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Title:

Antibiotics versus no treatment for asymptomatic bacteriuria in aged care residents: a systematic review and meta-analysis

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Abstract

Background: Asymptomatic bacteriuria (ASB) is common amongst residents of residential aged care facilities (RACFs). However, differentiating between an established urinary tract infection and ASB in older adults is difficult. As a result, the overuse of dipstick urinalysis, as well as the subsequent initiation of antibiotics, is common in RACFs.

Aim: To find, appraise and synthesize studies that reported the effectiveness, harms and adverse events associated with antibiotics treatment for elderly patients with ASB residing in RACFs.

Design and setting: A systematic review, using standard Cochrane methods of RACF residents with asymptomatic bacteriuria using antibiotics against placebo, or no treatment.

Method: We searched three electronic databases (PubMed, Embase, CENTRAL), clinical trial registries and citing-cited references of included studies.

Results: Nine randomised controlled trials, comprising 1,391 participants were included; 2 of which used a placebo comparator, and the remaining 7 used no therapy control groups. There was a relatively small number of studies assessed per outcome and an overall moderate risk of bias. Outcomes related to mortality, development of ASB, and complications were comparable between the two groups. Antibiotic therapy was associated with a higher number of adverse effects (4 studies; 317 participants; Relative Risk (RR)=5.62, 95% CI: 1.07-29.55, p=0.04) and bacteriological cure (9 studies; 888 participants; RR=1.89, 95% CI: 1.08-3.32, p<0.001).

Conclusion: Overall, whilst the antibiotic treatment was associated with bacteriological cure, it was also associated with significantly more adverse effects. The harms and lack of clinical benefit of antibiotic use for older patients in RACFs may outweigh its benefits.

Key words: Antibiotics; residential aged care facilities; asymptomatic bacteriuria

How this fits in

Asymptomatic bacteria (ASB) are often treated with antibiotics, contributing to the global burden of antibiotic resistance. Current evidence suggests no clinical benefit in treating ASB, with no significant differences between antiobiotic therapy and no therapy in the development of symptomatic UTI, complications or death. However, it is not clear if the results would be applicable to residential aged care facilities (RACFs) residents. We found out that whilst antibiotic therapy was associated with bacteriological cure, it was also associated with significantly more adverse effects. The harms and lack of clinical benefit of antibiotic use for older patients in RACFs may outweigh its benefits.

Introduction

The high use and misuse of antibiotics within residential aged care facilities (RACFs), is well recognised as a significant concern within healthcare systems.[1] The non-specific symptoms associated with infection in the older patient population, as well as the fear for patient deterioration, often leads to the initiation of early antibiotic therapy as a safety net.[2,3] In Australian RACFs, recurring antibiotic use issues have been consistently identified since 2016.[4] These issues include: high rates of antibiotic use for residents who do not meet the criteria for infection, use of antibiotics prophylactically for urinary tract infections (UTIs) and for a duration lasting longer than 6 months, high use of broad-spectrum antibiotics, no adherence to national guidelines recommendations and poor quality of documentation around antibiotic prescriptions.[4]

Asymptomatic bacteriuria (ASB) in particular is common amongst residents of RACFs, with estimated prevalence rates in women of 25-50% and 15-40% in men.[5-7] High rates of urinary retention, urinary incontinence, frailty, increased use of invasive devices, immobility, comorbidities and decreased immunity as well increased exposure to organisms (resident-resident, resident-visitor and resident-carer contact) increase potential infection risk among residents.[2] Differentiating between an established urinary tract infection and ASB in older adults is difficult.[8,9] Patients with chronic symptoms or cognitive impairments are often unable to recognise or communicate the symptoms of a UTI and coupled with non-specific presentation of symptoms renders this condition particularly challenging for clinicians to diagnose.[8,10] As a result, despite poor quality evidence supporting the use of dipstick tests in patients >65 years of age, these are commonly overused in RACFs and lead to the subsequent initiation of antibiotics. [11]

A Cochrane systematic review evaluated the evidence of the safety and effectiveness of antibiotics prescribed for ASB in the adult population (patients over 18) and in any healthcare setting.[12] The authors found no clinical benefit in treating ASB, with no significant differences between antibiotic therapy and no therapy in the development of symptomatic UTI, complications or death. However, antibiotics were associated with significantly more adverse events and it is not clear if the results would be applicable to RACF residents[12], thus highlighting the need for the present review which specifically focuses on older adults in long-term care facilities.

Elderly patients are at particular risk of adverse drug reactions due to polypharmacy as well as changes in organ sensitivity and pharmacokinetics.[13] Systematic reviews of antibiotic-associated harms are generally unavailable for older patients in long-term care facilities, however different studies have reported on antibiotic-associated harms for this population.[14-16]

This systematic review focuses on assessing the effectiveness and harms of antibiotics treatment versus no antibiotics for residents of RACFs with ASB.

