QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

THE ASSOCIATION BETWEEN PRIOR ANTIBIOTIC EXPOSURE AND ANTIBIOTIC RESISTANT URINARY TRACT INFECTION IN PRIMARY HEALTH CARE CLIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

BY

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ABSTRACT

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Title: The association between prior antibiotic exposure and antibiotic resistant urinary tract infection in primary health care clients: a systematic review and meta-analysis

Supervisor of Thesis: Mohammed, F, Alam

This systematic review and meta-analysis aimed to quantify the association between prior antibiotic exposure and subsequent antibiotic resistant urinary tract infection (UTI) in clients in primary healthcare settings. Additionally, it aimed to evaluate the relationships between the timeframe, type of antibiotic, number of courses, dose, and duration of antibiotic exposure, and the likelihood of subsequent antibiotic resistant UTI.

A database search of PubMed, Embase, ProQuest and, Scopus was performed to identify relevant articles. Random-effects meta-analysis was conducted to provide pooled estimates of the associations.

The data search yielded 1196 articles. Screening of titles and abstracts followed by full text screening yielded 27 relevant articles reporting 77 measurements of association between prior antibiotic exposure and subsequent resistant UTI in primary healthcare clients. Compared to those with no antibiotic treatment for UTI, participants with antibiotic exposure in the previous 12 months of UTI onset were more than twice as likely to have a subsequent antibiotic resistant UTI (pooled odds ratio = 2.289 [95% CI; 2.006-2.612]). Subgroup analysis indicated that participants with antibiotic exposure within the previous 1 month were more than 4 times more likely to have a subsequent antibiotic resistance UTI compared to those with no antibiotic exposure. Resistance to quinolones was the most likely, and participants exposed to quinolones had over five

times the odds of subsequent resistance to quinolones. The likelihood of resistance was higher when a patient was exposed to 3 or more antibiotic courses in the previous 12 months compared to 2 or 1 antibiotic course. The OR of the association between resistance and consumption of >=3 antibiotic courses in the last 12 months was 3.315 [95%CI; 3.32-8.12]**,** followed by 2.34 [95%CI; 1.38-4.16] for the consumption of two antibiotic courses, and 1.58 [95%CI; 1.22-2.04] for the consumption of a single antibiotic course. The OR of resistance was non-significant in one study that compared a high dose to lower dose of β-lactams, OR = 1.00 [95%CI; 0.99-1.01], P-value=0.62. However, in the second included study, a lower dose of amoxicillin was associated with higher odds of ampicillin resistance compared to a higher dose, OR=2.19 [95%CI; 1.08–4.41]. The effect of a longer duration of prior AB course on the likelihood of resistance is greater than the effect of a shorter courses. Based on the results of the single included study evaluating this association, the OR comparing the effect of a longer course to a shorter course of trimethoprim on ampicillin resistance was 2.89 [95%CI; 1.44 to 5.78], and the OR comparing the effect a long course to a short course of amoxicillin on ampicillin resistance was 1.50 [95%CI; 0.76 to 2.92]. Results of this study can support clinicians' decisions upon AB prescribing for UTI in primary care clients when resistance is of concern.

DEDICATION

To my beloved parents and sisters

ACKNOWLEDGMENTS

I would like to extend my warmest thanks to my supervisors, Dr. Mohammed Fasihul Alam and Dr. Susu Zughaier for their guidance, encouragement and for making this work possible.

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CHAPTER 1: INTRODUCTION AND BACKGROUND

Antimicrobial resistance happens when microorganisms develop mechanisms to evade the influence of previously effective antibiotics (AB) (1). Resistance developed by microbes results in AB inefficiency and persistent infections. AB resistance is a major global health concern, hindering the ability to prevent and treat a wide range of infectious diseases (2). Although AB resistance occurs naturally, overuse and misuse of ABs have accelerated the development of new resistance mechanisms by bacteria and contributed to the emergence of bacterial species that are resistant to all existing ABs, collectively known as superbugs (3).

It is difficult to accurately estimate the burden of antimicrobial resistance, mainly because of the lack of reliable information resources on the geographical distribution, prevalence, and incidence of antimicrobial resistance. This limits the ability to measure the burden and to design strategies for control (4). In 2014, the World Health Organization (WHO) published a report on the surveillance of AB resistance which evaluated data drawn from 114 countries. The report showed that resistant bacteria result in the death of at least 50,000 persons each year in Europe and the United States of America (USA) (5) A review on antimicrobial resistance estimated that globally, there are around 700,000 deaths annually caused by antimicrobial-resistant bacterial infections. The review estimated that annual deaths caused by antimicrobial-resistant infections will increase to 10 million by 2050 if no effective measures are implemented to counteract the public health issue (6). ABs resistance also results in a major economic burden for health systems. The annual estimated overall cost of ABs resistant infections in Europe is €1.5 billion and $55 billion in the USA (7). However, the review on

antimicrobial resistance commissioned in July 2014 by the UK Prime Minister, which analyzed the global problem of rising drug resistance stated that the actual cost might increase to $100 trillion by 2050 (8).

Urinary tract infection (UTI) is one of the most common types of infection in clinical practice worldwide and it is among the most common reason for physicians' visits in both USA and Europe (9). It accounts for a significant proportion of AB prescriptions in both community and hospital settings and represents a significant burden for national health services (9). In general practice, dysuria and frequency are major reasons for consultation and are common symptoms of UTI reported in 27% and 34% of women, respectively (10).

In UTI, the issue of AB resistance is increasing. Currently, more than 20% of bacteria responsible for UTI are resistant to trimethoprim/sulfamethoxazole (TMP-SMX) and cephalosporins. Additionally, resistance rates to fluoroquinolones have reached 10% (11). In the primary healthcare setting, the treatment of UTI is usually empirical. Many factors that contribute to the decision about which treatment to use including clinical guidelines, the sensitivity of the organism to AB, drug marketing, and practitioner's and the patient's preference. The major challenge that physicians face in treating UTI is the balance between choosing an effective AB and minimizing drug resistance in the population(2).

As previously stated, UTI is one of the most common reasons for prescribing in primary care (12). Additionally, primary care AB prescribing during pregnancy has been studied in the UK and showed that UTI accounted for the highest proportion of ABs in pregnant women (13). UTI is the second most common bacterial infection for which ABs are prescribed in the general practice and a frequent indication for the prescribing of antimicrobials. (14) Thus studying the association between prior AB exposure and

resistant UTI in primary care is important, considering the contribution of primary care to high level of prescribing and UTI being a frequent infection for primary care visits.

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CHAPTER 2: LITERATURE REVIEW

2.1 History of antimicrobial evolution

Infectious diseases were the main cause of death until the beginning of the 1900s. By the mid-1900s, deaths caused by infectious diseases had undergone a remarkable decline as a result of the commercialization of ABs in addition to other factors such as the improvements in living conditions, sanitation, and availability of better nutrition (15)(16). Due to the huge influence ABs had on the survival of humankind at that time, they were regarded as the medical miracle (15).

Paul Ehrlich came up with the concept of the "magic bullet" that selects and targets the organism causing the infection but not the host. This was based on his observation that synthetic dyes such as aniline could stain selected microorganisms but not others. His screening for the magic bullet started in 1891 (17, 18). Paul Ehrlich began his screening program, led with the magic bullet concept, and resulted in the discovery of arsphenamine which was used for the treatment of syphilis (18). Through the screening approach and the continuation of Ehrlich's work, sulfa drugs were synthesized later by Beyer scientists and were the first effective broad-spectrum antimicrobials discovered (19).

Years later, Sir Alexander Fleming marked the AB era with the accidental discovery of penicillin. In 1928 Fleming had left a staphylococcus bacteria culture plate uncovered and went for a vacation. On his return from vacation, he noted that a *staphylococcus* bacteria culture plate was contaminated by *Penicillium notatum* fungus. *Penicillium notatum* had created a bacterium-free zone on the culture plate. Fleming isolated the fungus and grew it in a pure culture, which resulted in the inhibition of the bacterial

growth (20). Penicillin G became widely available in 1945 and novel AB classes became available from the 1950s to 1970s. This period of AB discovery was named the golden era of AB (21).

The discovery of ABs radically revolutionized the treatment of infectious diseases worldwide – although with lower impact in low and middle income countries – and shifted the causes of death from being primarily attributed to communicable diseases, to being mainly caused by non-communicable diseases (21).

The ABs golden age ended as scientists were unable to maintain the pace of AB discovery in the face of emerging resistant pathogens (22). The emergence and spread of AB resistance over the years has been perceived as a leading and growing public health threat affecting millions worldwide. Unfortunately, nearly all ABs available in healthcare markets currently have resistance developed against them (23). Vancomycin was developed and made available to clinical practice in 1972 as a treatment for methicillin resistant *S. aureus* and coagulase-negative staphylococci. At the time, scientists thought that it was extremely difficult to induce resistance against vancomycin, and it was believed unlikely to occur in a clinical setting. However, in 1979 cases of resistance against vancomycin were reported (23).

2.2 Antimicrobial resistance

Resistance is recognized when bacteria develop the ability to resist the effect of ABs to which they were initially sensitive(24). Some bacterial strains have a natural resistance that existed even before ABs were discovered, while other bacterial strains developed resistance through genetic mutations that provided means for them to mitigate the effect of ABs as a consequence of evolution, via natural selection (25, 26).

Between the 1950s and 1960s, bacterial resistance to multiple AB was observed among enteric bacteria Salmonella, Shigella and, E-coli which resulted in many cases of death.

As the use of ABs increased, more cases of resistance were noted, especially in countries where ABs were highly available without the requirement of any prescription (22).

The unsuccessful attempts by scientists to develop or discover new AB in addition to excessive AB use by prescribers and patients were the main factors associated with the development of AB resistance (22).

Major epidemiological surveillance networks documented that multidrug resistance in various bacterial species has reached a pandemic level during the last 20 years (27).

The Center for Disease Control and Prevention (CDC) estimates that in the US, more than 2 million people are annually infected with AB resistant microbes, resulting in the mortality of at least 23,000 infected patients (28).

Antimicrobial-resistant infections are estimated to cause 700,000 deaths every year globally (28). It is predicted that by 2050, antimicrobial resistance related mortality would likely increase to 10 million, with a cumulative cost of $100 trillion, if no action was taken (29).

2.3 Antibiotic prescribing in primary care

Primary health care is defined as "the essential health care made accessible to individuals and families in the community, by means acceptable to them, through their full participation and at a cost that the community and the country can afford. It forms an integrated part of the country's health care system, of which it is the nucleus, and of the overall social and economic development of the country" (30). It is the first level of contact a patient has with the health system and it accounts for 80–90% of all ABs prescriptions in Europe (31). Most of the ABs used in humans in the United States are prescribed in outpatient healthcare settings (32). In 2016, it was estimated that there were 270.2 million outpatient AB prescriptions dispensed in the US (33). Many studies

that evaluated the appropriateness of AB prescribing, indicated that many of the AB's prescriptions were inappropriate (34, 35). A study aimed to evaluate the appropriateness of outpatient AB prescribing for a cohort of children adults in the US, found that among 15,455,834 outpatient AB prescriptions, only 12.8% were appropriate (36).

Half of the primary care prescriptions are for respiratory tract infections, while many of the cases do not warrant an AB prescription (31). One-sixth of the prescriptions in ambulatory care are prescriptions for UTIs (31). Thus, AB overprescribing in primary care contributes majorly to the development of antimicrobial resistance (37). Due to the easier transmission of community-acquired infection in the community, community-acquired antimicrobial resistance is of a particular concern. Although it is well recognized by general practitioners that ABs are not recommended for patients with coughs, colds, and viral sore throat, a survey conducted in UK general practices, revealed that 50% of all patients consulting for coughs, colds, and viral sore throats conditions were prescribed an AB course (38). Many general practitioners prescribe ABs for mild infections such as sore throat or otitis media, because of concerns over the risk of suppurative complications (38). Some studies highlighted that it is a daily challenge for general practitioners to ensure that patients who are unlikely to benefit from ABs are not prescribed any AB, whereas those who require AB receive the right class, at the right time, at the right dose (39).

2.4 Antibiotic stewardship programs

Antimicrobial resistance is a barrier to public health efforts in the control of infectious diseases. AB stewardship programs have been implemented in many hospital settings to address inappropriate AB prescribing and efforts have shown promising signs of benefits associated with their adoption (12). Most of the efforts were made to implement AB stewardship programs in inpatient settings. Unfortunately, antimicrobial

stewardship strategies in primary care settings have been neglected. The Centers for Disease Control has released a framework addressing the core elements of outpatient AB stewardship for outpatient facilities in the recognition of the inappropriate use and overprescribing of antimicrobials in primary care that can be associated with a higher risk of AB resistant bacteria for individual patients (14).

Antibiotic stewardship opportunities in UTIs include the use of AB only when appropriate. It is suggested that asymptomatic bacteriuria should be screened for and treated only in selected conditions, such as pregnancy and prior to urologic surgery. The use of appropriate antimicrobial should include an empiric choice for cystitis, and it is suggested to use an agent with low risk of collateral damage. For uncomplicated pyelonephritis and complicated UTIs, it is recommended to obtain pre-treatment urine culture and de-escalate as appropriate to narrow spectrum agent. Additionally, short-course treatment for cystitis is a more appropriate duration of treatment. It is also important to consider non-antimicrobial preventive strategies for recurrent uncomplicated cystitis such as behavioral modification, use of cranberry, and probiotics (40).

