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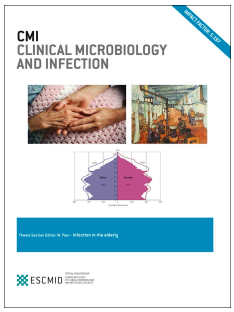

Estimating daily antibiotic harms: an umbrella review with individual study meta-analysis

Jennifer Curran, BSc., PharmD, Jennifer Lo, BScPhm, PharmD, Valerie Leung, BScPhm, MBA, Kevin Brown, MSc, PhD, Kevin L. Schwartz, MD, MSc, Nick Daneman, MD, MSc, Gary Garber, MD, Julie HC. Wu, MSc, Bradley J. Langford, BScPhm, PharmD

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AUTHORS

1. Jennifer Curran, BSc., PharmD[1]
2. Jennifer Lo, BScPhm, PharmD[2]
3. Valerie Leung, BScPhm, MBA[3,4]
4. Kevin Brown, MSc, PhD[3,5]
5. Kevin L. Schwartz, MD, MSc[3,5]
6. Nick Daneman, MD, MSc[2,3,6,7,]
7. Gary Garber, MD[3,8,9]
8. Julie HC Wu, MSc[3]
9. Bradley J Langford, BScPhm, PharmD[3,10]

[1]Antimicrobial Stewardship Program, Sinai Health/University Health Network **(also Corresponding Author information)**

Munk Building, Room 8-PMB 100-132

585 University Avenue

Toronto, Ontario M5G 2N2

T. 416 340 4800 x 5490

E. jennifer.curran@uhn.ca

[2]Department of Pharmacy, Sunnybrook Health Sciences Centre

2075 Bayview Ave

Toronto, Ontario M4N 3M5

[3]Department of Antimicrobial Stewardship, Public Health Ontario

480 University Avenue, Suite 300

Toronto, Ontario M5G 1V2

[4]Department of Pharmacy, Michael Garron Hospital

825 Coxwell Ave

East York, Ontario M4C 3E7

[5]Dalla Lana School of Public Health, University of Toronto

155 College St Room 500

Toronto, Ontario M5T 3M7

[6]Institute of Health Policy, Management and Evaluation, University of Toronto

155 College St 4th Floor

Toronto, Ontario M5T 3M6

[7]Institute of Clinical Evaluative Sciences

2075 Bayview Ave

Toronto, Ontario M4N 3M5

[8]Department of Medicine, University of Ottawa

Roger Guindon Hall, 451 Smyth Rd #2044

Ottawa, Ontario K1H 8M5

[9]Ottawa Hospital Research Institute

1053 Carling Ave

Ottawa, Ontario K1Y 4E9

[10] Hotel Dieu Shaver Health and Rehabilitation Centre

541 Glenridge Ave

St. Catharines, Ontario L2T 4C2

Abstract

Background:

There is growing evidence supporting the efficacy of shorter courses of antibiotic therapy for common infections, however the risks of prolonged antibiotic duration are underappreciated.

Objectives: We sought to estimate the incremental daily risk of antibiotic-associated harms.

Methods: We searched three major databases to retrieve systematic reviews from 2000 to July 30, 2020 in any language.

Eligibility: Systematic reviews were required to evaluate shorter versus longer antibiotic therapy with fixed durations between 3 and 14 days. RCTs included for meta-analysis were identified from the systematic reviews.

Participants: Adult and pediatric patients from any setting.

Interventions: Primary outcomes were the proportion of patients experiencing adverse drug events, superinfections and antimicrobial resistance.

Risk of Bias Assessment: Each RCT was evaluated for quality by extracting the assessment reported by each systematic review.

Data Synthesis: The daily odds ratio (OR) of antibiotic harm was estimated and pooled using random effects meta-analysis.

Results

Thirty-five (35) systematic reviews encompassing 71 eligible randomized controlled trials were included. Studies most commonly evaluated duration of therapy for respiratory tract (n=36, 51%) and urinary tract infections (n=29, 41%). Overall, 23,174 patients were evaluated for antibiotic-associated harms. Adverse events (n=20,345), superinfections (n=5,776), and AMR (n=2,330) were identified in 19.9% (n=4,039), 4.8% (n=280), and 10.6% (n=246) of patients, respectively. Each day of antibiotic therapy was associated with 4% increased odds of experiencing an adverse event (OR 1.04, 95% CI [1.02 to 1.07]). Daily odds of severe adverse effects also increased (OR 1.09, 95% CI [1.00 to 1.19). The daily incremental odds of superinfection and AMR were OR 0.98 (0.92 to 1.06) and OR 1.03 (0.98 to 1.07), respectively.

Conclusion

Each additional day of antibiotic therapy is associated with measurable antibiotic harm, particularly adverse events. These data may provide additional context for clinicians when weighing benefits versus risks of prolonged antibiotic therapy.

Introduction

Antibiotics are an essential part of the management and prevention of bacterial infections in modern medicine. However, there are associated harms including adverse drug events, super-infections such as *Clostridoides difficile (C. difficile)*, as well as selective pressure driving antibiotic resistance.[1]

One opportunity to reduce the harm of antibiotics is by prescribing a shorter course of therapy, reducing patient exposure to the antibiotic.[2] There is a growing body of evidence demonstrating the efficacy and safety of shorter durations of therapy for common, non-deep seated infections, including pneumonia,[3] urinary tract infection (UTI),[4] and intra-abdominal infection (IAI).[5] However, antibiotics are still prescribed for prolonged durations, despite evidence that longer courses are not associated with additional benefit and may increase the risk of harm.[6,7,8,9,10]

Meta-analyses evaluating long versus short courses of antibiotic therapy are aimed at establishing efficacy, and often evaluate harms only as secondary outcomes; as such they are typically not powered to establish differences between shorter and longer durations. While harms associated with antibiotic use have been well-established, there is a paucity of literature designed to quantify the risk of attributable harm from prolonged duration of therapy.

In the pursuit of minimizing antimicrobial resistance and individual patient harms, antimicrobial stewardship programs often rely on efficacy data to promote shorter, appropriate duration of therapy, in addition to a general acceptance that antibiotic harms are associated with prolonged exposure. However, prescribers may overestimate the benefits of prolonged antibiotic duration,

while underestimating their risks.[11,12,13,14] Robust data on the incremental daily risk of adverse effects, risk of secondary infections due to resistant organisms, or superinfections secondary to selective pressure (such as *C. difficile*), may provide clinicians the ability to more accurately analyze risks and benefits for individual patients. The objectives of this study are to describe the harms of antibiotic therapy and estimate the incremental daily risk of adverse effects, superinfections such as *C. difficile* or candidiasis, and antimicrobial resistance.