Method

We aimed to find, appraise and synthesise studies that reported the effectiveness, harms and adverse events associated with antibiotics treatment for elderly patients with asymptomatic bacteriuria residing in residential aged care facilities (RACF). The protocol for this systematic review was prospectively developed and registered at the Center for Open Science on the 3rd of December 2021 (Link: https://osf.io/f8uka/). This systematic review followed the 2-week systematic review process [17] and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (PRISMA 2020).[18]

Inclusion and exclusion criteria

Study designs

We included randomised and non-randomised controlled trials, and observational studies with a comparator group (cohort or case control studies). We excluded case reports, case series, letters to the editor, before and after, interrupted time series, and cross-sectional design studies as well as qualitative studies, and reviews (systematic, literature, narrative, meta-analyses, etc.)

Population/Participants

Studies were included if their populations of interest comprised individuals residing in residential aged care facilities, who were diagnosed with an asymptomatic bacteriuria or bacteriuria. However, studies involving hospitalised older patients or those residing in their own homes or were attending GP or community health clinics were excluded.

Interventions

Therapeutic or prophylactic antibiotic treatment of any type, dose, duration, or administered by any route of delivery (i.e. oral, topical, intravenous and intramuscular). The use of concomitant medications was permitted, if also given to the comparator group.

Comparators

We included studies with a comparator involving placebo, no prescribing, delayed prescribing or withheld prescribing of antibiotics.

Outcomes (primary, secondary)

The primary outcomes were: development of symptomatic UTI, any cause of mortality, and adverse effects of antibiotic use. Secondary outcomes included antibiotic resistance, disease complications, and bacteriological cure or recurrence.

Information sources and search strategy

Electronic databases, including PubMed (MEDLINE), Embase, and CENTRAL via the Cochrane Library were searched for potentially relevant primary studies from inception until November 2021. The search string was designed in PubMed, and translated for use in other databases using the Polyglot Search Translator.[17,19]

The following components were included in the search string: MeSH terms (i.e. anti-infective agents, infections, homes for the aged, adverse effects) or other subject terms, synonyms and search filters. Searches strings were constructed and run by a Cochrane information specialist. The complete list of search strings for all databases are provided in Supplementary Box 1.

In addition, a backwards and forwards citation search of the included studies was undertaken using Scopus on all of the included studies identified in the database searches, to identify any further relevant studies.

Ongoing trials in clinical registries were searched for via Cochrane CENTRAL, which contains the WHO International Clinical Trials Registry Platform (ICTRP) and clinicaltrials.gov.

No restrictions by language or publication date were imposed. We included publications that were published in full; publications available as abstract only (e.g. conference abstract) were included only if they had a clinical trial registry record, or other public report, with the additional information required for inclusion. We excluded publications available as abstract only (e.g. conference abstract) with no additional information available.

Screening and Data extraction

Two pairs of review authors (NK and MB or CF and AMS) independently screened the title and abstract of every record retrieved against the inclusion criteria to determine which studies should be assessed further. Screening was conducted using the *Screenatron* feature of the Systematic Review Accelerator [17,19]. One author (NK) retrieved full-text and two pairs of review authors (NK and MB or CF and AMS) screened the full-texts for inclusion. Disputes were identified using the *Disputatron* feature of the Systematic Review Accelerator and were resolved by discussion or by consulting a third author (AMS or MB).[17] A PRISMA flow diagram outlining the selection process (Figure 1) as well as a list of excluded full-text articles and the corresponding reasons for exclusion are provided (Supplementary Table 2).
For studies that fulfilled the inclusion criteria, three review authors (NK and CF or MB) independently extracted key information on participant and intervention characteristics as well as outcomes using standard data extraction templates. The form was piloted on 2 studies. Any disagreement was resolved by discussion, or if required, by a third author. Three data extraction forms were used to collect relevant information including: Table of Characteristics form, Primary and Secondary Outcomes data form, and Risk of Bias form. (see Box 1).

Box 1. List of extracted information

- Study characteristics: country, study design, setting, duration
- Participants: sample size, age, gender, co-morbidities, recent hospitalisation, recent antibiotic use, indwelling catheter
- Intervention: type of antibiotic (name and class), dose, frequency, route of administration, duration
- Comparator: placebo or no treatment
- Primary and secondary outcomes: development of symptomatic UTI, any cause mortality, adverse effects of antibiotic use, antibiotic resistance, disease complications, and bacteriological cure or recurrence. We extracted data from cohort studies on reasons for bacteriuria testing (e.g., policy recommendation), when applicable.

