (infectious)	Any; During pregnancy.	Lab confirmed. Lactating females.	Healthy breastfeeding women with no clinical symptoms of mastitis and negative milk culture.	368 cases 148 controls.	OR 5.38 (2.85–10.14)	Age, personal and family history, infection, comorbid, drugs and pregnancy, childbirth and breastfeeding related factors
Armstrong[18]	2016; UK	Meningitis	Any; 1 year.	Identified from GP records. All ages.	Matched on age, sex, GP practice, and index date.	7346 cases 29384 controls	OR 2.04 (1.91–2.18)	13 variables including demographic factors, lifestyle, comorbidities and medications.
Chun[19]	2015; USA	Pneumococcal disease (invasive)	Any; 3 months.	Lab confirmed. Age: 0-12 years.	Matched by age, Health Plan membership, and length of membership.	171 cases 342 controls	OR 1.57 (1.06–2.33)	Sex, race, age, risk status, Health Plan membership, and pneumococcal vaccination.
Doorduyn[20]	2016; Netherland	Salmonella	Any; 4 weeks.	Lab confirmed. All ages.	Matched for age, sex, degree of urbanization and season.	193 cases 3119 controls	OR 1.9 (1.0–3.4)	Age, sex, degree of urbanization and education.

Gradel[29]	2008; Denmark	Salmonella	Any; 1 year.	Lab confirmed. Age: 1-99 years.	Residents of same county matched for specimen date, gender, and age.	1882 cases. 18820 controls	OR 1.59 (1.43–1.77)	Gender, Antibiotic Score*, Patient Group, Age, NTS infection month and Serovar.
Delarocque-Astagneau[21]	2000; France	Salmonella	Any; 1 month.	Lab confirmed Age: <14 years.	Matched for age and place of residence.	101 cases 101 controls	OR 2.3 (1.0–5.5)	Consumption of various food items.
Banatvala[25]	1999; UK	Salmonella	Any; 1 month.	Lab confirmed. All ages.	1. Case nominated and matched for age, gender and area of residence. 2. Randomly selected from London area.	209 cases & matched control. 854 random controls.	**Matched:** OR 1.3 (0.6–2.8) **Unmatched**: OR 1.3 (0.6–2.6)	Not available
Neal[23]	1994; UK	Salmonella	Any; 1 year.	Lab confirmed and notified. Age ≥45 years.	Next two patients in the practice records system matched for age and sex.	188 cases 376 controls	Past year: OR 1.4 (1.0–2.1)	Gastric surgery, H2 antagonist treatment, and other drug use.
Kass[22]	1992; USA	Salmonella	Any; 'Recent'.	Lab confirmed and notified. Age ≥10 years.	Matched for region.	120 cases 265 controls	OR I.96 (0.86–4.37)	Prior health problems and prior medical therapies.
Pavia[24]	1989; USA	Salmonella	Any; 30 days.	Lab confirmed. Age >1 year.	Matched for Age, neighbourhood and telephone exchange.	35 cases 70 controls.	OR 3.8 (1.2–11.9)	Immunosuppression, use of antacids or H2-blocking agents
Early[27]	2012; Hawai	*S. aureus* skin infection	Any; 6 months.	Lab confirmed. Age: 6 months to 17 years.	Matched for age, clinician, and date of clinician visit.	71 cases 146 controls	OR 2.90** (1.29–6.61)	Household contact, Abrasions/wounds, skin disorders, weight, sharing bed linens and towels.
Srikantiah[33]	2007; Uzbekistan	Typhoid fever	Any; 2 weeks.	Lab confirmed. All ages.	Age and community-matched controls.	97 cases 192 controls	OR 12.2 (4.0–37.0)	Occupation, consumption of various food and drink items.
Luby[30]	1998; Pakistan	Typhoid fever	Any; 2 months.	Lab confirmed. All ages.	Neighbourhood and age-matched.	100 cases 200 controls	OR 5.7 (2.3–13.9)	Consumption of various food and drink items.

Abbreviations: NTS infection, Nontyphoid Salmonella Infection.

**Antibiotic score (0 to 5); Antibiotics were classified according to their potential impact on the intestinal flora, with higher scores being associated with increasing impact on the intestinal* flora.

***Association reached significance For Native Hawaiians and Pacific Islanders (NHPI) ethnic category but not for the non-NHPI ethnic category (OR: 1.93, 95% CI: 0.93 to 4.01).*

563 **Table 2: Data Extraction Table for Cohort Studies**

First Author (Year)	Publication Year; Country	Data Source and Study Population	Infection studied	Exposure definition	Case definition and follow-up	Comparison	Sample size	Fully adjusted outcome (95% CI)	Confounders variables adjusted for
Shallcross[34]	2015; UK	Registered with THIN participating GP practice, any age, and sought care for a boil, abscess, carbuncle or furuncle.	Recurrent boil or abscess	Antibiotic prescription in the 6 months prior to the date of index consultation	Second consultation for a boil or abscess within 3 weeks to 12 months.	Patients without a repeat consultation for boil or abscess.	Cohort of 164,461 patients. 10% developed a repeat boil or abscess.	RR 1.4 (1.3–1.4)	Age, Sex, BMI, Diabetes, Skin Disease, Prior Antibiotic, Smoking status.
Margolis[31]	2005; UK	Registered with GPRD participating GP practice, aged 15 to 35 years and recorded diagnosis of Acne vulgaris.	1. Upper Respiratory Tract Infection (URTI) 2. Urinary Tract Infection (UTI).	Prescription >6weeks of oral erythromycin or an oral tetracycline or topical erythromycin or clindamycin or a combination of both.	UTI or URTI within 12 months after enrolment.	Patients without acne antibiotic use were considered unexposed	84,997 exposed 33,519 unexposed	**URTI:** OR 2.23 (2.12–2.34) **UTI:** OR 1.10* (1.01–1.19)	Age, year of diagnosis, sex, contraceptive use or counselling (only for UTIs), practice, diabetes, asthma, visit frequency, and the number of prescriptions for acne antibiotics.

564

565 *Abbreviations: THIN, The Health Improvement Network; BMI, Body Mass Index; GPRD, General Practice Research Datalink, now known as Clinical Practice Research Datalink (CPRD).*
566 **The OR for UTI is statistically significant however the authors of the study concluded that it was not clinically meaningful*