Methods

Design

We performed a modified Umbrella review, with meta-analysis of individual randomized controlled trials (RCTs). This design leverages existing systematic reviews across a wide range of infectious syndromes to identify individual RCTs evaluating harms associated with antibiotic duration of therapy. The Cochrane group defines an Umbrella review, also termed an Overview, as the use of systematic methods to integrate evidence for a specific research question across a range of existing systematic reviews.[15] In addition to the Umbrella review identifying relevant systematic reviews, we also evaluated the individual underlying trials for each systematic review. Although prior systematic reviews would have identified relevant RCTs, they may not have fully reported on our primary outcome of interest, antibiotic-associated harms. In contrast with a traditional systematic review, which would be largely unfeasible due to the breadth of literature, this approach harnesses the efforts of a vast number of existing systematic reviews on the topic of antibiotic duration. Therefore, we designed a two-phase study, which included Phase 1: the search and identification of systematic reviews comparing shorter versus longer duration of antibiotic therapy and Phase 2: identification, screening, and data extraction of eligible RCTs

(Figure 1). The study protocol was developed in accordance with Cochrane Overview of Reviews recommendations [15], and was registered in PROSPERO, an international registry for systematic reviews and meta-analyses (Registration number: CRD42020203233).

Search Strategy

In consultation with a library and information specialist we searched Ovid MEDLINE, Embase, and EBSCO host Cochrane Database of Systematic Reviews to retrieve systematic reviews from 2000 to July 30, 2020 in any language. Search concepts included antibiotics, duration of therapy, and systematic reviews/meta-analyses. A full search strategy of terms is reported in Supplementary material. No restrictions were imposed on publishing timeframe or language for RCTs. Upon screening, studies in all languages were eligible for inclusion.

Eligibility Criteria

Phase 1: Systematic Reviews

For inclusion into Phase 1 of the review, systematic reviews evaluating a shorter versus longer duration of systemic antibiotic therapy in any setting and for both adult and pediatric populations were considered. Studies evaluating duration of therapy for *H. pylori* infections (since these studies include non-antibiotics as part of the treatment regimen), studies evaluating duration of surgical prophylaxis, and systematic reviews without quality assessment or risk of bias appraisal were excluded.

Phase 2: Randomized Controlled Trials

Studies eligible for inclusion in Phase 2 were RCTs identified from the above systematic reviews comparing fixed durations of shorter versus longer arms of antibiotic therapy in any age group. Antibiotic durations evaluated were required to be greater than or equal to 3 days, and less than or equal to 15 days for inclusion. Additionally, antibiotic agents being compared in shorter and longer durations had to be the same agent, or left to the discretion of the prescriber in each arm (prescriber's choice). Different doses or formulations in each arm were acceptable. Studies were required to report one or more antibiotic harm, defined as adverse drug events, antimicrobial resistance after therapy, and/or superinfection (including candidiasis, *C. difficile*) to be included.

Study Selection

Search results and selection criteria were incorporated into an online systematic review software (Covidence, Melbourne, Australia). Two review authors (BL, JL) independently screened study abstracts, followed by full text review of the included abstracts. Studies were included or excluded based on the criteria outlined above. Conflicts were discussed amongst review authors following title and abstract screening, and then full text screening. A third reviewer was available in cases where consensus could not be reached.

Data Collection

Two review authors (JC, BL) independently extracted outcomes for short and long treatment arms of each RCT, and data was collected within Excel spreadsheets. Two additional review authors (JL, VL) performed second checks on all studies included for review. Discrepancies were discussed amongst authors and resolved by consensus.

Study Characteristics

Author, year of publication, country, health care setting, and single versus multicenter study characteristics were extracted. Sample size, participant mean or median age, type of infection(s) studied and number of patients lost to follow-up were all collected for short and long treatment arms.

Intervention Characteristics

Antibiotic class, name, route, dose and formulation were extracted by study arm. If drug dose or formulation were different between long and short arms, this was documented. Antibiotic duration in days was collected by short and long arm as categorized by the study authors, and follow-up period in days was also documented.

Characteristics of Outcome Measures

Number of patients experiencing each type of harm was collected for both arms of each study.

Outcomes

Primary Outcomes

The primary outcomes were the proportion of patients experiencing adverse drug events, superinfections (such as C. *difficile* infection and candidiasis infection), and antimicrobial resistance as defined by study authors. For adverse events, the number of patients experiencing at least one adverse event was captured. When distinctions were made between all adverse events and drug related events, only drug related events data were collected. For superinfection, any of the following terms qualified: superinfection; *C. difficile*; nosocomial infection; candidiasis.

Antimicrobial resistance was defined as the number of patients with documented resistant isolates, either infection or colonization, after treatment. Refer to Supplementary material Table 1 for outcome definitions.

Quality Assessment

Each study was evaluated for quality by extracting the risk of bias or quality assessment reported by each systematic review. We then categorized the quality of each RCT based as low, medium, or high risk of bias based on the categorization performed by the systematic review authors (see Supplementary material Table 2 for further detail). In cases where studies were included in multiple systematic reviews, the most conservative (i.e., lowest) quality rating took precedence.

Statistical Analysis

Harms outcomes were extracted for each study in the shorter duration arm and the longer duration arm. We fit separate logistic regression models estimating the proportion of patients with a given antibiotic harm as the outcome variable, and with the number of antibiotic days as the only exposure variable. Each model allowed us to estimate a daily odds ratio for antibiotic harm for each study and each outcome. Each of the resulting odds ratios were pooled across studies using random effects meta-analysis to estimate the overall daily odds ratio for harm for a given outcome. Resulting ORs were presented in forest plots. We then estimated the odds of additional risk of antibiotic-associated harm for common duration selection decisions in clinical practice. Sensitivity analyses were performed to 1) include only studies where the same antibiotic dose was used in both short and long arms, and 2) evaluate antibiotic harms stratified by study quality. Subgroup analysis was performed to stratify harms by study population.

Results

Study Characteristics

Our search strategy yielded a total of 1195 systematic reviews. Of those, 35 systematic reviews evaluating fixed shorter versus longer durations of antibiotic therapy were included (Figure 1).[4,16–49] Fifteen systematic reviews (46.8%) included studies evaluating respiratory tract infections (including upper and lower tract), 7 systematic reviews (21.8%) were focused on UTI (including upper and lower tract), and 5 systematic reviews (15.6%) included all infectious diseases.