Risk of bias assessment

Three review authors (NK, MB and CF) independently assessed the risk of bias for each included RCT using the Cochrane Risk of Bias 1.0 tool.[20] Tool 1.0 was used in preference to Tool 2.0 as the former allows the assessment of biases from conflict of interest and funding (under the 'other sources of bias' domain), whilst the latter does not. The following domains were assessed using the Cochrane tool:

1. Random sequence generation
2. Allocation concealment

3. Blinding (participants and personnel)
4. Blinding (outcome assessment)
5. Incomplete outcome data
6. Selective reporting
7. Other sources of bias

Each potential source of bias was graded as low, high or unclear, and each judgement was supported by a quote from the relevant study.

Two review authors (NK, MB) independently assessed the risk of bias for observational studies using ROBINS-I.[21] The following domains were assessed using the ROBINS-I tool:

1. Bias due to confounding
2. Bias in selection of participants in the study
3. Bias in classification of interventions
4. Bias due to deviations from intended interventions
5. Bias due to missing data
6. Bias in measurement of outcomes
7. Bias in selection of the reported result

Any disagreements were resolved by discussion or by referring to a third author (AMS).

Data synthesis

Review Manager 5.4 was used to calculate the effect of interventions.[22] A meta-analysis was conducted where data were sufficient to pool (i.e. 2 or more trials reporting on the same outcome). For dichotomous outcomes, risk ratios were calculated together with 95% confidence intervals. We used a random effects model, in anticipation of considerable heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic.

The individual was used as the unit of analysis, where possible. However, where data on the number of individuals with primary and secondary outcomes of interest were not available, we extracted the information as it was presented (for example, mean scores for the differences between groups). We did not contact investigators or study sponsors to provide missing data.

A funnel plot was not created, as fewer than 10 studies were included in the analysis. Sub-group analyses were conducted according to duration of follow-up.

As none of the included studies were graded at 'high' risk of bias in three or more domains, a pre-specified sensitivity analysis assessing the impact of excluding trials rated at high risk of bias for 3 or more domains, was not conducted.

Results

Search results

The electronic search retrieved 284 references, supplemented with 1,379 references from forward and backward citations of the included studies and 8 records identified from the clinical trial registry search, resulting in 1,520 records to screen after deduplication. Screening these on title and abstract excluded 1,477 references, leaving 43 articles for which we obtained full-text. Screening of these full texts excluded another 34 which left nine RCTs for inclusion in this systematic review (see figure 1).

Reasons for exclusions are reported in Supplementary Table 2. All clinical trials that were excluded are listed in Supplementary Table 3. Our search did not identify any relevant cohort studies.

Study Characteristics

Characteristics of the nine included studies are presented in Table 1. Four trials were conducted in Greece [23-26], three in the USA [27-29] and two in Canada [30,31]. Antibiotic therapies varied across trials, and included: Norfloxacin, Ofloxacin, Tobramycin, Netilmicin, Trimethoprim+/-Sulfamethoxazole, Cotrimoxazole, Ceforanide and Cefaclor. One study did not specify what antibiotic therapy was used.[27] Two trials used a placebo comparator [27,28], with the remaining seven comparing against no therapy control groups. None of the identified studies investigated delayed antibiotics as a comparator arm.

[Insert Figure 1 here]

[Insert Table 1 here]

Risk of bias assessment

Risk of bias was generally unclear or high for random sequence generation, due to poor reporting of randomisation procedure or non-randomisation in the included trials (2 of the included studies were non-randomised controlled trials), and similarly for allocation concealment. Two studies were rated at low risk of bias from blinding of participants and personnel, as well as outcome assessment; the remainder were rated either unclear (3 studies) or high risk of bias (4 studies) due to the non-reporting or absence of blinding. Risk of bias due to attrition was low for most of the included studies, and risk of bias due to selective reporting was low for all studies. The potential for other bias (arising from funding and conflict of interest issues) was mostly unclear, due to the absence of conflict of interest and/or funding statements. (Supplementary Figure 4 and 5)

Primary outcome: Development of UTI symptoms

4 studies (317 participants in aggregate) reported on the number of individuals who developed a UTI. There was no difference between the antibiotic group and the comparator group (no antibiotic) (RR 1.18, 95% CI: 0.45 to 3.07, p=0.73). The high heterogeneity (I^2=67%) may be explained by a variety of methods used to report the outcome (e.g., self- vs investigator-administered forms). (Figure 3)

[Insert Figure 2 here]

Primary outcome: Adverse events

4 studies (303 participants in aggregate) reported on the number of participants experiencing adverse events, with two studies reporting no adverse events in either the antibiotic or the no-antibiotic group. Significantly more participants receiving antibiotics experienced adverse events (RR 5.62, 95% CI: 1.07 to 29.55, p=0.04), with no heterogeneity (I^2=0%). (Figure 3)