2.5 Guidelines recommendation on urinary tract infection treatment in primary care

According to the Infectious Diseases Society of America (IDSA) (41), the use of TMP-SMX (cotrimoxazole), nitrofurantoin, fosfomycin, or pivmecillinam is recommended if the infecting microorganism is sensitive to them or in cases where the local resistance rates of microorganisms causing acute uncomplicated UTIs do not exceed 20%. Other recommended alternatives are fluoroquinolones or β-lactams such as cephalosporins (41).

Nevertheless, the rate of the E. coli strains resistant to ABs is consistently increasing worldwide (42-44). More importantly, Enterobacteriaceae has a gene that can make it

resistant to most of the ABs and this feature can be transferred between bacteria by plasmids harboring these resistance determinants (45). Thus, the emergence of the resistance to the new ABs is just a matter of time. Consequently, adherence to the guidelines in clinical practice and the wise use of ABs in the cases of infections are very important strategies to minimize the risk of ABs resistance emergence (26).

2.6 Resistance to urinary tract infection treatment

UTIs are categorized into complicated and uncomplicated courses of infection. The uncomplicated courses of UTIs usually affect individuals with normal anatomical and neurological urinary tract. The complicated UTI infects individuals who have factors that compromise the urinary tract or the immune system such as urinary obstruction, immunosuppression, or renal failure. The infection in the lower urinary tract is known as cystitis while pyelonephritis is the infection in the upper urinary tract (23).

E-coli is the major causative pathogen in both complicated and uncomplicated UTIs. E-coli accounts for around 80% of UTIs followed by Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, group B Streptococcus (GBS), Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Candida species (26).

2.7 Impact of prior level of exposure to antimicrobial on the level of bacterial resistance to infection

Prior AB exposure is a known risk factor for resistance emergence (46). If the prior exposure to AB is a causal risk factor for AB resistance, then a dose-response relationship between prior the AB use and the subsequent AB resistance can be expected. Various levels of prior AB exposure whether in terms of dose, frequency, or duration should have varying impacts on the likelihood of resistance. For instance, increasing the dose of amoxicillin while decreasing the duration of treatment was

suggested in cases of infections caused by highly resistant bacteria to prevent treatment failure (47). This was indicated in a study among children, that evaluated the impact of prior exposure to β-lactams on pharyngeal carriage of penicillin resistance S. pneumonia species, low daily doses (lower than clinical recommendation) of the last β-lactam were associated with an increased resistance risk compared to higher daily dose, long duration of β-lactams treatment (>5 days) was also found to promote penicillin-resistance in S. pneumonia species (47). However, the same study found an insignificant association between the frequency of daily doses and increased penicillin resistant S. pneumonia species (47). Another study that evaluated the effect of β-lactams exposure in terms of frequency and dose, on susceptibility patterns of S. pneumoniae in the community while incorporating pharmacodynamics into mathematical modeling, demonstrated that when the frequency of AB exposure per year was kept constant, the dose had a strong effect on the levels of resistance following a 50-year simulation. The lowest doses resulted in a high prevalence of resistant strains, whereas high doses resulted in a lower prevalence of resistant strains (48).

A retrospective multicenter cohort study among elderly subjects aimed to evaluate E-coli resistance status in urine samples collected from study participants in association to the prior AB's consumption using mathematical modeling. The results from the mathematical model revealed that *E. coli* resistance was higher when more frequent ABs were previously prescribed especially in females (49).

Another study conducted at the British general practice level aimed to evaluate the changes in the pattern of ABs dispensing and its association with ABs resistance in coliform isolates from urine samples. The study authors estimated a significant overall decrease in ampicillin resistance per decrease of 50 amoxicillin items dispensed per 1000 patients per annum using multilevel modeling (50).

2.8 General mechanisms by which bacteria develop resistance to UTI treatment

Bacteria can achieve resistance to β-lactams and cephalosporins in several ways, including the enzymatic degradation using β-lactamase enzyme and the altered binding to penicillin-binding proteins (PBPs) target (51). While resistance to fluoroquinolones can be via gene mutation that alters the target active binding site, or the enhanced production of multidrug-resistance (MDR) efflux pumps (52). Trimethoprim resistance is mediated by the loss of bacterial drug-binding capacity and the increased production of dihydrofolate reductase (53).

2.8 Current state of knowledge and gaps in the literature

Several studies have established the association between prior AB exposure and subsequent resistant UTIs in primary care clients (54-59). A systematic review and meta-analysis summarizing evidence of this association was also published by Costelloe et al. in 2010, generated evidence on the association between AB resistance to several types of infections (which included UTIs, respiratory tract infections, and skin infections) and prior AB exposure (60). Since then, several new studies have been published which allows for updating previous evidence. Furthermore, Costelloe et al. reported the association between resistance and prior AB exposure within overlapping periods of 12 months' time frame of UTI diagnosis. This methodological weakness has been acknowledged in their review as they mentioned that the associations with longer time periods could reflect long or short-term relations. Thus, to fill in this gap, we aim to generate a pooled estimate of the association between prior AB exposure and subsequent UTI resistance from studies reporting measurement of association of non-overlapping time periods within a 12-month time frame of prior AB exposure. Furthermore, up to our knowledge, the association between level of prior AB exposure, in terms of dose, duration, and the number of AB courses, and subsequent resistant

infection in clients in primary healthcare settings has not been evaluated in any systematic review and meta-analysis, this systematic review aims to fill this gap specifically for UTIs as one of the most common infections in the community for which ABs are prescribed.

CHAPTER 3: METHODS

3.1 Aim and Objectives

Overall aim

To quantify the association between prior AB exposure and subsequent AB resistant UTI in clients in primary healthcare settings.

Objectives

1- To evaluate the association between time since most recent AB exposure and subsequent AB resistant UTI in clients in primary healthcare settings.
2- To evaluate the association between recent AB exposure and subsequent resistance to different AB types commonly used for UTIs in clients in primary healthcare settings.
3- To evaluate the association between the number of recent AB courses and subsequent AB resistant UTIs in clients in primary healthcare settings.
4- To evaluate the association between dose and duration of recent AB course and subsequent AB resistant UTI in clients in primary healthcare settings.

3.2 Data sources and search strategy

This systematic review and meta-analysis was conducted following the guidance of the Cochrane Collaboration Handbook (61). The findings were reported with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (62).

An electronic database search of PubMed, ProQuest, Embase, and Scopus was conducted. Exploded Mesh/Emtree terms and broad keywords included “antibiotic exposure”, “antimicrobial prescribing”, “antibiotic resistance”, “multidrug resistance”, “urinary tract infection”, primary care”, “ambulatory care”**,** combined with selected

keywords that included “antibiotic treatment”, “antibiotic use”, “antibiotic prescription”, “antibiotics” cystitis, pyelonephritis, bacteriuria, pyuria, "urinary pathogen", UTI and uropathogen. Boolean operators including AND/OR were used to combine the key words and Mesh/Emtree terms. A hand search for the reference list of the selected publications was also performed. For a detailed search strategy, see *Appendix A.*

3.3 Study selection

Study selection was conducted in Endnote reference manager in four steps: duplicates identification and removal, primary screening of titles and abstracts for identification of articles that are potentially relevant, full-text screening of potentially relevant articles; and manual screening of the reference list of the relevant articles. Two independent reviewers (RA, ZA) performed the title and abstracts screening. Articles full-text was retrieved and evaluated for eligibility by two reviewers (RA, ZA) and disagreements were resolved by consensus-based discussion.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

We included studies that report an association between prior exposure to AB prescribed in primary care settings and resistance to UTI in patients presenting to primary care setting. Studies that provided enough information to compute the measurement of association between the exposure and the outcome were also included. Randomized controlled trials (RCTs), or observational studies were eligible for inclusion.

All studies regardless of the population type were included, with no age, gender, region, year, or language restrictions, for non-English studies identified, google translate was intended to be used for translation. Only studies that reported individual level data were eligible for inclusion.

Prior ABs exposure was defined as exposure to ABs within the past 12 months of UTI onset or of sample collection for susceptibility testing.

3.4.2 Exclusion criteria

Studies that only provided a p-value for the association between prior AB exposure and resistant UTI without the outcome measures were excluded.

3.5 Data extraction and synthesis

Several variables were extracted by (RA) from the included articles including publication details, study design, country of origin, site description, study population characteristics, the site from which the sample was obtained, bacterial type, method of ascertainment of AB exposure, type of susceptibility test, type of recent AB prescribed, type of AB to which resistance was measured and time frame of recent AB exposure. Additional variables were extracted for the studies evaluating the specific level of exposure to ABs, such as the number of previous AB courses, the dose of the prescribed AB, and the duration of the previous AB course. Data from the included articles were stratified based on the type of prior AB used, type of AB to which resistance was measured, number of the previous ABs courses used, and the time since last AB exposure.

3.6 Quality assessment

The Newcastle-Ottawa Scale (NOS) (63) for assessing the quality of non-randomized studies to be included in the systematic review and meta-analysis was used to evaluate the quality of the included case-control and cohort studies. A modified version of the NOS was used for the quality assessment of cross-sectional studies (64). The NOS is one of the most widely used validated quality assessment tools for observational studies. There are few methodological quality assessment tools available for meta-analyses of observational studies, many authors used checklists for evaluating the

quality of the included studies (such as STROBE(65)). Which may be seen as a simple checklist. NOS is validated, quick to do, and adaptable. The NOS uses a 'star system' in which the study is appraised based on three main domains: selection of the study group, comparability of the groups on basis of the design or analysis, ascertainment of either the exposure or the outcome in case of case-control or cohort/cross-sectional studies respectively. The scale identifies high/low quality assessment choices with a star and awards a maximum of one 'star' for each item within the 'Selection' and 'Exposure/Outcome' categories; and a maximum of two 'stars' for 'Comparability. The Cochrane risk of bias tool was used to assess the risk of bias in randomized control trials (RCTs), which is the recommended risk of bias assessment for randomized controlled trials included in Cochrane reviews. It emphasizes different aspects of trial design, conduct, and report, and evaluates the risk of bias as low or high or has some concerns. Two reviewers performed quality assessments independently. While evaluating the quality of the included articles, each reviewer extracted evidence from the text to support the evaluation for each question in the NOS into a data-extraction sheet. The two reviewers resolved their disagreement by consensus.

3.7 Publication bias assessment

A funnel plot was created for the association between prior AB exposure and resistant UTI to examine possible publication bias.

3.8 Meta-analysis

To estimate the overall effect of prior ABs exposure on resistance developed to ABs used for the treatment of UTI in primary care, meta-analysis was used to combine and summarize odds ratios (ORs) from all identified individual studies using Comprehensive Meta-Analysis Software (CMA) (66). The random-effects model was used to estimate the pooled OR which accounts for sampling variation and

heterogeneity in effect size.

The Cochrane Q test (67) was used to evaluate the existence of heterogeneity between included studies. The extent of between-study variation, due to true difference in prevalence across studies and not due to sampling error, was estimated using the I^2 measures. The prediction interval was calculated to characterize the uncertainty in the distribution of the effect size of possible new studies selected from the population of the included studies.

3.8.1 Subgroup analyses

Subgroup analyses were performed to compare the association between prior AB exposure and resistant UTI among different subgroups. Subgroup analyses were conducted by the type of AB to which resistance was measured, type of recent AB used, time since recent AB exposure, and the number of prior AB courses.

3.8.2 Meta-regression

To identify which variables can explain variance in resistance to UTI at study level, we performed random-effects meta-regression analyses for the overall outcome of the association between prior ABs exposure and resistant UTI. The possible predictor variables investigated included: the method of ascertainment of prior exposure, type of susceptibility test used, and population type (adult versus children). The variables included for subgroups analyses (type of AB to which resistance was measured, type of recent AB used, time since recent AB exposure, and the number of prior AB courses), were also considered for inclusion in meta-regression. From the univariate analysis, predictor variables with a p-value ≤ 0.25 were included in the multivariable model. Variables with a p-value ≤ 0.05 in the multivariable model were considered significantly associated with resistance to AB used to treat UTI.

CHAPTER 4: RESULTS

4.1 Search results

A total of 1196 publications were retrieved from the electronic database search, 615 from ProQuest, 237 from PubMed, 198 from Scopus, and 146 from Embase. Twenty-two articles were eligible for inclusion following full-text screening, and five eligible articles were included from the reference list search. A total of 27 articles were included in the systematic review and meta-analysis reporting 77 measurements of association between prior AB exposure and AB resistant UTI in primary care. Figure 1. depicts the screening process.

4.2 Characteristics of the included studies

The publication year of the included studies ranged between 1981 and 2019. There was a variation in the size of the sample among studies, the study with the lowest sample size enrolled 81 subjects while the study with the highest sample size enrolled 8833 subjects. Most of the studies were conducted on the adult population only (20 out of 27), while few studies enrolled the children population only (4 out of 27), only three studies enrolled subjects without regard to population age. The studies included both males and females, 8 enrolled only the female population, and a single study enrolled only the male population. All the included followed observational design, except for a single RCT. Most of the studies were conducted in USA or Europe, a single study was conducted in countries such as China, Israel, Senegal and, Turkey. Overall, the quality of the included studies varied between intermediate to high.