From the systematic reviews evaluated, 70 unique studies including 71 RCTs were eligible for inclusion.[2,8–10,50,50–66,66–116] One study included two RCTs[102], and each RCT is listed in Table 1 separately. A total of 23,174 patients were evaluated for harms in the RCTs. Half of the patients (11,586) (50.0%) patients were enrolled in shorter treatment duration arms, and 11,588 (50.0%) were enrolled in longer arms. Fifty-two (73.2%) studies included adult patient populations (age >18 years), and 17 (23.9%) studies evaluated pediatric patient populations. Two studies (3.0%) included both adult and pediatric populations (Table 1).

The majority of studies (39, 54.9%) were conducted in community settings, while the remaining studies were conducted in acute care inpatient (14, 19.7%), mixed inpatient/outpatient settings (5, 7.0%), not specified (12, 16.9%), or emergency department (1, 1.4%). Thirty-six studies (50.7%), with a total of 15,349 patients, included patients with respiratory infections (most

commonly community acquired pneumonia, COPD exacerbation or chronic bronchitis exacerbation, and bacterial sinusitis, pharyngitis or tonsillitis). UTIs were the focus of 29 studies (40.8%), in which 6,301 patients were enrolled.

Antibiotics

Fluoroquinolones were the most commonly evaluated class of antibiotic, with 20 studies enrolling 7,047 patients (30.4%). Penicillins were studied in an additional 5,595 patients (24.1%), cephalosporins in 5,145 patients (22.2%) and carbapenems in 729 patients (3.1%). The majority of studies evaluated the same dose of antibiotic in both arms, however 15 studies (21.1%) evaluated the same antibiotic dosed differently in short versus long arms. Short arms received higher doses in 8 of these studies (53.3%), whereas dosing differences were not specified in 5 (33.5%), and 2 studies (13.3%) had higher dosing in the long arm. Four studies left antibiotic dosing to the discretion of the prescriber, totaling 893 patients (3.9%).

Durations

In shorter duration treatment arms there were 18, 14, and 4 studies enrolling patients to 3, 5, or 7/8 days of therapy respectively. Of the 11,586 patients evaluated for harms in short duration treatment arms, 4,333 (37.4%), 6,004 (51.8%), and 1,251 (10.8%) patients were assigned to receive 3, 5, or 7/8 days of therapy respectively. In longer duration treatment arms there were 3, 13, 17 and 4 studies enrolling patients to 5, 7/8, 10, or 14/5 days of therapy respectively. Of the 11,588 patients evaluated for harms in long duration treatment arms, 1,628 (14.1%), 4176 (36.0%), 5,127(44.3%), and 655(5.7%) patients received 5, 7/8, 10, or 14/15 days of treatment

respectively. The most frequent comparisons of durations were 5 versus 10 days (21 studies, 29.6%), followed by 3 versus 7 days (17 studies, 23.9%).

Quality Assessment

Twenty-four studies (32.8%) were determined to be at high risk of bias, and an additional 16 studies (21.9%) were assessed to be low risk of bias. The remaining 33 studies (45.2%) had unclear risk of bias (Table 1).

Outcomes

Of the 23,174 patients evaluated for harms in 71 studies, a total of 4,565 antibiotic-associated harm events were reported (19.6%), including 4,039 adverse drug events (88.4%), 280 superinfections (6.1%), and 246 cases of antimicrobial resistance (5.3%).

Adverse Drug Events

Sixty-five studies evaluated 21,937 patients for any category of adverse events. Six studies with 1592 patients were only evaluated for severe adverse events or adverse events leading to discontinuation. Of the 20,345 patients who were evaluated for total adverse drug events, 4,039 patients (19.9%) were reported to have experienced an adverse drug event. Each day of antibiotic therapy was found to be associated 4% increased odds of experiencing an adverse event (OR 1.04, 95% CI [1.02 to 1.07]). (Figure 2) Dermatological adverse events were associated with an 13% increased odds with each additional day of antibiotics (OR per additional day 1.13, 95% CI [1.05 to 1.21]). (Figure 3)

There were 125 severe adverse drug events reported, which resulted in a 9% increased odds of experiencing a severe adverse event with each additional day of antibiotic therapy (OR 1.09, 95% CI [1.00 to 1.19]). (Figure 3)

Finally, antibiotic related adverse events leading to discontinuation of therapy were reported in 445 instances (OR 1.02, 95% CI [0.98 to 1.07]) (Figure 3)

Antimicrobial Resistance

A total of 9 studies and 2,330 patients evaluated for antimicrobial resistance, in which there were 246 (10.6%) reports of development of antimicrobial resistance. We estimated a 1.03-fold increase in the odds of resistance associated with each additional day of antibiotics (OR 1.03, 95% CI [0.98 to 1.07]) (Figure 2).

Superinfections

Twenty studies evaluated a total of 5,776 patients for superinfections, which were subsequently reported in a 280 patients (4.8%). Upon meta-analysis, no association was found between days of antibiotic therapy and the daily risk of superinfections (OR 0.98, 95% CI [0.92 to 1.06]). (Figure 2).

Of the 280 superinfections, there were 5 (1.8%) cases of *C. difficile,* and 127 (45.4%) cases of candidiasis. No significant differences were found between shorter and longer duration arms of therapy in either *C. difficile* infections (OR 1.04, 95% CI [0.77 to 1.40]), or candidiasis (OR 1.05, 95% CI [0.93 to 1.17]). (Table 2)

330

331 ***Sub-analysis of selected antibiotic associated-harms by group***

332 *Drug Class – Adverse events*

333 Adverse events were most commonly evaluated in patients receiving fluoroquinolones (19
334 studies evaluating 6,960 patients), penicillins (13 studies evaluating 5,470 patients), and
335 cephalosporins (12 studies evaluating 3,459 patients). Six studies with 2,238 patients evaluated
336 adverse events due to macrolides. Cephalosporins, macrolides, and penicillins were all associated
337 with significant increases in odds of developing adverse events with each day of therapy
338 (cephalosporins OR 1.07, 95% CI [1.01 to 1.12]; macrolides OR 1.05, 95% CI [1.01 to 1.10]);
339 penicillins OR 1.06, 95% CI [1.00 to 1.12]) (Figure 4)

340

341 *Sensitivity Analyses*

342 When limiting studies to only those that used the same dose in each arm, there were similar
343 findings for the daily odds of adverse events (OR 1.05, 95% CI [1.03 to 1.07]), antimicrobial
344 resistance (OR 1.03, 95%CI [0.85 to 1.27]), and superinfections (OR 1.01, 95% CI [0.93 to
345 1.10]). A sensitivity analysis stratifying study outcomes based on quality revealed similar
346 findings but wider confidence intervals. (Figure 5)

347

348 When harms outcomes were evaluated by study population subgroups (ie. age group, setting,
349 antibiotic class, physiological system), the point estimates for daily harms were relatively
350 consistent across settings and age groups. (Supplementary material Table 3).
351 The heterogeneity measure I^2 was zero for all estimates, indicating a lack of statistical
352 heterogeneity in the harms outcomes.