Only Nicolle 1987 reported a breakdown of the types of adverse events experienced by participants. For the antibiotic group, these included: diarrhoea, rash, candidiasis and swollen mouth. The corresponding comparator group (no therapy) reported only one side effect of dizziness.[31]

[Insert Figure 3 here]

Primary outcome: Mortality

7 studies reported on participant mortality at a variety of time-points up to 9 years. 3 studies (310 participants) reported on mortality at 6 months, with no differences between the antibiotic and comparator group (RR 0.53, 95% CI: 0.16 to 1.71, p=0.29, I^2=0%). There were also no differences between groups at 1-3 years (RR 1.10, 95% CI: 0.74 to 1.66, p=0.63, I^2=0%) or at 5-9 years (RR 0.93, 95% CI: 0.74 to 1.18, p=0.55, I^2=0%). (Figure 4)

[Insert Figure 4 here]

Secondary outcome: Complications

Two studies (81 participants) reported on complications, which included, for example, epididymo-orchitis and bacteraemia. There was no difference between groups in the number of participants experiencing complications (RR 1.89, 95% CI: 0.77 to 4.63, p=0.16, I^2=0%). (Supplementary Figure 6)

Secondary outcome: Antibiotic resistance

Antibiotic resistance was rarely reported among the included studies, with only four studies reporting resistance of bacteria causing the infection. [23,24,30,31] This precluded a meta-analysis. In one trial [24], authors reported that two-thirds of the positive urine cultures during 3 years of follow-up were resistant to ofloxacin; however, they did not report the between group difference. In another trial [23], more than 50% of the positive urine cultures were new bacteria resistant to ofloxacin, irrespective of antibiotic exposure arm. In the third trial [30], authors report superinfections caused by resistant organisms, however it is not reported which organism, and the authors did not report the between group differences. In the fourth trial [31], authors reported one resident in the no therapy group with relapse/persistent infection compared to nine reported in therapy group; however, no additional data or explanations were provided to explain the difference (Supplementary Table 7).

Secondary outcome: Bacteriological cure

9 studies (888 participants in aggregate) reported on the number of participants who experienced bacteriological cure. Significantly more participants in the antibiotic group than in the comparator groups experienced bacteriological cure (RR 1.89, 95% CI: 1.08 to 3.32, p<0.001), however, the heterogeneity was very high (I^2 = 81%) (Figure 5). The high heterogeneity could be explained by the different types of antibiotic treatment, doses and duration.

[Insert Figure 5 here]

Discussion

Summary

This systematic review of nine eligible RCTs (total of 1,391 participants) suggests that antibiotic therapy compared to placebo/no therapy for older patients in RACFs was significantly more effective at achieving bacteriological cure, irrespective of developing a UTI. However, antibiotic therapy was also associated with a higher number of adverse effects, which is consistent with the findings of other reviews.[32,33] Outcomes related to mortality, development of symptomatic bacteriuria, and complications were comparable between the two groups. This suggests that for older patients in RACFs, the harms of antibiotic therapy for ASB may outweigh the benefits. However, these findings are based on a small number of trials and risk of bias was unclear for the majority of the domains with low quality reporting of randomisation, allocation concealment and blinding of participants, personnel and outcome assessors. When considering these factors in addition to the age of studies and the significant clinical and statistical heterogeneity, these findings should be interpreted with caution.

Strengths and limitations

The strengths of this review lie in the search strategy, which was comprehensive, and comprised searches of: three databases, trial registries, forward and backward citation searches.

The review is also subject to some limitations. First, due to the strict inclusion/exclusion criteria the review only included a small number of RCTs with relatively small sample sizes. Studies were limited to nursing home settings, and as such this excluded a number of trials which were based in the community (GP clinic) or hospital setting, but included participants who were based in an RACF. There was high heterogeneity across the included studies. Furthermore, there are a number of confounding variables which may affect the generalisability of results. Older patients in RACFs experience many different comorbidities, have in-dwelling catheters and it is difficult to solely attribute adverse effects and mortality to antibiotic usage in this population. Furthermore, there was a lack of detail in each of the included studies outlining the diagnostic criteria used to assess ASB. This lack of information precluded comparison between studies and any conclusions being formed on the impact of diagnostic criteria differences on the results.

Comparison with existing literature

The findings of our review align with a Cochrane review investigating the use of antibiotics for ASB in the general adult population, across all care settings.[12] The review showed that there were no observed differences between antibiotics and no treatment for death, complications or the development of symptomatic UTI.[12] Similarly, antibiotics were superior to no treatment for bacteriological cure and were also associated with more adverse events. The present review focuses specifically on RACF residents and includes three additional trials. Moreover, we expanded our search to include observational studies and non-randomised trials with a control arm.