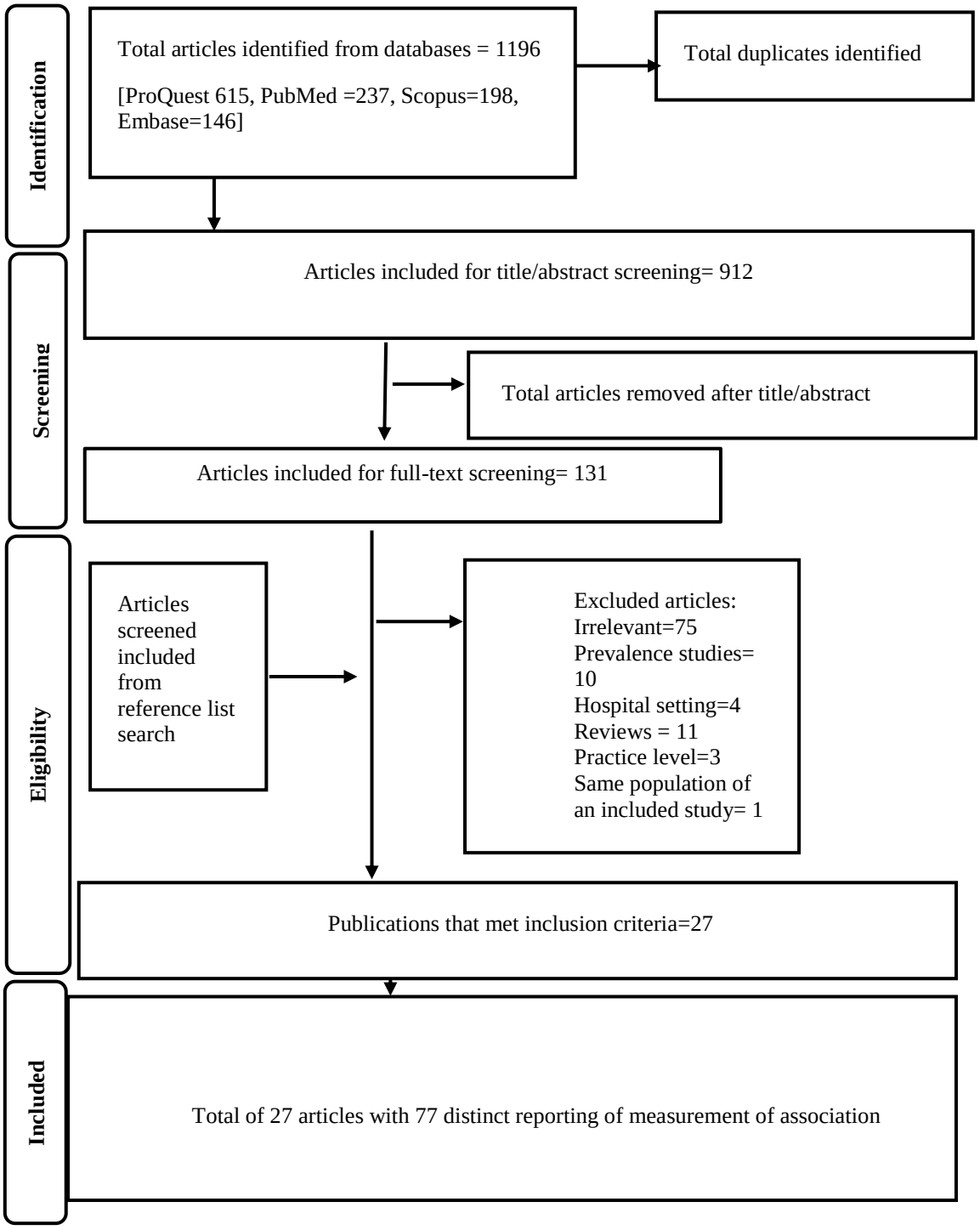


Figure 1. PRISMA Flow chart of articles selection

4.2 Pooled odds ratio estimate of the association between prior AB exposure and AB resistant UTI

In this section, we aim to describe results related to the overall aim of the systematic review and meta-analysis**:** to quantify the association between prior AB exposure and subsequent AB resistant UTI in clients in primary healthcare settings.

Twenty-seven articles were identified reporting a total of 77 distinct association measures related to recent exposure to ABs and their impact on resistant UTI. The pooled OR of the association between the resistance developed by patients with UTIs and recent ABs exposure was 2.289 [95% CI; 2.006-2.612]. The pooled effect size indicates an increased likelihood of AB resistance to be acquired among UTI patients with prior exposure to ABs within the previous 12 months prior to UTI onset. which indicates that the true effect size lies between 2.006 and 2.612 in 95% of the population comparable to population included in the analysis. Similarly, the z-value for testing the null hypothesis (that there is no association between the exposure and outcome) is 11.987 with a corresponding p-value < 0.001 which indicates strong evidence against the null hypothesis.

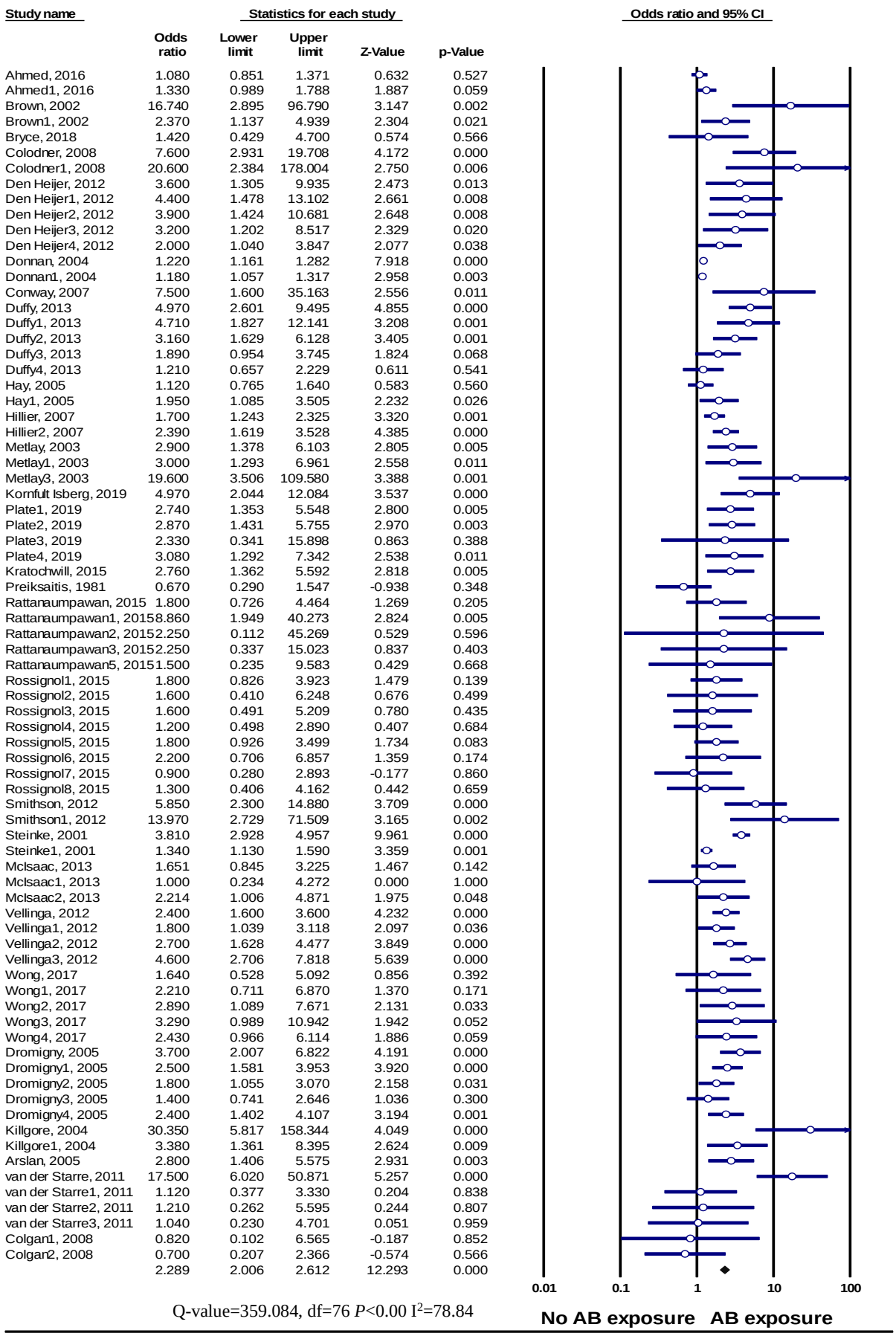


Figure 2. Forest plot for the association between prior AB exposure and resistant UTI

4.2.1 Heterogeneity in results

The Cochran Q statistic value is 359.084, with 76 df and P-value <0.001, the statistically significant p-value, indicates heterogeneity in effect size across the included studies. The I^2 heterogeneity measure is 78.84 which reflects that 78.84% of the observed variation is due to true variation in ORs between the studies rather than sampling error.

4.2.2 Prediction interval

As illustrated in Figure 3, the 95% prediction interval ranged between 1.00 to 5.22, which demonstrates that in 95% of cases, the true effect size from all comparable new studies will fall in the interval between 1.00 to 5.22. Based on the value of the interval outlined, there will be some populations where the impact of prior ABs exposure on resistant UTI is minimal and for some populations where it is likely to be large. Since the meta-analysis was performed across heterogenous studies, subgroup analyses were performed to investigate heterogeneity in the pooled OR.

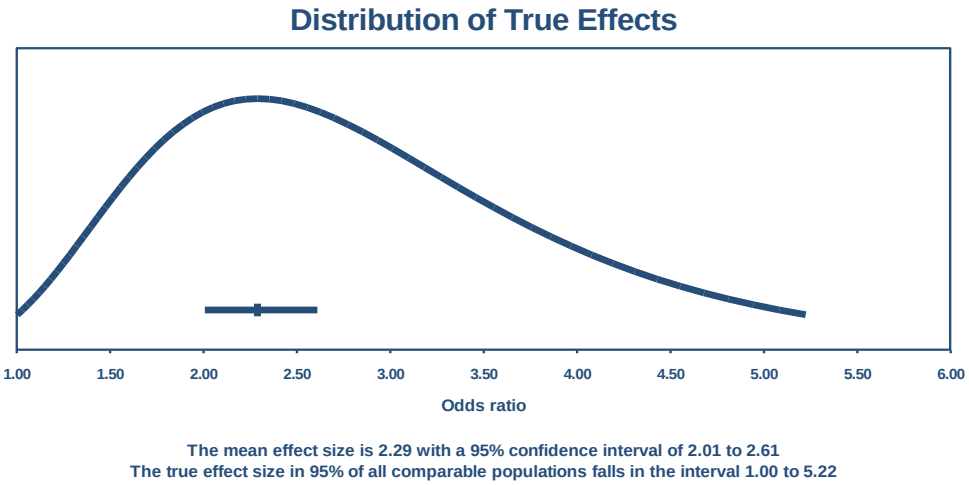


Figure 3. Prediction interval of the association between prior AB exposure and resistant UTI

Table 1. Included studies characteristics and pooled OR of the association between prior antibiotic exposure and resistant UTI

Study	Design	Country	Sample size	Population age group	Population gender	Sample	Bacterial type	Identification of AB exposure	Test of AB susceptibility	Recent AB prescribed	AB to which resistance measured	Time since last AB exposure	OR
Ahmed, 2016[68]	R-CS	USA	1159	Children	Mixed	urine	E-coli	Medical Record	Vitek	Any AB	Ampicillin	6	1.08
Ahmed, 2016[68]	R-CS	USA	1159	Children	Mixed	urine	E-coli	Medical Record	Vitek	Any AB	TMP-SMX	6	1.33
Brown, 2002[69]	CS	US	574	Adult	Women	urine	E-coli	Not clear	Microdilution	TMP-SMX	TMP-SMX	1	16.74
Brown, 2002[69]	CS	US	574	Adult	Women	urine	E-coli	Not clear	Microdilution	Any AB-except TMP-SMX	TMP-SMX	1	2.37
Bryce, 2018[70]	CS	UK	694	Children	Mixed	urine	E-coli	Medical Record	Microdilution	Any AB	any AB	12	1.42
Colodner, 2008[71]	P-CC	Israel	300	Adult	Mixed	urine	E. coli	Medical Record	unclear	Ciprofloxacin	Quinolones	6	7.60
Colodner, 2008[71]	P-CC	Israel	300	Adult	Mixed	urine	E. coli	Medical Record	unclear	Ofloxacin	Quinolones	6	20.60
Den Heijer, 2012[72]	CS	Netherlands	434	Adult	Women	Urine	E-coli	self-report	Microdilution	TMP-SMX	Amoxicillin	3	3.60
Den Heijer, 2012[72]	CS	Netherlands	434	Adult	Women	Urine	E-coli	self-report	Microdilution	TMP-SMX	Amoxicillin-clavulanic acid	3	4.40
Den Heijer, 2012[72]	CS	Netherlands	434	Adult	Women	Urine	E-coli	self-report	Microdilution	TMP-SMX	Trimethoprim	3	3.90
Den Heijer, 2012[72]	CS	Netherlands	434	Adult	Women	Urine	E-coli	self-report	Microdilution	TMP-SMX	TMP-SMX	3	3.20
Den Heijer, 2012[72]	CS	Netherlands	434	Adult	Women	Feces	E-coli	self-report	Microdilution	TMP-SMX	Trimethoprim	3	2.00