Clinical Implications

Given the most common durations evaluated were three, five, and seven days, we applied our findings of the daily increased odds of adverse events to typical clinical scenarios. The cumulative odds of an individual patient experiencing an adverse drug event 1.09 fold higher (95% CI [1.04 to 1.14]] when treated for 5 days instead of 3. Compared to a three day course, a seven day course increases the risk of an adverse event by 1.19 fold odds (95% CI [1.09 to 1.30]).

Discussion

Our Umbrella review determined that for antibiotic courses between 3 and 15 days, each day of therapy is associated with a 4% increased odds of experiencing an adverse drug event. Furthermore, the odds of patients experiencing an adverse drug event categorized as 'severe' were found to be 9% higher with each additional day of antibiotic exposure. Although we did find a numerically increased odds of daily harm for superinfection and antimicrobial resistance, these associations were not statistically significant.

Similar to our findings, a recent retrospective cohort study by Tamma et al. demonstrated that in hospitalized patients receiving antibiotics, 20% experienced an adverse drug event. They also determined that every 10 days of therapy conferred an additional 3% risk of an adverse drug event.[50] Our study found similar effect sizes that indicate each additional day of treatment is associated with risk. Additionally, we have provided further detail on the daily risk of multiple antibiotic-associated harms across an array of patient populations.

Applying our data to a clinical scenario, the cumulative odds of an individual patient experiencing an adverse drug event is 1.09 fold higher when treated for five days instead of three and 1.19 fold higher if continuing therapy for seven days instead of three. These data may help provide additional context for clinicians when considering the benefits versus the risks of prolonged antibiotic therapy for their patients. As decision support technology advances, quantifiable benefits and harms data will be increasingly valuable as a means of providing point of care risk estimates tailored for individual patients.

In contrast, duration of therapy was not strongly associated with superinfections or antimicrobial resistance in our study. Specifically, only three studies evaluated *C. difficile* as an outcome[76,98,108] and none found an association with duration of therapy. Studies may have underestimated the risk of these outcomes for multiple reasons. First, there is a lack of routine and rigorous assessment for harms outcomes such as AMR and *C. difficile*, as the study is designed to evaluate efficacy outcomes relating to clinical or microbiologic resolution. Additionally, randomized controlled trials assessing antimicrobial resistance evaluate individual patients rather than at a population level, which cannot account for the risk of transmission of antimicrobial resistant organisms to any patient regardless of their antimicrobial receipt. Finally, randomized controlled trials evaluating duration often had short follow-up periods, which may not provide sufficient time for particular harms outcomes to be captured (for example, as the majority of patients were not followed beyond 30 days, it is plausible that episodes of *C.difficile* and colonization or infection with antibiotic resistant organisms could occur outside this timeframe). Despite these challenges, it has been well established that prolonged exposure to antimicrobials

increases the risk of selecting for resistant organisms [1,7,8] Two retrospective cohort studies demonstrated a relative risk of *Clostridioides difficile (C. difficile)* infections to be 12.8% and 9% respectively, with each additional day of therapy.[117,118] Two other retrospective cohort studies found antibiotic exposure to increase daily risk of acquired resistance to anti-pseudomonal agents and pneumococcal resistance to penicillins respectively.[119,120,]

There were notable limitations to this umbrella review. Many studies did not evaluate patients for superinfections or resistance outcomes, which limits the power to detect these outcomes. It will be essential for future randomized trials to thoroughly evaluate these important antibiotic-associated harms as primary outcomes through larger cluster RCTs (to detect AMR in the population) with long follow up periods (to account for the time to select for resistant organisms), that account for the risk of additional antibiotic therapy in each regimen, and time-to-event analyses to more precisely estimate the relative risk of harm associated with different antibiotic durations of therapy.[121] Additionally, although dermatologic adverse events were a substantial driving factor to the primary harms outcomes, we noted not only an increased daily risk of overall adverse events but also serious adverse events, reinforcing the potential harm associated with each additional day of antibiotic therapy. Given variability in reporting and low event numbers for certain strata, a precise granular assessment of daily harms across antibiotics and organ systems was not possible. However, with the added statistical precision of pooling data we aimed to provide a practical estimate that clinicians could use in practice in different scenarios. Further research should aim to estimate the duration-associated harms for different organ systems and in different populations. While underlying risk study bias (lack of allocation concealment/blinding) may have impacted our findings, a sensitivity analysis of daily odds of

harm stratified by risk of bias, appears to show similar findings regardless of study quality assessment.

Finally, our approach to identifying primary studies for inclusion leverages previously published systematic reviews rather than performing an extensive review of the primary literature. While we are confident that key studies were included, it is possible that some studies were overlooked. However, the umbrella review with individual study review model provides an efficient yet broad overview of existing literature that may not be otherwise feasible with conventional literature searching techniques.

Conclusion

This umbrella review with meta-analysis of systematic reviews quantified the daily risk of antibiotic-associated harms and found that each additional day of antibiotic therapy is associated with a 4% per day increased odds of adverse events and 9% per day increased odds of serious adverse events. Prospective, controlled studies with large sample sizes and long time horizons are needed which are designed to quantify all antibiotic harms, including population-level AMR and superinfections.

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Table 1: Characteristics of randomized controlled trials evaluating shorter versus longer arms of antibiotic therapy

Author, Year	Country	Included in Systematic Review	Setting	Size	Age Group	Type of Infection	Short Arm, days	Long Arm, days	Class of Antibiotic	Overall Risk of Bias	Evaluated Adverse Events	Evaluated Antimicrobial Resistance	Evaluated Superinfection
Bennett, 1988	United Kingdom	Stolbrink, 2018	Acute Care	41	Adult	Respiratory	3	7	Penicillin	Unclear	✓		
Capellier, 2012	France	Dimopoulous, 2013 Pugh, 2015 Royer, 2018 Arulkumaran, 2020	Acute Care	225	Adult	Respiratory	8	15	Prescriber's Choice	High	✓	✓	✓
Catania, 2004	Italy	Kozyrskyj, 2010	Community	400	Pediatric	Respiratory	5	10	Cephalosporin	Unclear	✓		
Chastre, 2003	France	Havey, 2011 Dimopoulous, 2013 Pugh, 2015 Royer, 2018	Acute Care	401	Adult	Respiratory	8	15	Prescriber's Choice	High		✓	
Chodosh, 2000	North America	Elmoussaoui, 2008 Falagas, 2008 Stolbrink, 2018	Community	614	Adult	Respiratory	5	10	FQ	Unclear	✓		
Cohen, 1998	France	Kozyrskyj, 2010	Not specified	382	Pediatric	Respiratory	5	10	Penicillin	High	✓		