In the context of cohort studies, a recently published retrospective cohort study, which explored antibiotic management in elderly patients from a general practice setting diagnosed with UTI, [34] found that compared to antibiotic therapy, deferred or no antibiotic treatment was associated with significant increases in bloodstream infection and all-cause mortality, and as such the authors recommended first-line antibiotics for UTI in the older population.[34] However, it must be noted that this study assessed outcomes in a slightly different cohort of patients to the present review, as they excluded patients with asymptomatic bacteriuria and focussed on those with a clinical UTI diagnosis.

Furthermore, the study had limitations common to observation studies using health record data, and potential biases or coding inconsistencies.

In another matched cohort study focused on the prevention of UTI compared older adults (≥66 years) receiving antibiotic prophylaxis with patients who did not receive prophylaxis had similar findings to this review.[35] Authors found that the long-term antibiotic prophylaxis was associated with higher acquisition of antibiotic resistance to any urinary antibiotic and any agent used for prophylaxis, increased risk of hospitalisation or emergency department visit due to UTI, sepsis or bloodstream infection compared to the control group.[35]

Implications for research and practice

There is a need for further trials to determine the safety, effectiveness and appropriateness of antibiotic therapy in older patients in RACFs for infections requiring antibiotic treatment. In our review, we identified only 9 studies with fewer than 50% of the included studies reporting on 3 of the 5 usual outcomes that would need to be typically reported for this setting, age, and reported condition. This is beside the generally high or unclear risk of bias for the included studies. Future trials should aim to recruit larger sample sizes and have clearly defined outcome criteria defining treatment failure. There is also a significant gap in knowledge relating to adverse events and antibiotic resistance data specifically in the older patient population. This could be improved but the use of standardised tools for reporting harms outcomes such as CONSORT harms checklist and by the adoption of checklists specific to reporting antibiotic resistance, such as the checklist developed by several authors of the present study.[36,37]

Overall, based on nine RCTs, whilst antibiotic therapy was associated with bacteriological cure, it was also associated with significantly more adverse effects. The harms and lack of clinical benefit of antibiotic use for older patients in RACFs may outweigh its benefits. To provide a better indication of the effectiveness and safety of antibiotics in RACF-based patients, further primary studies are warranted.

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Ethical approval

Not applicable.

Competing interests

All authors declare no competing interests.

Author Contributions

N.K., M.B., A.M.S. and C.D.M. drafted the protocol. J.C. designed the search strategy and performed the literature search. N.K., M.B., A.M.S and C.F. undertook the screening. N.K., M.B., and C.F. carried out the data extraction and quality assessment. A.M.S., N.K. and M.B. created the figures and prepared the supplementary materials. N.K., M.B., A.M.S., and C.D.M. drafted the original manuscript. All authors revised and approved the final manuscript.

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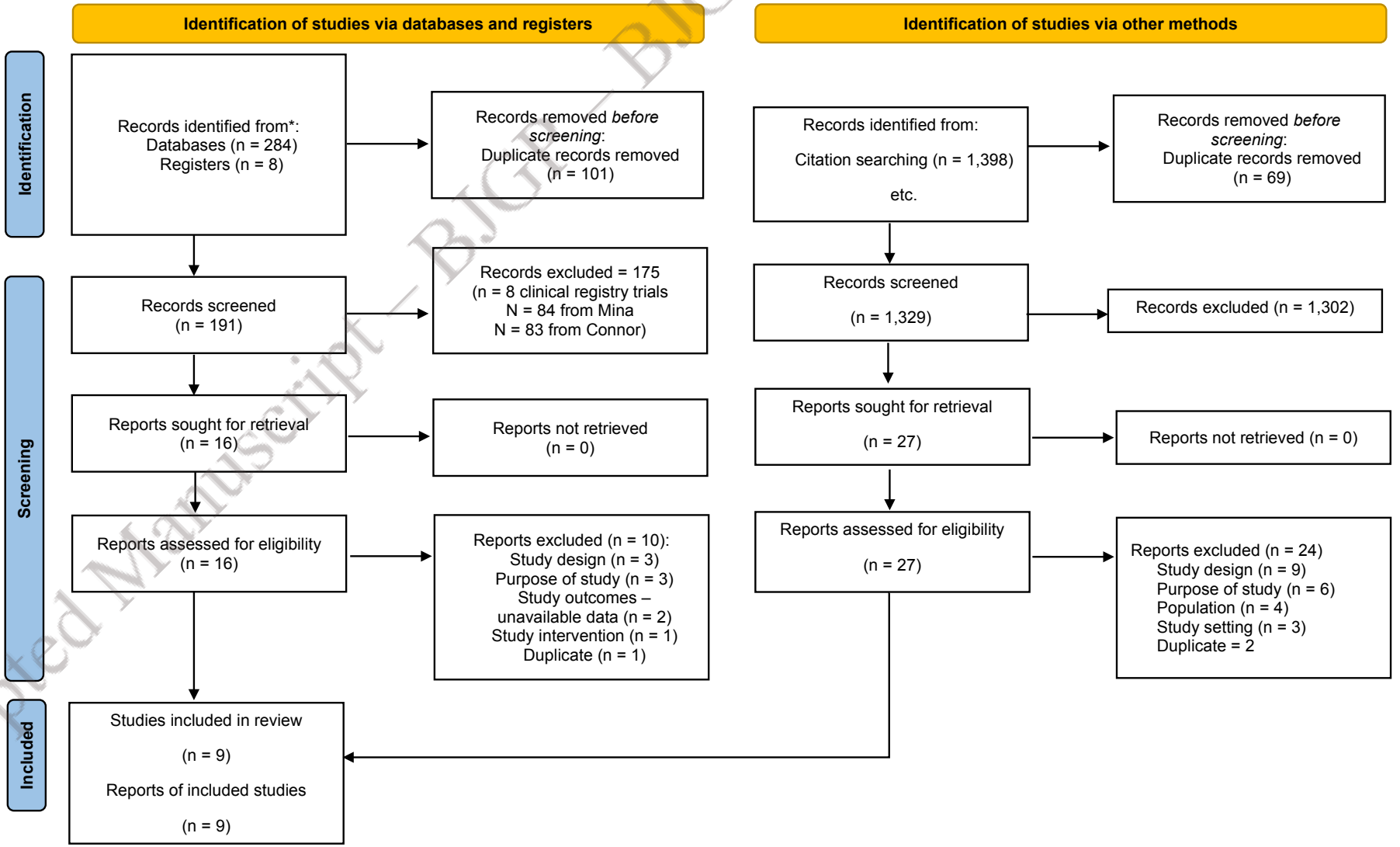
Table 1. Characteristics of included studies