Study	Design	Country	Sample size	Population age group	Population gender	Sample	Bacterial type	Identification of AB exposure	Test of AB susceptibility	Recent AB prescribed	AB to which resistance measured	Time since last AB exposure	OR
Donnan, 2004[73]	CS	Scotland	8833	Adult	Mixed	urine	not specified	Medical Record	unclear	Trimethoprim	trimethoprim	6	1.22
Donnan, 2004[73]	CS	Scotland	8833	Adult	Mixed	urine	not specified	Medical Record	unclear	Any AB other than Trimethoprim	trimethoprim	6	1.18
Conway, 2007[59]	N-CC	US	694	Children	Mixed	urine	not specified	Medical Record	unclear	Any AB	Any AB	12	7.50
Duffy, 2013[74]	RC	Scotland	1373	Children	Mixed	urine	E. coli	Medical Record	unclear	trimethoprim	trimethoprim	<1	4.97
Duffy, 2013[74]	RC	Scotland	1373	Children	Mixed	urine	E. coli	Medical Record	unclear	trimethoprim	trimethoprim	1	4.71
Duffy, 2013[74]	RC	Scotland	1373	Children	Mixed	urine	E. coli	Medical Record	unclear	trimethoprim	trimethoprim	2-3	3.16
Duffy, 2013[74]	RC	Scotland	1373	Children	Mixed	urine	E. coli	Medical Record	unclear	trimethoprim	trimethoprim	4-6	1.89
Duffy, 2013[74]	RC	Scotland	1373	Children	Mixed	urine	E. coli	Medical Record	unclear	trimethoprim	trimethoprim	6-12	1.21
Hay, 2005[75]	CS	UK	618	Adult	Mixed	urine	E-coli	Medical Record	BSAC	Any AB	Trimethoprim or Amoxicillin	12	1.12
Hay, 2005[75]	CS	UK	618	Adult	Mixed	urine	E-coli	Medical Record	BSAC	Any AB	Trimethoprim or Amoxicillin	12	1.95
Hillier, 2007[76]	CC	UK	903	Mixed	Mixed	urine	E. coli	Medical Record	BSAC	amoxicillin	ampicillin	12	1.70
Hillier, 2007[76]	CC	UK	903	Mixed	Mixed	urine	E. coli	Medical Record	BSAC	trimethoprim	trimethoprim	12	2.39
Metlay, 2003[77]	R-CC	USA	393	Mixed	Mixed	urine	E. coli	Medical Record	Vitek	TMP-SMX	TMP-SMX	6	2.90
Metlay, 2003	R-CC	USA	393	Mixed	Mixed	urine	E. coli	Medical Record	Vitek	Quinolones	TMP-SMX	6	3.00
Metlay, 2003[77]	R-CC	USA	393	Mixed	Mixed	urine	E. coli	Medical Record	Vitek	Tetracyclines	TMP-SMX	6	19.60
Kornfält Isberg, 2019[78]	CS	Sweden	304	Adult	Women	urine	E-coli	self report	EUCAST	Any AB	Mecillinam, trimethoprim, ciprofloxacin, cefadroxil or ESBL producing	12	4.97

Study	Design	Country	Sample size	Population age group	Population Gender	Sample	Bacterial type	Identification of AB exposure	Test of AB susceptibility	Recent AB prescribed	AB to which resistance measured	Time since last AB exposure	OR
Plate, 2019[56]	CS	Switzerland	729	Adult	Mixed	urine	E. coli	Unclear	Vitek2	Any AB	TMP/SMX	3	2.74
Plate, 2019[56]	CS	Switzerland	729	Adult	Mixed	urine	E. coli	Unclear	Vitek2	Any AB	Fosfomycin	3	2.87
Plate, 2019[56]	CS	Switzerland	729	Adult	Mixed	urine	E. coli	Unclear	Vitek2	Any AB	nitrofurantoin	3	2.33
Plate, 2019[56]	CS	Switzerland	729	Adult	Mixed	urine	E. coli	Unclear	Vitek2	Any AB	ciprofloxacin	3	3.08
Kratochwill, 2015[79]	RC	US	200	Adult	Mixed		E-coli	Unclear	unclear	Any AB	ciprofloxacin	3	2.76
Preiksaitis, 1981[80]	RCT	Canada	81	Adult	Women	urine	E-coli	Unclear	Disk diffusion	Nalidixic acid, cephalexin	nalidixic acid	2	0.67
Rattanaumpawan, 2015[81]	CC	US	2001	Adult	Women	urine	E-coli	Medical Record	Vitek2	any AB	levofloxacin	3	1.8
Rattanaumpawan, 2015[81]	CC	US	2001	Adult	Women	urine	E-coli	Medical Record	Vitek2	Nitrofurantoin	levofloxacin	3	8.86
Rattanaumpawan, 2015[81]	CC	US	2001	Adult	Women	urine	E-coli	Medical Record	Vitek2	TMP-SMX	levofloxacin	3	2.25
Rattanaumpawan, 2015[81]	CC	US	2001	Adult	Women	urine	E-coli	Medical Record	Vitek2	Penicillin	levofloxacin	3	2.25
Rattanaumpawan, 2015[81]	CC	US	2001	Adult	Women	urine	E-coli	Medical Record	Vitek2	β-lactams	levofloxacin	3	1.5
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	All AB	penicillin	3	1.80
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	penicillin	penicillin	3	1.60
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	Quinolone	penicillin	3	1.60
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	Other AB	penicillin	3	1.20

Study	Design	Country	Sample size	Population age group	Population Gender	Sample	Bacterial type	Identification of AB exposure	Test of AB susceptibility	Recent AB prescribed	AB to which resistance measured	Time since last AB exposure	OR
Rossignol, 2015	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	All AB	TMP-SMX	3	1.80
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	Penicillin	TMP-SMX	3	2.20
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	Quinolone	TMP-SMX	3	0.90
Rossignol, 2015[82]	CS	France	363	Adult	Women	urine	ENT	self-report	Disk diffusion	Other AB	TMP-SMX	3	1.3
Smithson, 2012[83]	PR-CS	Spain	153	Adult	Male	urine	E. coli	Medical Record	Disk diffusion	Any AB except	Quinolone	1	5.82
Smithson, 2012[83]	PR-CS	Spain	153	Adult	Male	urine	E. coli	Medical Record	Disk diffusion	Fluoroquinolone	Quinolone	1	13.97
Steinke, 2001[84]	N-CC	Scotland	3435	Mixed	Mixed	urine	Gram negative bacteria	Medical Record	Disk diffusion	Trimethoprim	Trimethoprim	3	3.81
Steinke, 2001[84]	N-CC	Scotland	3435	Mixed	Mixed	urine	Gram negative bacteria	Medical Record	Disk diffusion	AB other than trimethoprim	Trimethoprim	3	1.34
McIsaac, 2013[85]	CS	Canada	208	Adult	Women	urine	E-coli	self-report	unclear	Any AB	Ampicillin	3	1.65
McIsaac, 2013[85]	CS	Canada	208	Adult	Women	urine	E-coli	self-report	unclear	Any AB	Ciprofloxacin	3	1.00
McIsaac, 2013[85]	CS	Canada	208	Adult	Women	urine	E-coli	self-report	unclear	Any AB	TMP-SMX	3	2.214
Vellinga, 2012[86]	CC	Ireland	633	Adult		urine	E-coli	Medical Record	Disk diffusion	Trimethoprim	Trimethoprim	12	2.40
Vellinga, 2012[86]	CC	Ireland	633	Adult	Mixed	urine	E-coli	Medical Record	Disk diffusion	Ciprofloxacin	Trimethoprim	12	1.8

Study	Design	Country	Sample size	Population age group	Population gender	Sample	Bacterial type	Identification of AB exposure	Test of AB susceptibility	Recent AB prescribed	AB to which resistance measured	Time since last AB exposure	OR
Vellinga, 2012[86]	CC	Ireland	633	Adult	Mixed	urine	E-coli	Medical Record	Disk diffusion	trimethoprim	Ciprofloxacin	12	2.7
Vellinga, 2012[86]	CC	Ireland	633	Adult	Mixed	urine	E-coli	Medical Record	Disk diffusion	Ciprofloxacin	Ciprofloxacin	12	4.6
Wong, 2017[54]	PC	China	298	Adult	Women	urine	E-coli	Medical Record	Unclear	Any AB	Ampicillin	6	1.64
Wong, 2017[54]	PC	China	298	Adult	Women	urine	E-coli	Medical Record	Unclear	Any AB	Ciprofloxacin	6	2.21
Wong, 2017[54]	PC	China	298	Adult	Women	urine	E-coli	Medical Record	Unclear	Any AB	Ciprofloxacin	6-12	2.89
Wong, 2017[54]	PC	China	298	Adult	Women	urine	E-coli	Medical Record	Unclear	Any AB	TMP-SMX	6	3.29
Wong, 2017[54]	PC	China	298	Adult	Women	urine	E-coli	Medical Record	Unclear	Any AB	TMP-SMX	6-12	2.43
Dromigny, 2005[87]	CS	Senegal	398	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	Any AB	Ampicillin	6	3.7
Dromigny, 2005[87]	CS	Senegal	398	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	amoxicillin	Amoxicillin-clavulanic acid	6	2.5
Dromigny, 2005[87]	CS	Senegal	398	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	trimethoprim	Nalidixic acid	6	1.8
Dromigny, 2005[87]	CS	Senegal	398	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	TMP-SMX	Fluoroquinolones	6	1.4
Dromigny, 2005[87]	CS	Senegal	398	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	Quinolones	TMP-SMX	6	2.4
Killgore, 2004[88]	N-CC	USA	120	Adult	Mixed	urine	E-coli	Medical Record	MIC	Quinolone	Ciprofloxacin	1	30.35
Killgore, 2004[88]	N-CC	USA	120	Adult	Mixed	urine	E-coli	Medical Record	MIC	Quinolone	Ciprofloxacin	1	3.38

Study	Design	Country	Sample size	Population age group	Population gender	Sample	Bacterial type	Identification of AB exposure	Test of AB susceptibility	Recent AB prescribed	AB to which resistance measured	Time since last AB exposure	OR
Arslan, 2005[89]	CS	Turkey	611	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	Ciprofloxacin	Ciprofloxacin	12	2.80
van der Starre, 2011[90]	N-CC	Netherlands	420	Adult	Mixed	urine	E-coli	Medical Record	MIC	Ciprofloxacin	Fluoroquinolone	6	17.5
van der Starre, 2011[90]	N-CC	Netherlands	420	Adult	Mixed	urine	E-coli	Medical Record	MIC	Any AB	Fluoroquinolone	6	1.12
van der Starre, 2011[90]	N-CC	Netherlands	420	Adult	Mixed	urine	E-coli	Medical Record	MIC	Any AB	Fluoroquinolone	6	1.21
van der Starre, 2011[90]	N-CC	Netherlands	420	Adult	Mixed	urine	E-coli	Medical Record	MIC	Any AB	Fluoroquinolone	3	1.04
Colgan, 2008[91]	CS	US	103	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	TMP-SMX	TMP-SMX	3	0.85
Colgan, 2008[91]	CS	US	103	Adult	Mixed	urine	E-coli	self-report	Disk diffusion	any AB	TMP-SMX	3	0.49

CC= Case-control, N-CC=Nested case-control, R-CC=Retrospective case-control, CS=Cross-sectional, R-CS=Retrospective cross-sectional, MR=Medical record, PR-CS=Prospective-retrospective cross-sectional, PC=Prospective cohort, RC=retrospective cohort , ENT= Enterobacteriaceae

4.3 Subgroup analyses

4.3.1 Time since recent antibiotic exposure

In this section, we present results related to the first objective: To evaluate the association between time since most recent AB exposure and subsequent AB resistant UTI in clients in primary healthcare settings.

Figure 4 shows the forest plot representing subgroup analysis of the impact of prior AB exposure on resistance grouped by the time since the most recent AB exposure to the onset of UTI. Five publications reported a total of 9 distinct measurements of association of the impact of AB exposure within the prior 1 month on the development of resistance. The pooled OR was estimated as 4.73 [95% CI; 2.96-7.55], indicating that the odds of resistance were around 4.73 times greater among UTI patients exposed to ABs in the last month prior to their UTI onset, compared to those unexposed. The pooled OR was lower for exposure within the recent 2 to 3 months (OR= 2.31, [95%CI; 1.75- 3.05]), demonstrating a 50% lower level of association compared to exposure within the previous month.

Three publications evaluated a total of 7 distinct association measures related to recent exposure within the prior 4 to 6 months and resistance, estimated a pooled OR of 1.41 [95%CI; 0.95-2.10], and 3 publications evaluated a total of 7 distinct association measures related to recent exposure within the prior 6 to 12 months and resistance computed pooled OR of 1.55 [95%CI; 1.16- 2.06] The OR seems to be similar from 4-6 months and 6-12 months of prior AB exposure, suggesting that up to 4 months of prior AB exposure, the association is impacted by how recent is the time since last exposure within the previous 12 months' time period. Results from the mixed-effects model shows a Q-value of 19.987; df=3 and P-value < 0.001, the significant p-value shows the heterogeneity of the pooled OR across different subgroups.