Cohen, 2000	France	Kozyrskyj, 2010	Not specified	446	Pediatric	Respiratory	5	10	Cephalosporin	Low	✓		
Cosgarea, 2016	Germany	McGowan, 2018	Community	61	Adult	Dental	3	7	Penicillin	Low	✓		
Darouiche, 2014	United States	Royer, 2018	Acute Care	55	Adult	UTI	5	10	Prescriber's Choice	High	✓		✓
de Gier, 1995	Netherlands	Havey, 2011 Eliakim-Raz, 2013 Royer, 2018	Acute Care	45	Adult	UTI	7	14	FQ	High	✓	✓	✓
de Saintonge, 1982	England	Kozyrskyj, 2010	Community	84	Pediatric	Respiratory	3	10	Penicillin	Low	✓		
DeAbate, 1999	United States	Falagas, 2008	Community	388	Adult	Respiratory	5	10	FQ	Low	✓		✓
Dubreuil, 2001	France	Falagas, 2009	Community	401	Adult	Respiratory	5	10	Cephalosporin	Low	✓		
Dunbar, 2003	United States	Havey, 2011 Chen, 2019	Acute Care	521	Adult	Respiratory	5	10	FQ	Unclear	✓		
DURAPOP, 2018	France	Arulkumaran, 2020	Acute Care	212	Adult	Intra-abdominal	8	15	Prescriber's Choice	High		✓	✓
el Moussaoui, 2006	Netherlands	Havey, 2011 Dimopoulous, 2013	Acute Care	119	Adult	Respiratory	3	8	Penicillin	Unclear	✓		
Esposito, 2001	Italy	Casey, 2005 Falagas, 2008	Community	120	Pediatric	Respiratory	5	10	Cephalosporin	Unclear	✓		
Falck, 1998	Sweden	Kim, 2020	Community	479	Adult	UTI	3	7	FQ	Unclear	✓	✓	
Ferguson 2002	Multi-country	Falagas, 20089	Not specified	421	Adult	Respiratory	5	7	FQ	Low	✓		

Ferry, 2007	Sweden	Pinart, 2017 Kim, 2020	Community	657	Adult	UTI	3	7 7	Penicillin	High	✓	
Ficnar, 1997	Croatia	McMullan, 2016	Not specified	366	Pediatric	Respiratory	3	5	Macrolide	High	✓	
File, 2007	United States	Havey, 2011 Dimopoulous, 2013	Not specified	510	Adult	Respiratory	5	7	FQ	Unclear	✓	
Gordin, 1987	Finland	Milo, 2005	Community	132	Adult	UTI	3 3	10 10	Sulfonamide	Low	✓	✓
Gossius, 1984	Norway	Milo, 2005	Community	268	Adult	UTI	3	10	Sulfonamide	Unclear	✓	✓
Gossius, 1985	Norway	Milo, 2005	Community	114	Adult	UTI	3	10	Sulfonamide	Unclear	✓	
Gotfried, 2005	United States	Elmoussaoui, 2008 Falagas, 2008 Stolbrink, 2018	Ambulatory	485	Adult	Respiratory	5	7	Macrolide	Unclear	✓	
Greenberg, 1986	United States	Kozyrskyj, 2010 Kim, 2020	Emergency Department	54	Adult	UTI	3	7	Cephalosporin	Unclear	✓	
Haghighi, 2010	Iran	Kim, 2020	Community	76	Adult	UTI	3	7	FQ	Unclear	✓	
Halperin, 1997	Canada	Altunaiji, 2012	Community	168	Pediatric	Respiratory	7	14	Macrolide	High	✓	
Helin, 1981	Sweden	Michael, 2003	Community	53	Pediatric	UTI	3	10	Sulfonamide	Unclear	✓	
Hepburn, 2004	United States	Kilburn, 2010 Havey 2011 Brindle, 2019	Mixed outpatient /inpatient	87	Adult	SSTI	5	10	FQ	High	✓	
Hoberman 1997	Multi-country	Kozyrskyj, 2010	Mixed outpatient	580	Pediatric	Respiratory	5	10	Penicillin	Unclear	✓	

			/inpatient										
Iravani, 1983	United States	Milo, 2005	Community	134	Adult	UTI	37	14	Sulfonamide	Unclear		✓	✓
Iravani (Study 2), 1995	United States	Kim, 2020	Community	456	Adult	UTI	3	3	FQ	Unclear	✓	✓	✓
Iravani (Study 3), 1995	United States	Kim, 2020	Community	421	Adult	UTI	3	5	FQ	Unclear	✓	✓	✓
JansÃ¥ker, 2019	Denmark	Kim, 2020	Community	306	Adult	UTI	3	5	Penicillin	Low	✓		✓
Kafetzis 1997	Greece	Kozyrskyj, 2010 Altamimi, 2012	Community	560	Adult	Respiratory	5	10	Cephalosporin	High	✓		
Leophonte, 2002	France	Li, 2007 Havey, 2011 Dimopoulos, 2008 Royer, 2018	Acute Care	244	Adult	Respiratory	5	10	Cephalosporin	Unclear	✓		✓
Lin, 1985	United States	McMullan, 2016 Karageorgopoulos, 2000	Acute Care	70	Pediatric	CNS Infection	7	10	Cephalosporin	High	✓		✓
Lorenz, 1998	Germany	Elmoussaoui, 2008 Falagas, 2008 Stolbrink, 2018	Not specified	221	Adult	Respiratory	5	10	Cephalosporin	Unclear	✓		
Lutterman, 2003	Multi-country	Falagas, 2009	Community	498	Adult	Respiratory	5	10	Macrolide	Unclear	✓		✓