Author (Year, Location)	RCT design	Follow up	No randomised	Age years mean (SD)	Intervention	Pharmacotherapy regimen	Comparator: modality & dose
Abrutyn et.al. (1994, USA)[28]	Parallel quasi-RCT	9 years	358	I: 81.8[1] C: 82	Trimethoprim (O)[2] Norfloxacin (O)	200mg bd for 14 days[3] 400mg bd for 14 days	Placebo, 1 tab bd for 14 days
Abrutyn et.al. (1996, USA)[27]	Parallel quasi-RCT	9 years	358	I: 82 C: 81	Not specified	Not specified	Placebo, 1 tab bd for 14 days
Boscia et.al. (1987, USA)[29]	RCT	2 years	124	I: 85.8 (0.9) C: 85.8 (0.7)	Initial therapy: Trimethoprim or Cefaclor (O) Re-treatment: Trimethoprim or Cefaclor (O)	200mg (T) as a single dose 500mg (C) tds for 3 days 200mg (T) bd for 14 days 500mg (C) tds for 14 days	No therapy
Giamarellou et.al. (1998, GREECE)[23]	Open-label RCT	1 year	136	I1: 84.5 (6.1) I2: 82.8 (5.2) C: 82.9 (6.1)	Ofloxacin (O)	Intervention 1: 200mg bd for 3 days then daily for 12 weeks Intervention 2: 200mg bd for 3 days, fortnightly for 12 weeks.	No therapy
Giamarellou et.al. (2007, GREECE)[24]	Open-label RCT	3 months	132	I1: 84.5 (6.1) I2: 82.8 (5.2) C: 82.9 (6.1)	Ofloxacin (O)	Intervention 1: 200mg bd for 3 days then daily for 12 weeks Intervention 2: 200mg bd for 3 days, fortnightly for 12 weeks.	No therapy
Nicolle et.al. (1983, CANADA)[30]	RCT	2 years	36	I: 80.4 (12.1) C: 80.7 (9.6)	Trimethoprim/Sulfamethoxazole (O) or Tobramycin (IV)	T/S: 160mg/800mg for 2 weeks T (IM): 1.5mg/kg tds for 2 weeks	No therapy
Nicolle et.al. (1987, CANADA)[31]	RCT	1 year	52	I: 83.3 (8.7) C: 83.6 (9)	Trimethoprim/Sulfamethoxazole (O) or Tobramycin (IV)	Not specified	No therapy
Staszewska-Pistoni et.al. (1994, GREECE)[25]	RCT	5 years	102	I: 82.7 C: 82.6	Netilmicine (IM) Cotrimoxazole (IM) Ceforanide (IM)	N: 150mg d for 10 days Cotrimoxazole: 160/800mg d for 10 days Ceforanide: 1g d for 10 days	No therapy
Staszeweska-Pistoni (1995, GREECE)[26]	RCT	3 months	93	I1: 84.5 I2: 82.8 C: 82.8	Ofloxacin (O)	200mg bd for 3 days, then Intervention 1: d for 87 days Intervention 2: 3 days every fortnight for 3 months	No therapy