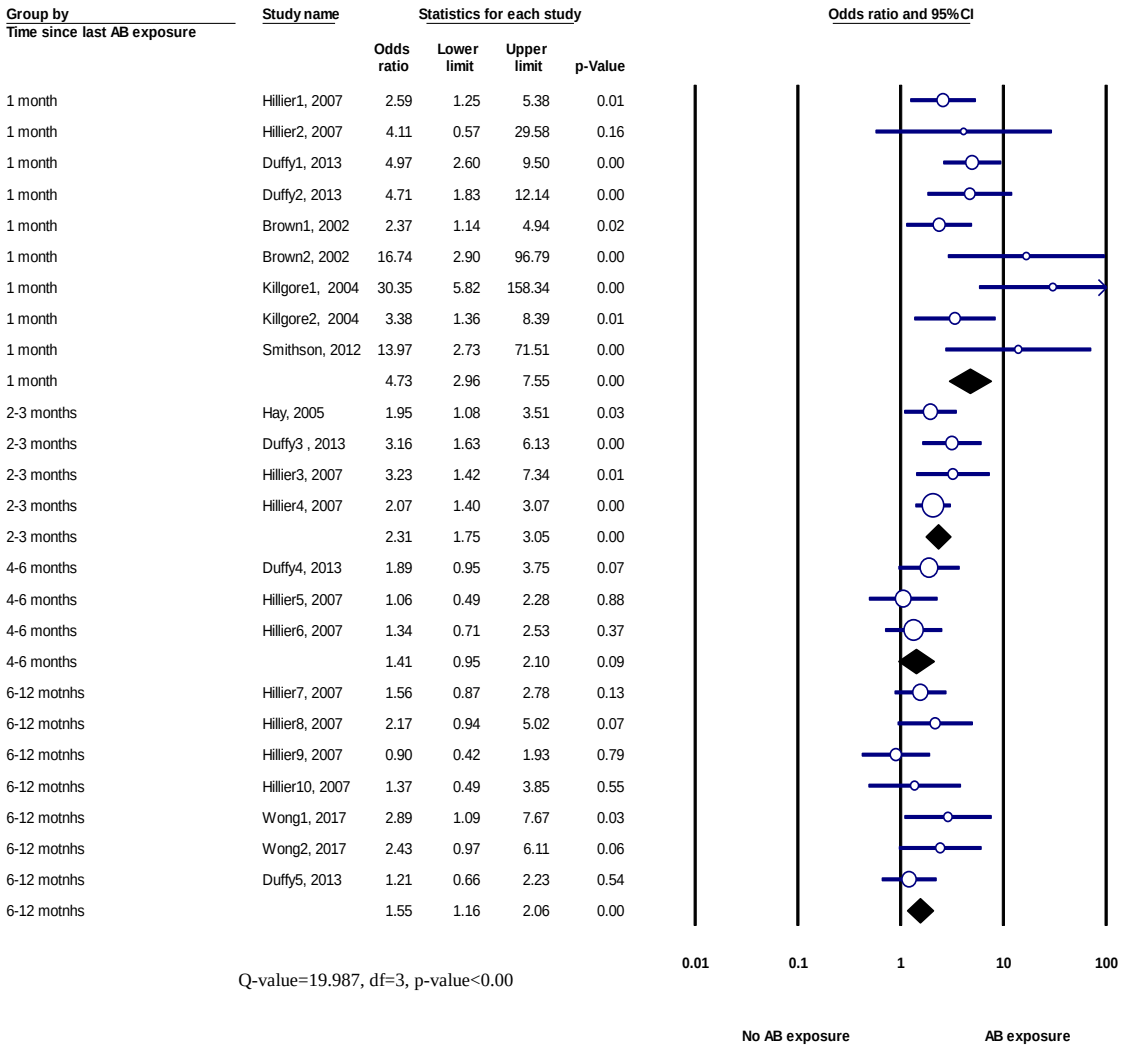


Figure 4. Forest plot showing the association between time since recent AB exposure and AB resistance

4.3.2 Type of antibiotic to which resistance was measured

This section and section 4.3.3 present results related to the second objective: To evaluate the association between recent AB exposure and subsequent resistance to different AB types commonly used for UTIs in clients in primary healthcare settings.

Eleven studies reported 18 separate measurements of association, 13 studies reported 20 separate measurements of association and 7 studies reported 9 separate measurements of association quantified the odds of resistance to quinolones, TMP-

SMX and β-lactams respectively, that are associated with prior exposure to any type of AB in the last 12 months.

Figure 5 presents the forest plot of subgroup analysis of the impact of prior AB exposure on resistance for different AB types. Resistance to quinolone had the highest level of association with prior AB exposure (OR=3.599, [95%CI; 2.55-5.06]), compared to TMP-SMX (OR=2.45, [95%CI; 1.96-3.11]) and **β**-lactams (OR=2.04, [95%CI; 1.45-2.88]). Mixed-effect model shows a Q-value of 5.64; d.f.=2 and P-value < 0.061 illustrating that there is not enough evidence to support that the pooled OR among different subgroups varies.

4.3.3 Type of the recent antibiotic used

Eight studies with 14 distinct measurements of association, assessed the impact of prior trimethoprim exposure on the development of trimethoprim resistance (Figure 6A).

The pooled OR for the association between the bacterial resistance to trimethoprim among patients with recent exposure to trimethoprim is 2.68 [95% CI; 1.79-4.02].

Six studies with 8 distinct measurements of association, estimated the impact of prior exposure to quinolones, on quinolones resistance. The estimated pooled OR is 5.49 [95% CI; 3.99-7.56] (Figure 6B).

Three studies estimated the impact of prior exposure to any quinolone on the development of trimethoprim resistance. The estimated pooled OR is 1.855 [95% CI; 1.086-3.17] (Figure 6C).

Three studies estimated the impact of prior exposure to trimethoprim on the development of quinolone resistance. The estimated pooled OR is 2.49 [95% CI; 1.55-4.00] (Figure 6D).

4.3.4 Number of prior antibiotic courses

This section of the results is related to the third objective: To evaluate the association between the number of recent AB courses and subsequent AB resistant UTI in clients in primary healthcare settings.

Four studies were identified to evaluate the association between the number of prior AB courses and UTI resistance. Figure 7 presents the forest plot for subgroup analysis of the impact attributed to the number of prior AB courses on acquiring resistance to UTI. As the plot illustrates, there is an increase in the odds of resistance to UTI AB treatment with the increase in the frequency of AB courses consumed by the patients. The OR of the association between resistance and consumption of >=3 AB courses in the last 12 months is 3.315 [95%CI; 3.32-8.12], followed by 2.34 [95%CI; 1.38-4.16] for the consumption of two AB courses, and 1.58 [95%CI; 1.22-2.04] for the consumption of a single course of AB. Results from the mixed-effects model shows a Q-value of 3.811; df=2 and P-value < 0.001 showing evidence that the pooled OR among different subgroups varies.

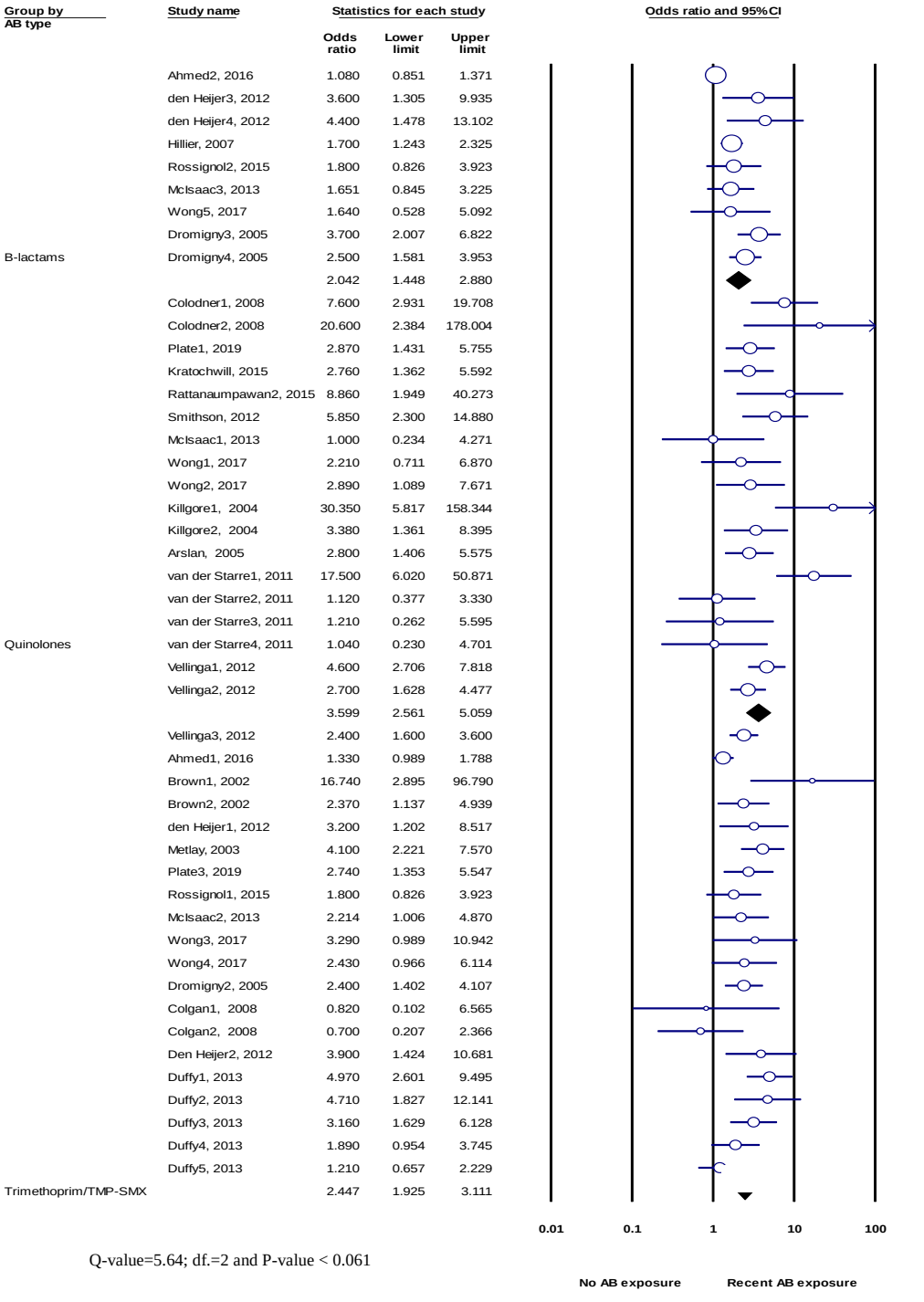


Figure 5. Forest plot of the association between recent AB exposure and resistance grouped by type of AB

4.3.5 Dose of prior antibiotic used

The results of the last objective: To evaluate the association between dose and duration of recent AB course and subsequent AB resistant UTI in clients in primary healthcare settings are presented in this section and section 4.3.6

Two studies evaluated the impact of the dose of the previous AB used on resistant UTI. Hillier, 2007 (92) assessed the impact of two different doses of amoxicillin prescribed in the previous 12 months on ampicillin resistance. Dose risk of 500mg was compared to 250mg for a single course prescribed 3 times daily. The OR of the association between prior intake of a low dose of amoxicillin and ampicillin resistance was 2.07 [95%CI; 1.39-3.06] when compared to patients unexposed to recent amoxicillin course. However, the OR of association between exposure to a high dose of amoxicillin and ampicillin resistance was 0.91 [95%CI; 0,49-1.70] which indicates no evidence of association. The OR comparing low dose with high dose was 2.19 [95%CI; 1.08–4.41]. Hay, 2005 (93) evaluated the association between trimethoprim dose and resistance to trimethoprim. The OR of resistance to trimethoprim associated with increasing the dose of trimethoprim by 200 mg compared with the normal dose of trimethoprim within the previous 12 months was 1.01 [95%CI; 1.01-1.02], P-value<0.001. The OR of resistance to amoxicillin associated with increasing the β-lactams dose by 500 mg compared to the normal dose of β-lactams within the previous 12 months was also evaluated, however, there was no evidence of association (OR = 1.00 [95%CI; 0.99-1.01], P-value=0.62.

4.3.6 Duration of prior antibiotic course

A single study examined the impact of the duration of prior AB courses on the development of resistant UTI(92). The study compared the effect of a short course of amoxicillin (<7 days) with a long course (>=7days) taken in the last 12 months on

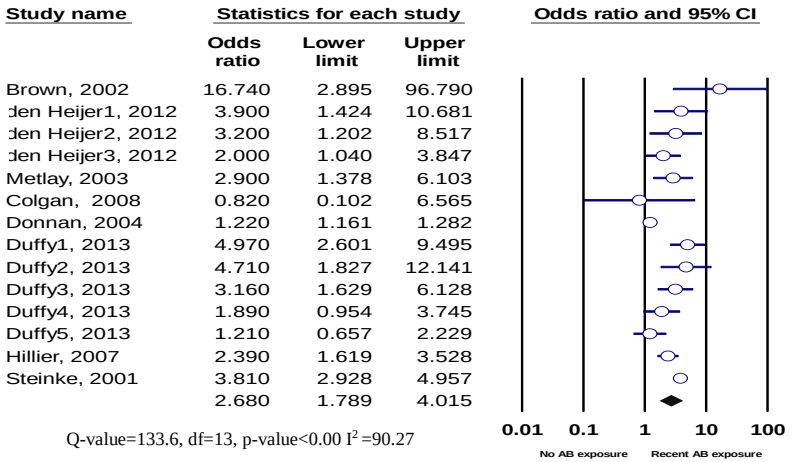
ampicillin resistance. The OR of resistance associated with the a short course was 1.20 [95%CI; 0.65–2.19] compare to no exposure, while the OR of resistance associated with the a long course was 1.79 [95%CI; 1.24–2.58] compared to no exposure, which indicates that longer AB courses duration is associated with higher odds of resistance. The OR comparing long course to short course was 1.50 [95%CI; 0.76 to 2.92]. The same study compared the effect of short course of trimethoprim (<7 days) with long course (>=7days) taken in the last 12 months on ampicillin resistance. The OR of resistance associated with the short course was 1.60 [95%CI; 0.92–2.77] compared to no exposure, while the OR of resistance associated with the long course was 4.62 [95%CI; 2.73–7.82] compared to no exposure. The OR comparing long course to short course was 2.89 [95%CI; 1.44 to 5.78].