Marsh, 1980	United Kingdom	Milo, 2005 Pinart, 2017	Community	127	Adult	UTI	3	7	Penicillin	High	✓		
MASCOT, 2002	Pakistan	Haider, 2008 Dimopoulos, 2008 Havey, 2011	Community	1953	Pediatric	Respiratory	3	5	Penicillin	Low	✓		
Masterton, 2001	Global	Elmoussaoui, 2008 Falagas, 2008 Stolbrink, 2018	Community	530	Adult	Respiratory	5	7	FQ	Unclear	✓		
Mehra, 1998	Multi-country	Casey, 2005 Falagas, 2008	Community	651	Pediatric	Respiratory	5	7	Cephalosporin	High	✓		
Molyneux, 2011	Multi-country	McMullan, 2016	Acute Care	1004	Pediatric	CNS Infection	5	10	Cephalosporin	High	✓		
Neringer, 1992	Sweden	Milo, 2005 Kim, 2020	Community	463	Adult	UTI	3	7	FQ	Unclear	✓	✓	
Peixoto, 1993	Switzerland	Falagas, 2008	Not specified	361	Adults/ Pediatrics	Respiratory	7	10	Cephalosporin	High			✓
Petersen, 1991	Denmark	Pinart, 2017	Mixed outpatient /inpatient	242	Pediatric	UTI	3	10	Sulfonamide	High	✓	✓	
Pichichero, 1994	United States	Casey, 2005 Falagas, 2008 Altamimi, 2012	Not specified	321	Pediatric	Respiratory	5	10	Cephalosporin	High	✓		
Piippo, 1990	Finland	Milo, 2005 Lutters, 2009	Community	394	Adult	UTI	3	7	FQ	Low	✓		
Poole, 2006	United States	Chen, 2019	Community	780	Adult	Respiratory	5	10	FQ	Unclear	✓		✓

Richards, 1984	England	Milo, 2005 Pinart, 2017 Kim, 2020	Community	178	Adult	UTI	3	7	Penicillin	High	✓	
Roede, 2007	Netherlands	Stolbrink, 2018	Acute Care	46	Adult	Respiratory	3	10	Penicillin	Unclear	✓	✓
Roos, 2002	Multi-country	Falagas, 2009	Community	333	Adult	Respiratory	5	10	Macrolide	Low	✓	✓
Runyon, 1991	United States	Havey, 2011 Royer, 2018	Acute Care	90	Adult	Intra-abdominal	5	10	Cephalosporin	High	✓	✓
Sandberg, 1985	Sweden	Kim, 2020	Community	202	Adult	UTI	3	7	Cephalosporin	High	✓	
Sandberg, 2012	Sweden	Eliakim-Raz 2013 Berti, 2018	Community	179	Adult	UTI	7	14	FQ	High	✓	✓
Sethi, 2005	Global	Elmoussaoui, 2008 Stolbrink, 2018	Mixed outpatient /inpatient	893	Adult	Respiratory	5	7	Penicillin	Unclear	✓	
Sinanian, 1972	United States	Falagas, 2008	Community	89	Adult	Respiratory	5	10	Lincomycin	High	✓	
Sutlieff, 1982	England	Pinart, 2017	Not specified	98	Adult	UTI	3	5	Penicillin	High	✓	
Tellier, 2004	United States	Li, 2007 Dimopoulos, 2008 Havey, 2011	Mixed outpatient/ inpatient	388	Adult	Respiratory	5	7	Macrolide	Unclear	✓	
Trieneken s, 1989	Netherlands	Milo, 2005 Kim, 2020	Community	327	Adults/ Pediatrics	UTI	3	7	Sulfonamide	Unclear	✓	
Trieneken s, 1993	Netherlands	Milo, 2005 Kim, 2020	Community	384	Adult	UTI	3	7	FQ	Unclear	✓	
Tsugawa, 1999	Japan	Milo, 2005	Community	96	Adult	UTI	3	7	FQ	Unclear	✓	

UpChurch, 2006	Multi-country	Falagas, 2008	Not specified	729	Adult	Respiratory	7	10	Carbapenem	Low	✓	✓
VanMerode, 2005	Netherlands	Lutters, 2009	Community	129	Adult	UTI	3	5	Sulfonamide	Unclear	✓	
Vogel, 2004	Canada	Lutters, 2009	Acute Care	177	Adult	UTI	3	7	FQ	Low	✓	
Williams, 1995	United States	Falagas, 2009	Community	80	Adult	Respiratory	3	10	Sulfonamide (with or without trimethoprim)	Low	✓	
Zaki, 1986	Kuwait	Michael, 2002 Michael, 2003	Not specified	26	Pediatric	UTI	3	10	FQ	Unclear	✓	
Zaki, 1986	Kuwait	Michael, 2002 Michael, 2003	Not specified	29	Pediatric	UTI	3	10	Sulfonamide	Unclear	✓	

*FQ = Fluoroquinolone

Prescriber's Choice = no fixed antibiotic regimen, although antibiotic duration was fixed antibiotic agent and dose was selected by prescriber

Iravani, 1995: One study included multiple RCTs; each RCT is listed separately.

Table 2: Odds ratios of antibiotic-associated harms outcomes with each additional day of antibiotic therapy

Outcome	Number of Studies **n**=71	Number of Patients **n**=23,174	Odds Ratio (95%CI)
Total Adverse Events, n(%)	60 (84.5)	4,039/20,345 (19.9)	1.04 (1.02—1.07)
Severe Adverse Events	18 (25.1)	125/9,049 (1.4)	1.09 (1.00—1.19)
Adverse Events leading to discontinuation of therapy	45 (63.3)	445/14,613 (3.0)	1.02 (0.98—1.07)
Adverse Events by System, n events			
Immunological	2 (2.8)	2/424 (0.5)	0.99 (0.49—2.01)
Dermatological	17 (23.9)	197/5,645 (3.5)	1.13 (1.05—1.21)
Musculoskeletal	3 (4.2)	11/769 (1.4)	0.89 (0.58—1.36)
Gastrointestinal	44 (62.0)	1836/12,715 (6.6)	1.03 (1.00—1.06)
Central nervous system	28 (39.4)	643/9,090 (7.1)	1.03 (0.97—1.09)
Genitourinary	6 (8.4)	25/1,294 (1.9)	0.99 (0.82—1.18)
Hepatic	5 (7.0)	94/2,005 (4.7)	0.84 (0.67—1.05)
Other	16 (22.5)	178/5,038 (3.5)	1.03 (0.96—1.11)
Antimicrobial Resistance, n(%) (Colonization or Infection)	9 (12.7)	246/2,330 (10.6)	1.03 (0.98-1.07)
Superinfection, n(%)	20 (28.1)	280/5,776 (4.8)	0.98 (0.92—1.06)
C. difficile infection	4 (5.6)	5/280 (1.8)	1.04 (0.77—1.40)
Candidiasis	11 (15.5)	127/280 (45.4)	1.05 (0.93-1.17)
Other	20 (28.1)	154/280 (55.0)	1.03 (0.96-1.11)