1. I = Intervention, C = Control
2. O = Oral, IM = Intramuscular, IV = Intravenous
3. D = Daily, BD = Twice a day, TDS = Three times a day

Figure 1. PRISMA Flowchart



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

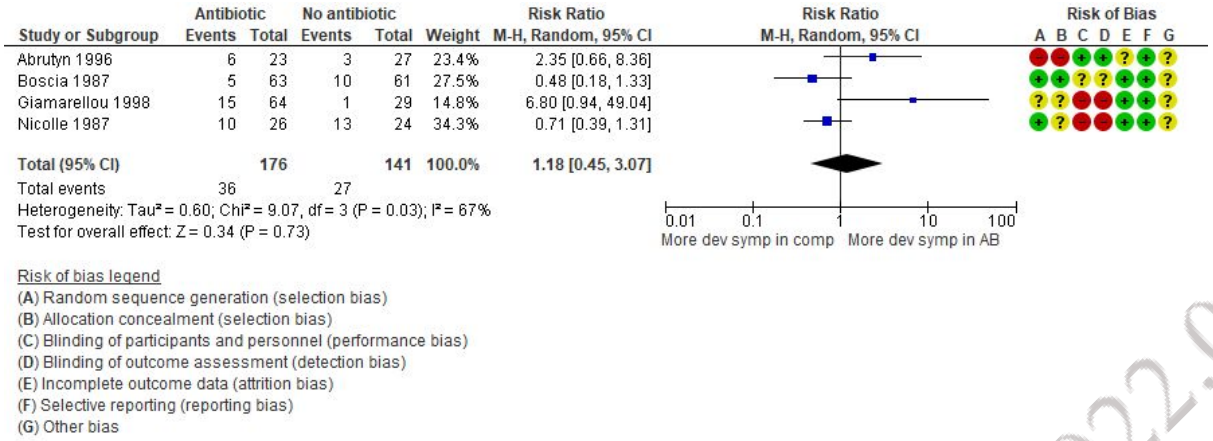


Figure 2. Proportion of participants who developed UTI symptoms