4.4. *Sources of between-study heterogeneity*

Not enough studies reported information on non-overlapping times of recent AB exposure, frequency of prior AB courses, or dose and duration of prior AB exposure, thus those possible effect modifiers were not considered for meta-regression analysis. The other predictor variables including type of AB, method of exposure ascertainment, type of susceptibility test and population type, were considered for meta-regression as they were reported in most of the studies.

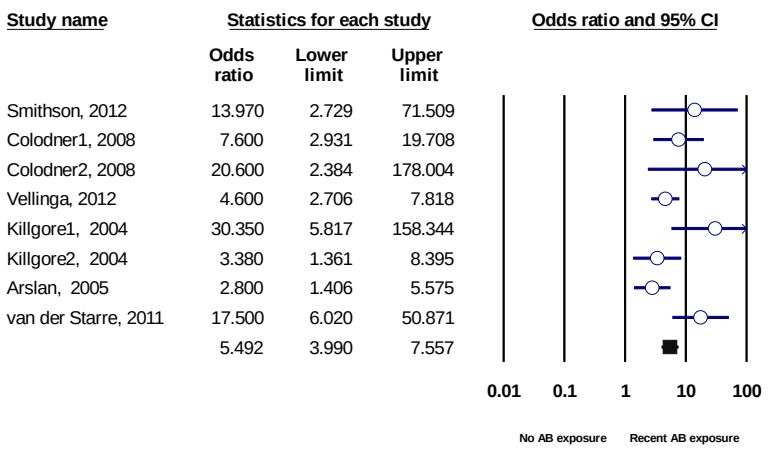
Results from univariable regression are presented in Figures 8, 9, 10, and 11, demonstrating that none of the specified predictor variables had a p-value<=0.25 except for AB type quinolones. Thus, predictor variables with non-significant p-value did not qualify for inclusion in multivariable regression as there is not enough evidence supporting their association with UTI resistance. Quinolones were associated with a statistically significant variability in the odds of resistance to UTI, p-value <0.0365 (Figure8).

A



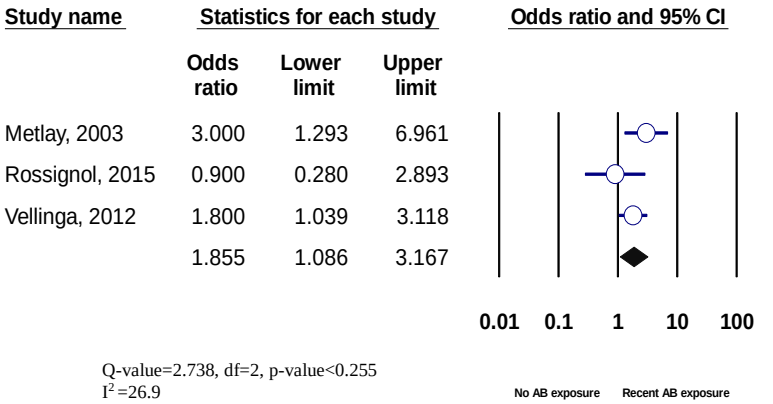
Impact of trimethoprim exposure on trimethoprim resistance

B



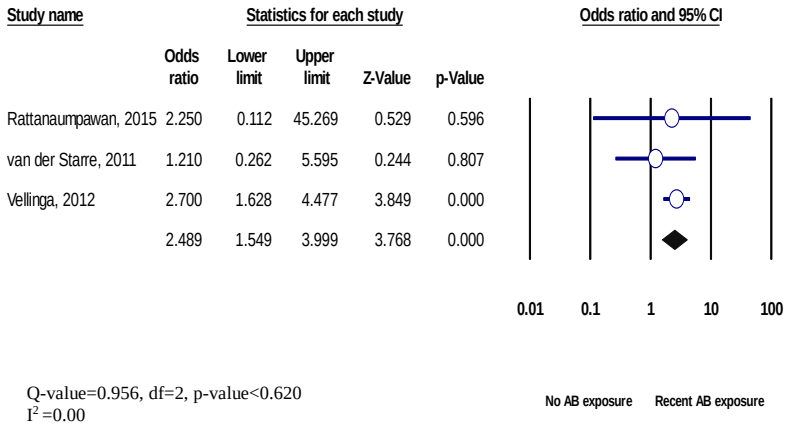
Impact of quinolones exposure on quinolones resistance

C



Impact of quinolones exposure on trimethoprim resistance

D



Impact of trimethoprim exposure on quinolones resistance

Figure 6. Forest plot for the association between recent AB exposure and resistance grouped by type of AB exposure

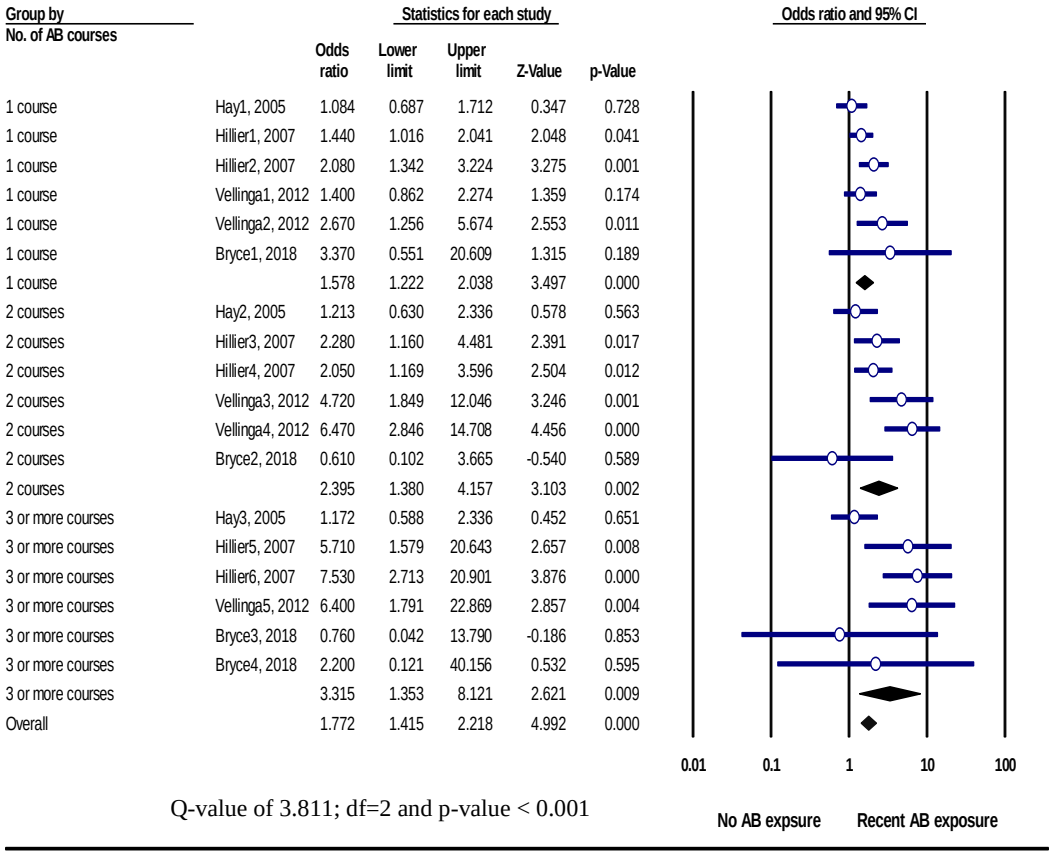


Figure 7. Forest plot for the association between recent AB exposure and resistance grouped by No. of prior AB courses

Main results for Model 1, Random effects (MM), Z-Distribution, Log odds ratio

Set	Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value	
	Intercept	0.6506	0.1550	0.3467	0.9545	4.20	0.0000	
Type of AB	Type of AB: Any AB	0.1330	0.2701	-0.3964	0.6623	0.49	0.6224	Q=5.68, df=3, p=0.1281
	Type of AB: Quinolone	0.4167	0.1992	0.0263	0.8071	2.09	0.0365	
	Type of AB: TMP-SMX/TMP	0.0997	0.1812	-0.2553	0.4548	0.55	0.5820	

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 5.68, df = 3, p = 0.1281

Goodness of fit: Test that unexplained variance is zero

Tau^2 = 0.1446, Tau = 0.3803, I^2 = 74.58%, Q = 287.22, df = 73, p = 0.0000

Figure 7. Univariable analysis of the association between type of AB for which resistance was measured and resistant UTI, ref. category is βB-lactams

Main results for Model 1, Random effects (MM), Z-Distribution, Log odds ratio

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0.7761	0.1036	0.5730	0.9792	7.49	0.0000
Exp. identification: M-record	0.0767	0.1334	-0.1848	0.3382	0.57	0.5654

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.33, df = 1, p = 0.5654

Goodness of fit: Test that unexplained variance is zero

Tau^2 = 0.1502, Tau = 0.3876, I^2 = 76.29%, Q = 316.28, df = 75, p = 0.0000

Figure 8. Univariable analysis of the association between method of exposure ascertainment and resistant UTI, ref. category is self-report

Main results for Model 1, Random effects (MM), Z-Distribution, Log odds ratio

Population type	Intercept	0.7150	0.1849	0.3525	1.0775	3.87	0.0001	Q=0.66, df=2, p=0.7206
	Population type: Adult	0.1214	0.2020	-0.2745	0.5174	0.60	0.5478	
	Population type: Mixed	0.2089	0.2601	-0.3010	0.7187	0.80	0.4220	

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.66, df = 2, p = 0.7206

Goodness of fit: Test that unexplained variance is zero

Tau^2 = 0.1808, Tau = 0.4252, I^2 = 77.24%, Q = 325.13, df = 74, p = 0.0000

Figure 10. Univariable analysis of the association between population type and resistant UTI, ref. category is children

Main results for Model 1, Random effects (MM), Z-Distribution, Log odds ratio

Susceptibility test	Intercept	0.7720	0.1096	0.5571	0.9869	7.04	0.0000	Q=0.43, df=2, p=0.8070
	Susceptibility test: MIC	0.0989	0.1512	-0.1975	0.3952	0.65	0.5132	
	Susceptibility test: missing	0.0463	0.1704	-0.2877	0.3802	0.27	0.7860	

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero

Q = 0.43, df = 2, p = 0.8070

Goodness of fit: Test that unexplained variance is zero

Tau^2 = 0.1507, Tau = 0.3882, I^2 = 72.19%, Q = 266.11, df = 74, p = 0.0000

Figure 9. Univariable analysis of the association between type of susceptibilty test and resistant UTI, ref. category is disk diffusion

4.4 Quality assessment

4.4.1 Quality assessment of case-control studies

A total of nine studies used a case-control design. Seven out of the 9 studies had adequate case definition with independent validation of cases. The studies used various antimicrobial susceptibility testing such as disc diffusion and vitik2, while two studies ascertained case definition based on record linkage. The studies recruited representative samples or consecutive series of cases, most of the studies used hospital controls rather than community controls. All controls were susceptible to the ABs studied confirmed by the mean of susceptibly test confirmation or by record linkage. Overall, a single study scored the maximum of 4 stars in the selection criteria, the rest of the studies scored 3 stars except for 2 studies which scored 2 stars. Seven studies adjusted for the most important factors or adjusted for additional factors, two studies did not adjust for confounding factors neither in the design nor in the analysis thus, two studies scored 0 stars in comparability criteria, and the scores of the rest of the studies varied between 1-2 stars. All the studies used record linkage to confirmed prior AB exposure except for one study which depended on structured interviews with the subjects to ascertain their AB exposure status, however, the same method of confirming the cases and controls was employed in all the studies. The response rate was not mentioned or unclear in most of the studies. Overall, scores in exposure criteria varied between 2-3 stars. Quality assessment of case-control studies is reported in Table 2.

4.4.2 Quality assessment of cohort studies

Four studies used cohort design. All the studies used a representative cohort of subjects (either all target subjects were included, or a random sample was drawn). The non-exposed cohort was selected from the same community as the exposed cohort. The

exposure status was identified based on secure medical records or structured subjects' interviews, none of the studies identified the status of resistance prior to AB exposure, which may not be a feasible option. All the studies scored 3 stars in the selection criteria. One study did not control for any confounders, another study controlled for a few confounding factors, while two studies controlled for important additional factors such as recent hospitalization, UTI history, time since most recent trimethoprim prescription, deprivation status, age and, diabetes status. One study scored 0 stars, one study scored 1 star and two studies scored 2 stars in the comparability criteria. Quality assessment of cohort studies is reported in Table 3.

4.4.3 Quality assessment of cross-sectional studies

Thirteen studies used a cross-sectional design, 8 recruited representative samples (all target population or used random sampling) the rest of the studies either did not include a clear description of their sampling frame or they included a selected group of participants sample size was justified and satisfactory in most of the studies with a description of sample size determination. The response rate was not described in most of the studies and no comparison between the characteristics of respondents and non-respondent was done. A validated measurement tool of previous exposure to AB was used in 50% of the studies while the rest relied on the subject report of prior AB consumption. Two studies scored 4 stars which is the maximin score for the selection criteria. The rest of the studies either scored 2 or 3 stars. The majority of the studies have comparable study groups as they adjusted for important confounding factors and thus scores varied between 1 or 2 stars, however, 2 studies did not report controlling for any confounding factor. Independent assessment of the resistance status was performed in all the studies, one study identified the outcome of resistance via record linkage. The statistical test used to analyze the data were clearly described in all the

studies. The overall score for all the studies for the outcome criteria was 2 stars. Quality assessment of cross-sectional studies is reported in Table 4.