FIGURES

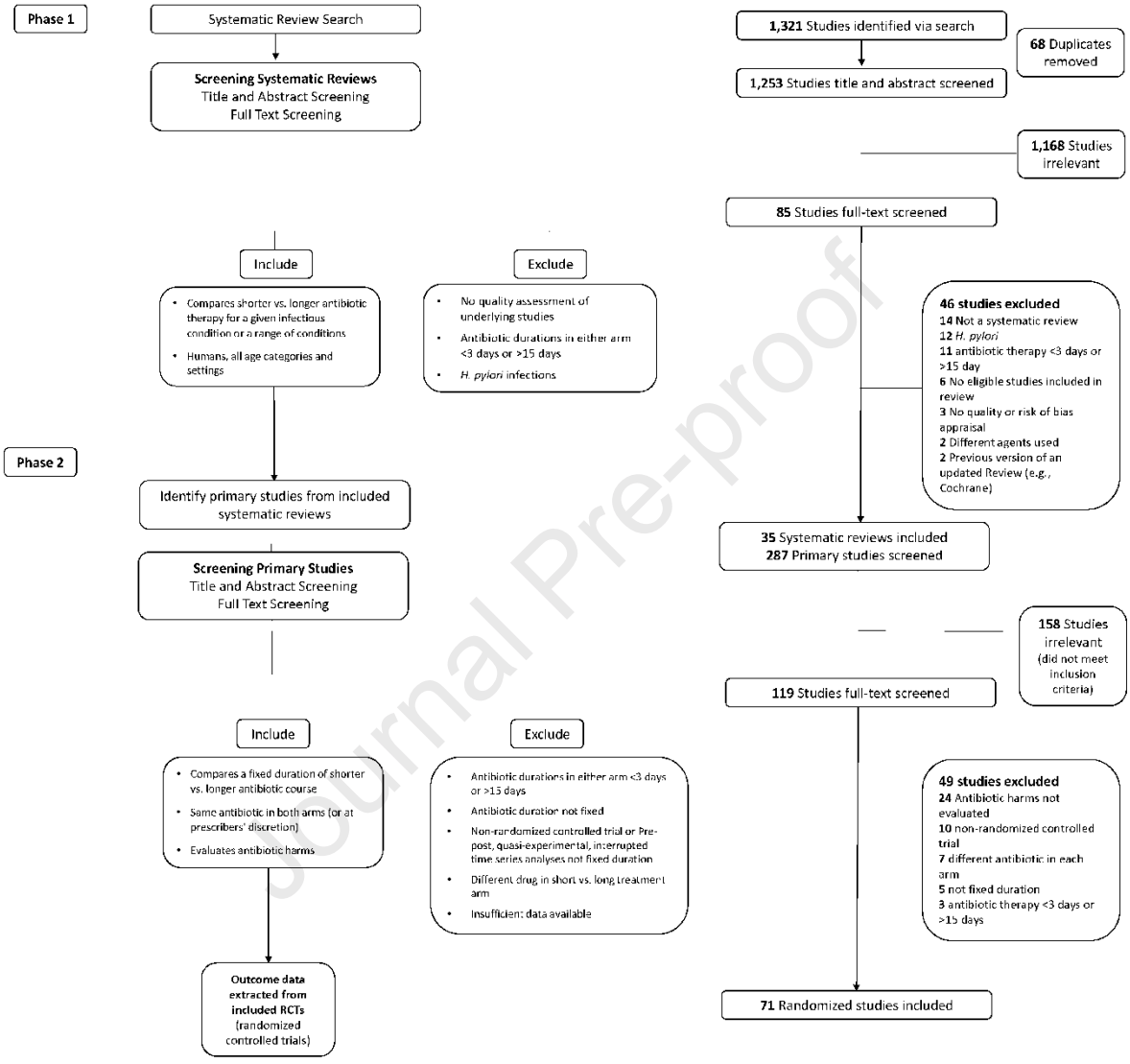

Figure 1: Flow diagram depicting methodology (left) and PRISMA flow diagram demonstrating inclusion and exclusion of randomized controlled trials (right)

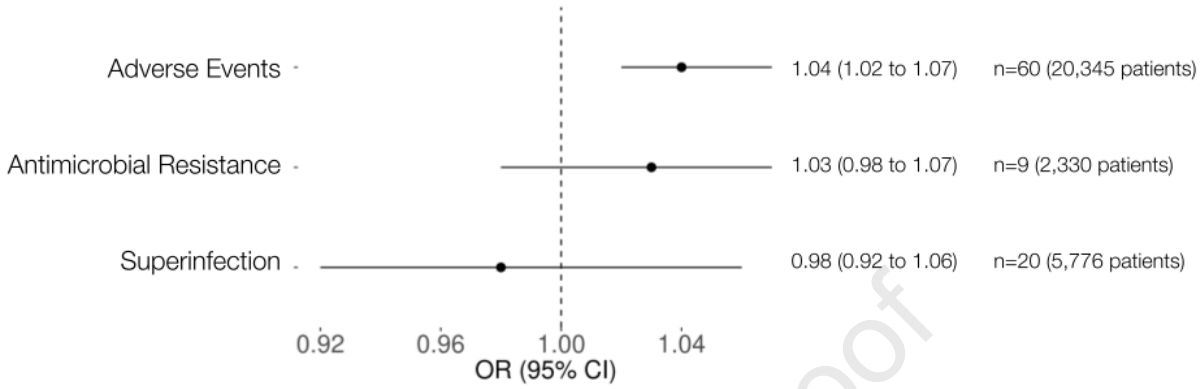

Figure 2: Forest plots of odds ratios for primary outcomes. CI, confidence interval OR, odds ratio