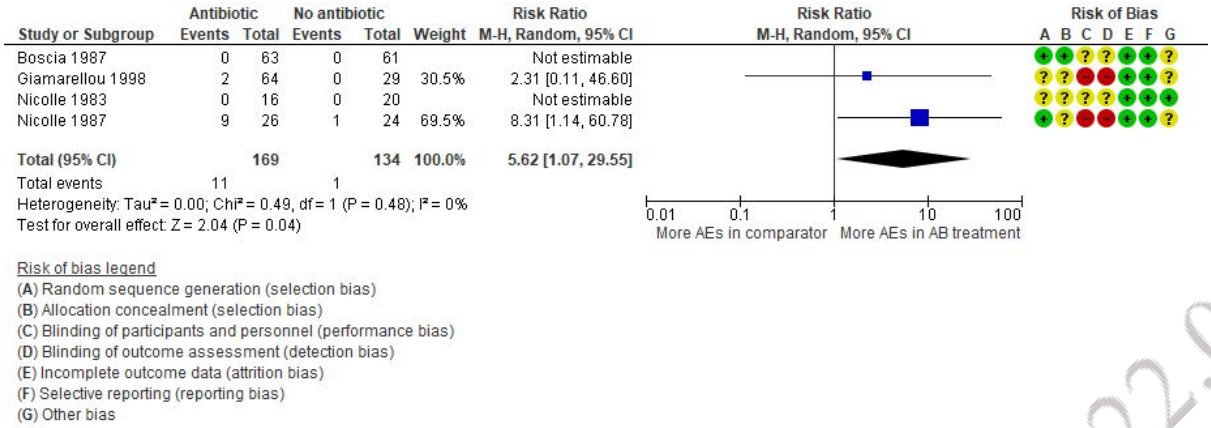


Figure 3. Proportion of participants experiencing adverse events

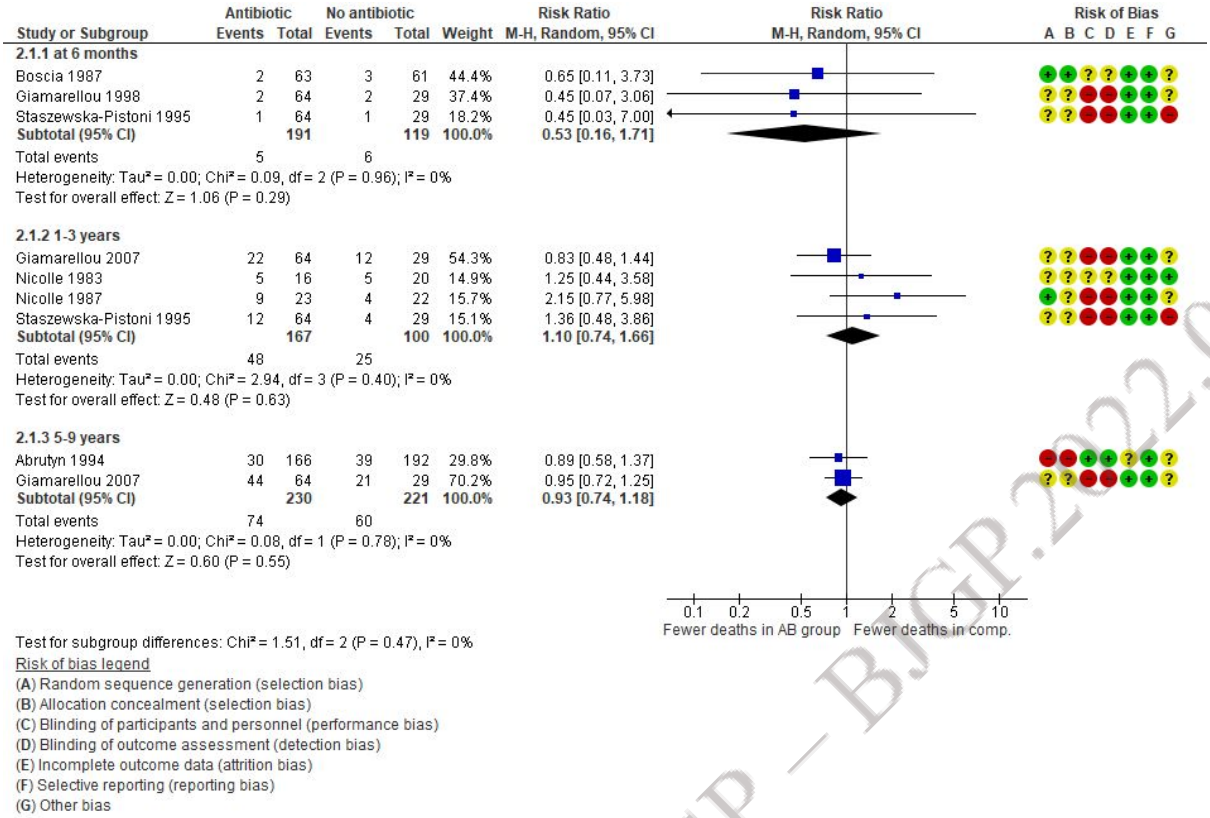


Figure 4. Proportion of participants who died

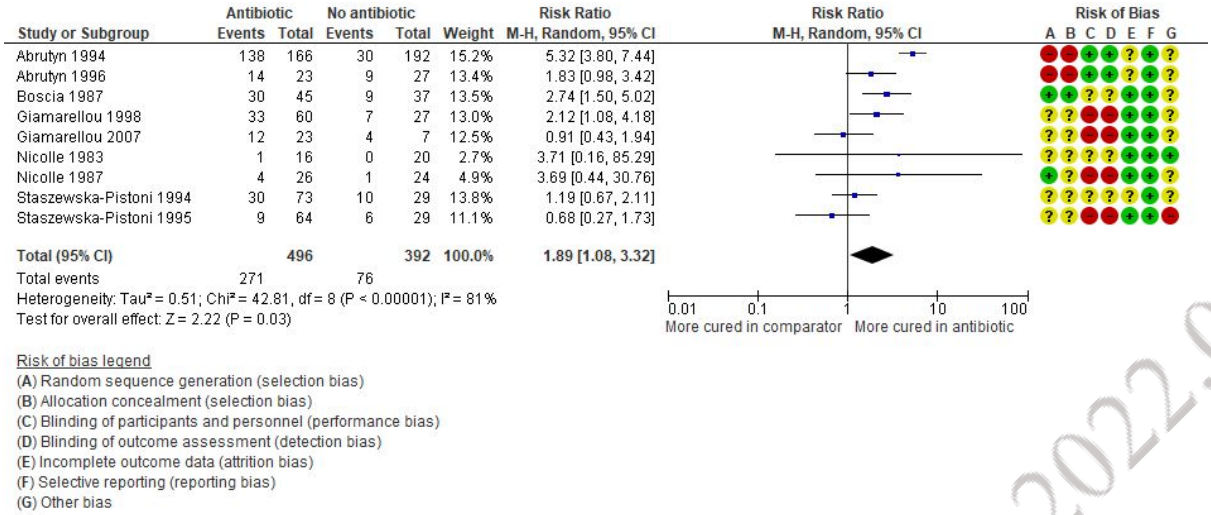


Figure 5. Proportion of participants with bacteriological cure