4.4.3 Quality assessment of randomized controlled trials (RCTs)

One study using an RCT design was included. Although patients were randomized to different AB treatment regimens, the authors did not specify how a random sequence was generated. The study was a single-blinded study where only participants were blinded to treatment allocation. Both research personnel and outcome assessors were not blinded to which AB the patient was taking. From both groups, the drop-out percentage was quite similar, and attrition bias risk was low as not more than 20% of participants dropped out from all the groups. The study had a low risk of reporting bias as All outcomes stated in the method section were fully reported. Quality assessment of the included RCT is reported in Table 5.

Table 2. Quality assessment of case-control studies using New-castle Ottawa Scale (NOS)

Auther, year	Is the case definition adequate?	Representative-ness of the cases	Selection of Controls	Definition of Controls	**Selection**	Comparability of cases and controls on the basis of the design or analysis	**Compar-ability**	Ascertain-ment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	**Exposure**	**Score**
Rattanaumpawan, 2015	yes, with independent validation*	consecutive or obviously representative series of cases*	Hospital controls	Susceptible controls *	***	Study controls for any additional factors **	**	Secure record *	Yes*	Same rate for both groups *	***	**8**
Vellinga, 2012	Yes, with independent validation *	consecutive or obviously representative series of cases *	Hospital controls	Susceptible controls *	***	For the outcome of interest, the study does not control for confounders	/	Secure record *	Yes*	Same rate for both groups *	***	**6**
Conway, 2007	Yes, with independent validation *	consecutive or obviously representative series of cases*	Hospital controls	Susceptible controls *	***	Study controls for the most important factor *	*	Secure record *	Yes*	Not described	**	**6**
Colodner, 2008	Yes, with independent validation *	consecutive or obviously representative series of cases *	Hospital controls	Susceptible controls *	***	Not comparable/ no enough adjustment of confounders	/	Secure record *	Yes*	Not described	**	**5**
Hillier, 2007	Yes, with independent validation*	consecutive or obviously representative series of cases*	Hospital controls	Susceptible controls *	***	Study controls for the most important factor *	*	Structured interview *	Yes*	Not described	**	**5**
Metlay, 2003	Yes, with record linkage	consecutive or obviously representative series of cases*	Hospital controls	Susceptible controls *	**	Study controls for the most important factor.*	*	Secure record *	Yes*	Not described	**	**5**

Auther, year	Is the case definition adequate?	Representative-ness of the cases	Selection of Controls	Definition of Controls	Selection	Comparability of cases and controls on the basis of the design or analysis	Comparability	Ascertain ment of exposure	Same method of ascertainme nt for cases and controls	Non-Response rate	Exposure	Score
Killgore, 2004	Yes, with independent validation*	consecutive or obviously representative series of cases*	Hospital controls	Susceptible controls *	***	Study controls for any additional factor ** (	**	Secure record *	Yes*	Not described	**	**7**
van der Starre, 2011	Yes, with independent validation*	consecutive or obviously representative series of cases*	Hospital controls	Susceptible controls *	***	Study controls for any additional factor **	**	Secure record *	Yes*	Not described	**	**7**
Steinke, 2001	yes, with record linkage	consecutive or obviously representative series of cases*	hospital controls	Susceptible controls *	**	Study controls for any additional factor **	**	Secure record *	Yes*	Not described	**	**6**

Table 3. Quality assessment of cohort studies using New-castle Ottawa Scale (NOS)

Author, year	Representa-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Selection	Comparability of cohorts on the basis of the design or analysis	Compara-bility	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Outcome	Score
Brown, 2002	Truly representative of the average in the target population. *	Drawn from the same community as the exposed cohort *	Structured interview*	No	***	Study controls for the most important factor*	*	Independent assessment-unblinded *	yes *	complete follow up - all subjects accounted for *	***	**7**
Duffy, 2013	Truly representative of the average target population *	Drawn from the same community as the exposed cohort *	Secure record *	No	***	Study controls for the most important factor*	*	Record linkage *	yes*	complete follow up - all subjects accounted for *	***	**7**
Kratochwill, 2015	Truly representative of the average target population *	Drawn from the same community as the exposed cohort *	Secure record)*	No	***	Study controls for any additional factors**	**	Record linkage *	yes*	complete follow up - all subjects accounted for *	***	**8**
Wong, 2017	Truly representative of the average target population*	Drawn from the same community as the exposed cohort *	Secure record *	No	***	Study does not control for confounders	/	Independent assessment - unblinded*	yes *	subjects lost to follow up unlikely to introduce bias *	***	**6**

Table 4. Quality assessment of cross-sectional studies using the modified New-castle Ottawa Scale (NOS)

Author, year	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	Selection	The subjects in different outcome groups are comparable	Compara-bility	Assessment of the outcome:	Statistical test	outcome	Score
Hay, 2005	Truly representative of the average in the target population.*	Justified and satisfactory. *	No description	Validated measurement tool. **	****	The study controls for the most important factor *	*	Independent un blinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value. *	**	**7**
Ahmed, 2016	Truly representative of the average in the target population.*	Not justified.	No description.	Validated measurement tool. **	***	The study control for any additional factors. **	**	Independent unblinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	**	**7**
Bryce, 2018	Truly representative of the average in the target population.*	Justified and satisfactory. *	No description	Validated measurement tool. **	****	The study controls for the most important factor *	*	Independent unblind assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	**	**7**
den Heijer, 2012	Selected group	Justified and satisfactory. *	No description	Non-validated measurement tool, but the tool is available or described. *	**	The study controls for the most important factor *	*	Independent unblinded assessment*	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	**	**5**
Donnan, 2004	No description of the sampling strategy.	Not justified.	No description of the.	Validated measurement tool. **	**	The study control for any additional factor. **	**	Record linkage. **	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	***	**7**

Author, year	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	Selection	The subjects in different outcome groups are comparable	Compara-bility	Assessment of the outcome:	Statistical test	outcome	Score
Kornfält Isberg, 2019	Somewhat representative of the average in the target population. *	Justified and satisfactory.*	No description	Non-validated measurement tool, but the tool is available or described. *	***	The study controls for the most important factor *	*	independent unblind assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented*	**	**6**
Plate, 2019	Truly representative of the average in the target population. *	Justified and satisfactory. *	Comparability between respondents and non-respondents' is established/ response rate is satisfactory. *	No description of the measurement tool.	***	The study control for any additional factor. **	**	Independent unblinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented*	**	**7**
Rossignol, 2015	Truly representative of the average in the target population. *	Justified and satisfactory. *	No description	Non-validated measurement tool, but the tool is available or described. *	***	did not control for the most important factors	/	Independent unblinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented*	**	**5**
Smithson, 2012	Truly representative of the average in the target population. *	Justified and satisfactory. *		Validated measurement tool. **	****	The study control for any additional factor. **	**	Independent unblinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented*	**	**8**

Author, year	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure	Selection	The subjects in different outcome groups are comparable	Compara-bility	Assessment of the outcome:	Statistical test	outcome	Score
McIsaac, 2013	Truly representative of the average in the target population. *	Justified and satisfactory. *	The response rate is unsatisfactory/ comparability between respondents and non-respondents is unsatisfactory.	Non-validated measurement tool, but the tool is available or described. *	***	The study does not perform multivariate logistic regression or adjustment for confounders for the variable prior AB exposure	/	Independent unblinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	**	**5**
Colgan, 2008	Truly representative of the average in the target population. *	Not justified.	The response rate is unsatisfactory/ comparability between respondents and non-respondents is unsatisfactory.	Non-validated measurement tool, but the tool is available or described. *	**	The study controls for the most important factor *	*	Independent unblinded assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	**	**5**
Arslan, 2005	Truly representative of the average in the target population. *	Not justified.	No description	Non-validated measurement tool, but the tool is available or described. *	**	The study control for any additional factor. **	**	Independent not blind assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	**	**6**
Dromigny, 2005	Selected group of users	Not justified.	No description	Non-validated measurement tool, but the tool is available or described.*	*	The study control for any additional factor. **	**	Independent not blind assessment. *	The statistical test used to analyze the data is clearly described and appropriate, measurement of the association is presented, including CI and the p value.*	*	**5**

Table 5. Quality assessment of RCTs by Preiksaitis, et al.[80](using Cochrane Collaboration's tool for assessing risk of bias adapted from Higgins and Altman[94]

Domain	Source of bias	Support for judgment	Review authors' judgment
Selection bias	Random sequence generation	Randomization list in the dispensing pharmacy was used to randomize patients however, no details on how the random sequence was generated	Unclear risk of bias
	Allocation concealment	It is a single blinded study, thus only the participants were blinded to treatment allocation	High risk of bias
Performance bias	Blinding of participants and personnel	Only participants were blinded however research personnel were not	High risk of bias
Detection bias	Blinding of outcome assessment	Outcome assessors were not blinded to treatment allocation	High risk of bias
Attrition bias	Incomplete outcome data	For nalidixic acid three-day regimen: two patients dropped out due to side effects of nalidixic acid. Follow-up data at 6 weeks were unavailable for 5 patients. For cephalexin three-day regimen: One patient was lost to follow-up at 2-weeks, 4 patients were lost to follow-up at 6 weeks. For nalidixic acid fourteen-day regimen: Two patients drop out due to adverse effects of cephalexin, 3 patients were lost to follow-up at 6 weeks. For cephalexin fourteen-day regimen: One patient dropped out due to adverse effects of cephalexin, five patients were lost to follow-up at 6 weeks. Attrition does not exceed 20%	Low risk of bias
Reporting bias	Selective reporting	All outcomes stated in the method section were fully reported	Low risk of bias
Other bias	Anything else, ideally prespecified	None	Low risk of bias

4.5 Publication bias assessment

A funnel plot was used to investigate publication bias in studies evaluating the effect of recent AB exposure on subsequent resistant UTI in primary care. Figure 12 shows some evidence of possible publication bias. The larger and stronger studies are placed at the top, however, the effect size from smaller studies is scattered at the bottom of the funnel plot. The funnel plot asymmetry indicates the possibility of publication bias; however, the heterogeneity of our meta-analysis results could explain the funnel plot asymmetry.

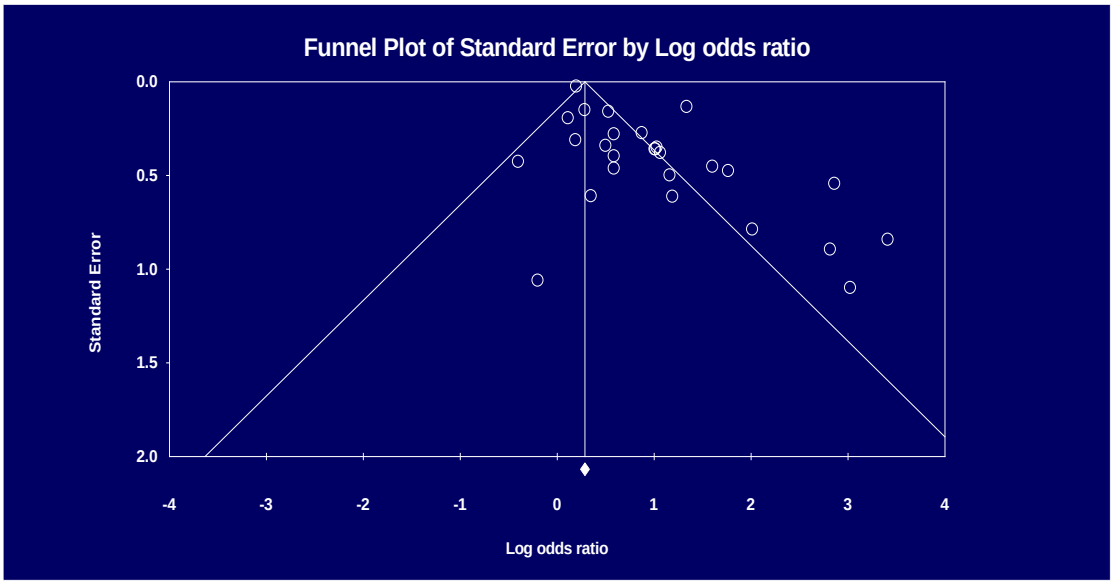


Figure 11. Funnel plot for the studies on the association between recent AB exposure and subsequent resistant UTI

CHAPTER 5: DISCUSSION AND CONCLUSIONS

5.1 Principal findings

This systematic review and meta-analysis systematically reviewed relevant studies from the literature and quantified the individual-level association between prior exposure to ABs and the development of resistant UTI in primary care. It also attempted to investigate the effect of various levels of prior AB exposure, in terms of the number of prior courses of ABs consumed by the patient, the dose of the AB used and, the duration of the course. Findings of the study indicated that the odds that the causative bacteria were resistant to AB treatment increased with the increasing number of ABs courses over the previous year.

It was not possible to pool results related to varying doses of ABs and their impact on resistance. Moreover, it was not possible to generate a pooled effect size that quantifies the relationship between the duration of the recent AB course and resistance, as few studies provided sufficient information from which an association could be estimated. However, the evidence from the two studies included by Hay et al. (75) and Hillier et al. (76) showed that the shorter the previous course and the higher the dose, the lower the odds of resistance.