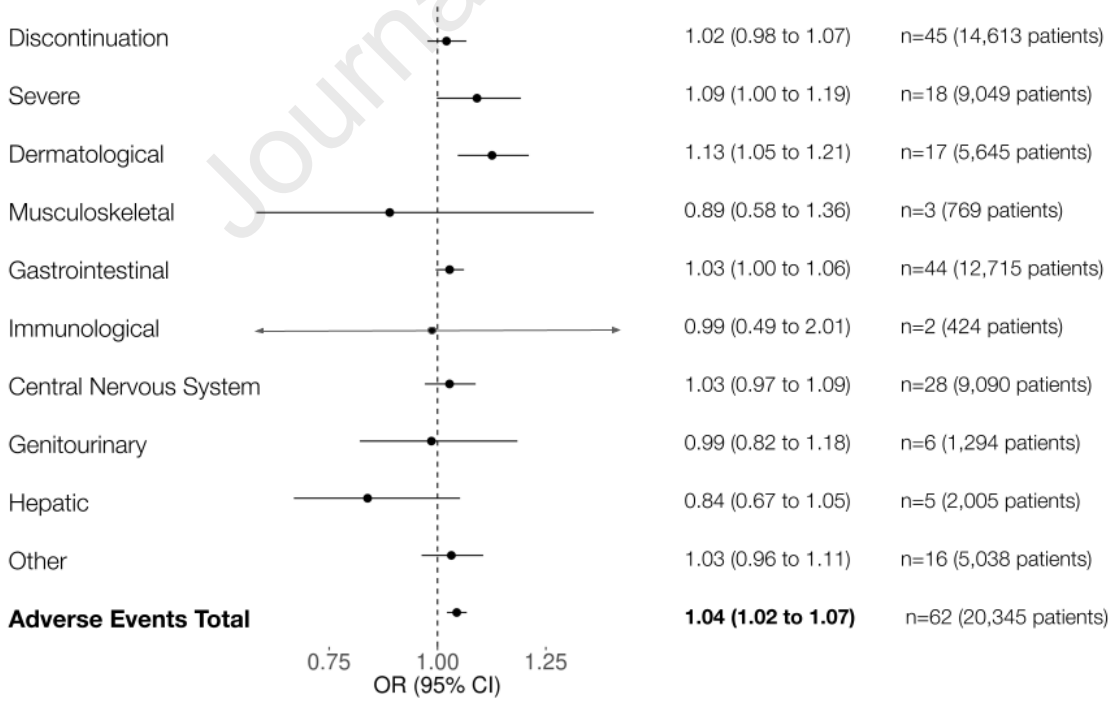

Figure 3: Forest plots of odds ratios for sensitivity analysis of adverse events by physiological system. CI, confidence interval OR, odds ratio

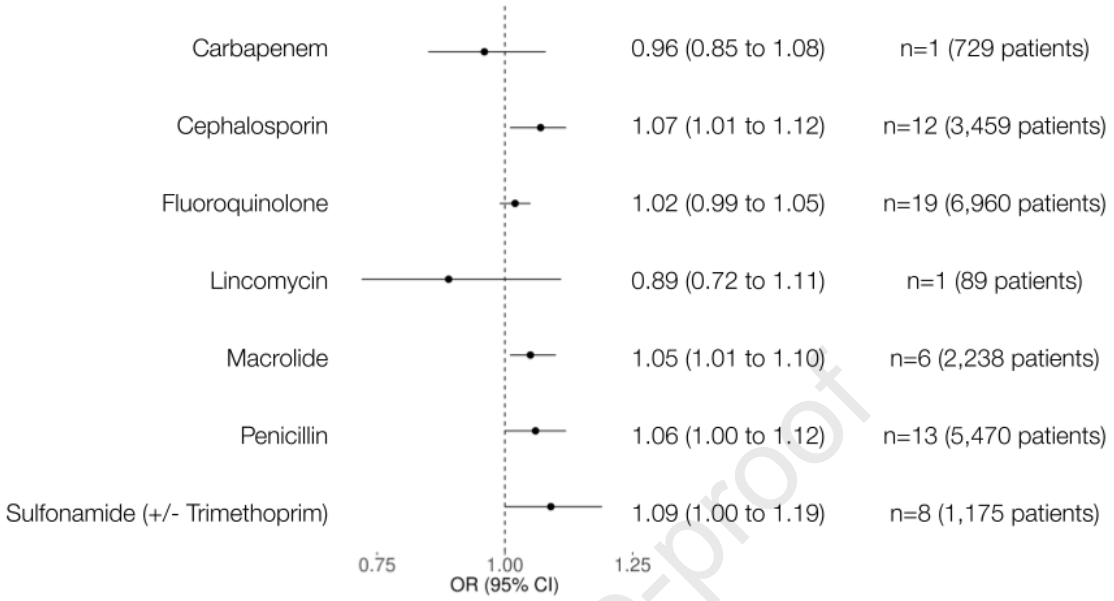

Figure 4: Forest plots of odds ratios for sensitivity analysis of adverse events by antibiotic class.
CI, confidence interval OR, odds ratio

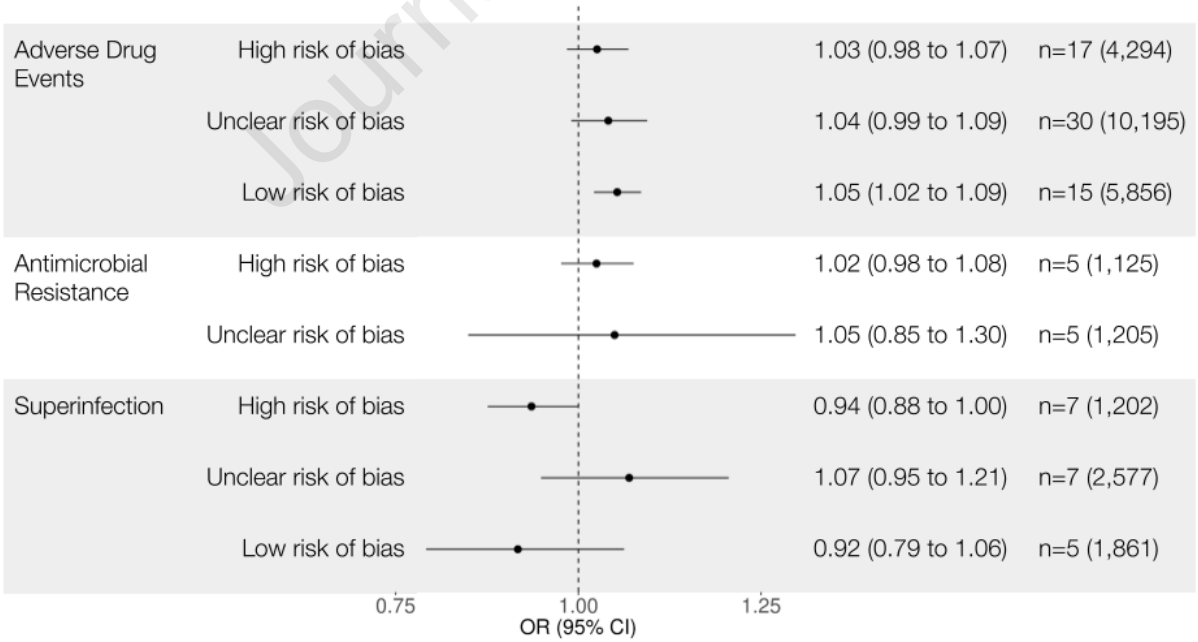

Figure 5: Forest plots of odds ratios for sensitivity analysis of studies stratified by risk of bias.
CI, confidence interval OR, odds ratio