This meta-analysis was able to identify evidence of higher odds of resistance with recent prescribing time periods over the period of 12 months. Unlike most of the included studies as well as previous the meta-analysis by Costelloe et al., (60) which reported overlapping prescribing times periods, this review – as a consequence of a higher number of included studies – was able to detect resistance in separate shorter time periods. The association was stronger when the period of prior AB exposure was closer to the UTI onset. This is an important finding as exposure as recent as 1 month to 4 months contributed considerably to higher odds of resistance compared to earlier

exposure within 6-12 months' time period. Our results from subgroup analysis showed great variation due to the time of the previous exposure, however, most of the individual studies in the literature looked at the period of 12 or 6 months of recent exposure as a single time period.

Findings from subgroup analyses suggested an association between trimethoprim exposure and quinolone resistance, in line with our findings, previous studies established an association between non-fluoroquinolones exposure and fluoroquinolones resistance(95, 96). Results from secondary analysis of data collected from a case-control study linking susceptibility results of *E. coli* in urine samples to prior exposure to non-fluoroquinolones in the previous year in patients seen at a primary, secondary and tertiary care, found that exposure to TMP/SMX in the year prior to sample collection was significantly associated with fluoroquinolone resistance (95). Another study found that higher purchase of TMP-SMX was associated with resistance to ciprofloxacin which also supports our findings (96). On the other hand, our results showed that trimethoprim/TMP-SMT exposure also increased quinolone resistance which could possibly be explained by resistance genes that code for resistance to both fluoroquinolones and TMP-SMX, such as the genes found in E-coli ST131 isolates which were found to have high resistance to both fluoroquinolones and TMP/SMX in a study performed across the United States (97).

Fluoroquinolones exert their AB action by inhibiting bacterial DNA gyrase enzyme which in turn inhibits DNA synthesis, consequently impeding growth and replication (98). Whereas TMP/SMX inhibits the folic acid pathway leading to purine production which is essential for DNA synthesis (99). Therefore, acquiring resistance to TMP/SMX may facilitate the abundance of purine metabolites and help bacteria compensate or overcome the effect of fluoroquinolones on inhibiting DNA synthesis

pathway. This is in addition to the selective pressure of fluoroquinolones use on arising DNA gyrase mutations that foster AB resistance.

Studies identified were not enough to pool the OR of the association between prior exposure to trimethoprim or quinolones and β-lactams resistance. The study by den Heijer et al. (72) found that prior exposure to TMP-SMX significantly increased resistance to amoxicillin and amoxicillin-clavulanic acid. This is consistent with results from ECO·SENS Project which aimed to determine the antimicrobial susceptibility of bacterial pathogens causing community-acquired UTI in 16 European countries and Canada, which found that in these countries, the main AB associated-resistance profiles involved ampicillin/sulfamethoxazole and ampicillin / sulfamethoxazole / trimethoprim / trimethoprim –sulfamethoxazole (100).

Most of the included studies adjusted for certain possible confounding factors such as age, gender, comorbidities such as diabetes, prior hospitalization and, catheter use, history of UTI, and use of certain medication, however, few studies assessed the impact of the type of UTI whether complicated or uncomplicated on subsequent resistance. In the included study by Plate et al. (56), complicated UTI was associated with higher odds of resistance to quinolones OR 1.79 [95%CI; 0.74, 3.9], when compared to uncomplicated UTI, for the association between 3 months' time frame of prior exposure to ABs and quinolones resistance, adjusted by type of UTI along with other factors, the OR dropped from 1.33 (0.77, 2.21) to 0.51 (0.23, 1.16). The other included study by Arslan et al., (89) assessed the association between complicated UTI and ciprofloxacin resistance, compared to uncomplicated UTI. The OR was estimated as 2.4 [95%CI; 1.54–3.61] adjusting for prior exposure to ciprofloxacin and age above 50. When the association between prior exposure to ciprofloxacin and ciprofloxacin resistance compared to no prior exposure was estimated, the corresponding OR was 2.8

[95%CI1.38–5.47], which suggests that complicated UTI is a contributing factor to resistance. However, most of the studies included in this review did not differentiate between type of UTI when assessing resistance.

This meta-analysis mainly included observational studies, which made it difficult to ascertain that no resistance existed prior to AB exposure. Such bias could have been reduced in prospective studies if baseline resistance data were collected and only incident cases were included. As it seems that none of the prospective studies collected baseline resistant data, it was not clear if only incident cases were reported.

5.2 *Strengths of the study*

To our knowledge, this is the first meta-analysis to provide a pooled estimate of the association between the level of prior AB exposure in terms of the number of previous AB courses used and resistant UTI. Additionally, this is the first meta-analysis that evaluates the association between non-overlapping time frames of prior AB exposure and subsequent AB resistance. Since an adequate number of studies were included, it was possible to investigate the impact of specific time frames of recent AB exposure of 1 month, 2-4 months, 4-6 months, and 6-12 months on resistant UTI.

This review was also able to quantify the association between highly prescribed ABs by general practitioners and resistance developed to specific ABs commonly prescribed for UTI such as TMP/SMX, quinolones, and β-lactams and to support some existing evidence of the possible concurrent/associated resistance patterns.

5.*3 Limitations of the study*

Many of the included studies stated that the prior AB prescriptions were prescribed in primary care and were accessed through databases that keep records of primary care prescriptions. Some studies only recruited general practitioners in specified primary care centers, accessed the prescriptions they prescribed, and linked them to patients'

subsequent UTI resistance status. Furthermore, some of the included studies excluded patients who recently presented to the hospital during the period when prior AB exposure was assessed which ensures that all the prior AB prescribing was done in a primary care setting. However, although in most of the studies it was mentioned that primary care records were accessed for collecting information related to prior AB exposure, it was not clearly stated in some studies whether these records were only limited to primary care prescriptions.

Another limitation is the regional distribution of the included studies. Most of the studies took place in high-income countries such as the US, UK and Netherlands, thus results from this systematic review and meta-analysis cannot be generalized to other countries in different regions.

5.4 Implications for practice

Results from this systematic review and meta-analysis can guide clinicians when prescribing ABs to treat UTI to consider prior ABs exposure, in terms of the number of prior courses, the dose of the previous AB, and the length of the prior courses. Most importantly it informs clinicians on how likely the patient will develop resistance considering the time since their last AB exposure. The type of the AB that the physician would decide to prescribe to the patient can be influenced by which type of AB the patient was recently exposed to. In this meta-analysis, we were able to quantify associations between two different ABs types/classes usually prescribed in the primary care settings. Thus, the results of this study will guide clinicians toward more informed decisions on prescribing for UTI and will emphasize on patient-level association between prior AB exposure and subsequent resistance.

5.5 Concluding remarks

Prior AB exposure is associated with resistance to UTI. The higher the level of exposure

and the closer the exposure to UTI onset, the higher the likelihood of resistance to AB treatment. The effect on resistance is greatest in the month following the AB exposure as well as in 2-4 months following exposure but can persist for up to 12 months also, higher number of courses is associated with a higher likelihood of resistance. Evidence evaluating the effect of dose or duration were limited and were not enough to draw conclusions. Prior exposure to trimethoprim or quinolones was highly associated with resistance to both trimethoprim and quinolones however, the greatest effect was on quinolones resistance upon prior exposure to quinolones. Evaluating the level and time of recent AB exposure can guide clinicians' judgment upon prescribing ABs by estimating the possible risk of resistance and treatment failure. It can also guide AB treatment selection. Future studies can assess the association between different doses and durations of prior AB exposure and resistant UTI in primary healthcare clients, we were able to include very limited number of studies and thus it would be clinically useful to have more studies that assess such associations.

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Appendix A: Search Strategy

PubMed	("Anti-Bacterial Agents"[MeSH Terms] OR "Antibiotic prescribing"[Title/Abstract] OR "Antimicrobial prescribing"[Title/Abstract] OR "antibiotic exposure"[Title/Abstract] OR "antibiotic treatment"[Title/Abstract] OR "antibiotic use"[Title/Abstract] OR "antibiotic prescription"[Title/Abstract] OR "antibiotic prophylaxis"[Title/Abstract]) AND ("drug resistance, microbial"[MeSH Terms] OR "drug resistance, bacterial"[MeSH Terms] OR "antibiotic resistant"[Title/Abstract] OR "antibiotic resistance"[Title/Abstract] OR "antimicrobial resistant"[Title/Abstract] OR "antimicrobial resistance"[Title/Abstract] OR "drug resistant"[Title/Abstract] OR "drug resistance"[Title/Abstract] OR "multidrug resistant"[Title/Abstract] OR "multidrug resistance"[Title/Abstract] OR "resistant bacteria"[Title/Abstract] OR "bacterial resistant"[Title/Abstract] OR "bacterial resistance"[Title/Abstract]) AND ("physicians, primary care"[MeSH Terms] OR "Primary Health Care"[MeSH Terms] OR "ambulatory care"[MeSH Terms] OR "Family Practice"[MeSH Terms] OR "primary care"[Title/Abstract] OR "primary-healthcare"[Title/Abstract] OR "ambulatory care"[Title/Abstract] OR "Family Practice"[Title/Abstract] OR "general practice"[Title/Abstract]) AND ("urinary tract infections"[MeSH Terms] OR "Bacteriuria"[MeSH Terms] OR "Pyuria"[MeSH Terms] OR "urinary tract infection"[Title/Abstract] OR "UTI"[Title/Abstract] OR "cystitis"[Title/Abstract] OR "pyelonephritis"[Title/Abstract] OR "Bacteriuria"[Title/Abstract] OR "Pyuria"[Title/Abstract] OR "urinary pathogen"[Title/Abstract] OR "uropathogen"[Title/Abstract])
Embase	('antibiotic resistance'/exp OR 'antibiotic resistance' OR 'multidrug resistance'/exp OR 'multidrug resistance') AND ('antibiotic prescribing' OR 'antimicrobial prescribing':ti,ab OR prescribing:ti,ab OR 'antibiotic use':ti,ab OR 'antibiotic treatment':ti,ab OR 'antibiotic exposure':ti,ab OR 'antibiotic prescription' OR 'antibiotic prophylaxis'/exp OR 'antibiotic prophylaxis') AND ('antibiotic resistance'/exp OR 'antibiotic resistance' OR 'antimicrobial resistance'/exp OR 'antimicrobial resistance' OR 'antibiotic resistant' OR 'antimicrobial resistant' OR 'drug resistant') AND ('primary medical care'/exp OR 'primary medical care' OR 'ambulatory care'/exp OR 'ambulatory care' OR 'primary health care':ti,ab OR 'familay practice':ti,ab OR 'general practice':ti,ab) AND ('urinary tract infection'/exp OR 'urinary tract infection' OR uti:ti,ab OR cystitis:ti,ab OR pyelonephritis:ti,ab OR bacteriuria:ti,ab OR pyuria:ti,ab OR 'urinary pathogen'/exp OR 'urinary pathogen' OR 'uropathogen'/exp OR uropathogen)
ProQuest	ab("antibiotic prescribing" OR "antimicrobial prescribing" OR "antibiotic exposure" OR "antibiotic treatment" OR "antibiotic use" OR "antibiotic prescription" OR "antibiotic prophylaxis") AND ("antibiotic resistance" OR "antimicrobial resistance" OR "antibiotic resistant" OR "antimicrobial resistant" OR "drug resistant" OR "drug resistance" OR "multidug resistant" OR "multidrug resistance" OR "resistant bacteria" OR "bacterial resistant" OR "bacterial resistance")AND ("primary care" OR "primary-healthcare" OR "ambulatory care" OR "family

	practice" OR "general practice") AND ("urinary tract infection" OR UTI OR cystitis OR pyelonephritis OR Bacteriuria OR Pyuria OR "urinary pathogen" OR uropathogen)
Scopus	('antibiotic resistance'/de OR 'multidrug resistance'/de OR 'antibiotic resistance':ti,ab OR 'antimicrobial resistance':ti,ab OR 'antibiotic resistant':ti,ab OR 'antimicrobial resistant':ti,ab OR 'drug resistant':ti,ab OR 'drug resistance':ti,ab OR 'multidrug resistance':ti,ab OR 'multidrug resistant':ti,ab) AND ('antibiotic prescribing':ti,ab OR 'antimicrobial prescribing':ti,ab OR 'antibiotic use':ti,ab OR 'antibiotic treatment':ti,ab OR 'antibiotic exposure':ti,ab OR 'antibiotic prescription' OR 'antibiotic prophylaxis') AND ('primary medical care'/de OR 'ambulatory care'/de OR 'primary health care':ti,ab OR 'familay practice':ti,ab OR 'general practice':ti,ab OR 'primary heath-care':ti,ab) AND ('urinary tract infection'/de OR 'urinary tract infection':ti,ab OR uti:ti,ab OR cystitis:ti,ab OR pyelonephritis:ti,ab OR bacteriuria:ti,ab OR pyuria:ti,ab OR 'urinary pathogen':ti,ab OR uropathogen:ti,ab)

Appendix B. Quality assessment tools

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✵
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✵
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✵
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✵
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview where blind to case/control status ✵
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✵
   b) no

3) Non-Response rate
   a) same rate for both groups ✵
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✵
   b) somewhat representative of the average _____ in the community ✵
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview ✵
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✵
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✵
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✵
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✵
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection: (Maximum 5 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (non-random sampling)

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. *

b) Not justified.

3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

a) Validated measurement tool. **

b) Non-validated measurement tool, but the tool is available or described.*

c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (select one). *

b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. **

c) Self report. *

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

Cochrane Collaboration's tool for assessing risk of bias (adapted from Higgins and Altman)

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere