Economic burden of community-acquired antibiotic-resistant urinary tract infections: a systematic review and meta-analysis

Nina Jiayue Zhu, Misghina Weldegiorgis, Emma Carter, Colin Brown, Alison Holmes, Paul Aylin

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Abstract

Background: Antibiotic resistance (ABR) poses a major burden to global health and economic systems. ABR in community-acquired urinary tract infections (CA-UTIs) has become increasingly prevalent. Accurate estimates of the clinical and economic burden of ABR are needed to support medical resource prioritisation and cost-effectiveness evaluations of UTI interventions.

Objective: This study aims to systematically synthesize the evidence in the economic costs associated with ABR in CA-UTIs, using published studies comparing the costs of antibiotic-susceptible and antibiotic-resistant cases.

Methods: We searched PubMed, Ovid Medline and Embase, Cochrane Review Library, and Scopus databases. Studies published in English from 01 January 2012 to 31 January 2023 reporting the economic costs of ABR in CA-UTI of any microbe were included. Independent screening of title/abstracts and full texts were performed based on pre-specified criteria. Quality assessment was performed using the Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS) tool. Data in UTI diagnosis criteria, patient characteristics, perspectives, resources costed, and patient and health economic outcomes, including mortality, hospital length of stay (LOS), and costs was extracted and analysed. Monetary costs were converted into 2023 USD.

Results: This review included 15 studies with a total of 57,251 CA-UTI cases. All studies were from high- or upper middle-income countries. Fourteen (93%) studies took a health system perspective. Thirteen (87%) focused on hospitalised patients. Fourteen (93%) reported the UTI pathogens. E. coli, K. pneumoniae, and P. aeruginosa are the most prevalent organisms. Twelve (80%) studies reported mortality, of which, 7 reported increased mortality in the ABR group. Random effects meta-analyses estimated an odds ratio of 1.50 (95% CI: 1.29, 1.74) in the ABR CA-UTI cases. All 13 hospital-based studies reported LOS, of which, 11 reported significantly higher LOS in the ABR group. The meta-analysis of reported median LOS estimated a pooled excess LOS ranged from 1.50 days (95% CI: 0.71, 4.00) to 2.00 days (95% CI: 0.85, 3.15). The meta-analysis of reported mean LOS estimated a pooled excess LOS of 2.45 days (95% CI: 0.51 – 4.39). Eight (53%) studies reported costs in monetary terms, none discounted the costs. All these 8 studies reported higher medical costs spent treating patients with ABR CA-UTI in hospitals. The highest excess cost was observed in UTI caused by Carbapenem-resistant Enterobacteriaceae. No meta-analysis was performed for monetary costs due to heterogeneity.

Conclusions: ABR attributed to increased mortality, hospital LOS, and economic costs among the patients with CA-UTI. The findings of this review highlighted the scarcity of research in this area, particularly in patient morbidity and chronic sequelae and costs incurred in the community healthcare. Future research calls for cost-of-illness analysis of infections standardising therapy-pathogen combination comparators, medical resources, productivity loss, and intangible costs to be captured, and data from community sectors and low-resourced settings and countries. Clinical Trial: PROSPERO CRD42023374551

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Economic burden of community-acquired antibiotic-resistant urinary tract infections: a systematic review and meta-analysis

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Keywords

Cost-effectiveness; urinary tract infection; antibiotic resistance; mortality; hospital length of stay

Abstract (450/450)

Background

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ABR attributed to increased mortality, hospital LOS, and economic costs among the patients with CA-UTI. The findings of this review highlighted the scarcity of research in this area, particularly in patient morbidity and chronic sequelae and costs incurred in the community healthcare. Future research calls for cost-of-illness analysis of infections standardising therapy-pathogen combination comparators, medical resources, productivity loss, and intangible costs to be captured, and data from community sectors and low-resourced settings and countries.

Trial Registration

PROSPERO CRD42023374551

Introduction

Urinary tract infections (UTIs) are defined as an infection of the kidneys, bladder, or urethra, defined by a combination of clinical features and the presence of bacteria in urine. These are one of the most common conditions managed in primary care with approximately 75% of women experiencing at least one episode in their lifetime [1]. Consequently, UTI is the second most common reason for primary care antibiotic prescribing in England [2,3]. However, it is estimated that up to 50% these prescriptions were inadequate [4,5]. If managed inappropriately, in cases such as undertreating, subsequent sequelae include recurrent infections, bacteraemia, sepsis, and potential mortality (2). In addition, inappropriate management of UTI includes over-using antibiotics, i.e. using antibiotics when not required or for prolonged durations, accelerates the emergence and transmission of antibiotic resistance (ABR) in the long-term [6]. An increasing level of ABR in the community poses challenges to infection due to higher risk of first-line antibiotic regime failure [7]. In the UK, *Escherichia coli* (*E. coli*), the most common cause of UTIs, susceptibility to first line treatments trimethoprim and nitrofurantoin is declining [8]. This may have resulted in a rise in bacteraemia caused by drug-resistant Gram-negative bacteria as over 40% *E. coli* bacteraemia had a urinary source [9].
Drug-resistant UTIs impose an economic burden on individuals, healthcare systems, and society as a whole [10–13]. The reduced effectiveness of UTI antibiotics can lead to repeated and more extensive treatment, hospital admission and prolonged length of stay (LOS), increased medical costs, and mortality [14]. The UK government has set new commitments in the National Action Plan (NAP) to improve prevention and control of UTIs in the community, particularly the elderly, and to gain better understanding of the economic impacts of ABR [15]. Despite the high prevalence of UTI in the community, the evidence in the financial and human costs associated with drug-resistant UTI is scarce, particularly due to the difficulties in quantifying costs incurred outside secondary care [16]. An understanding of clinical and economic burden of antibiotic-resistant UTI is key to evaluating the cost-effectiveness of stewardship interventions, including those aimed at using point-of-care diagnosis, clinical decision support tools, and reducing prescribing in the community [17]. In this research, we sought to systematically synthesise the evidence in the economic burden associated with antibiotic-resistant community-acquired UTIs (CA-UTIs), using published studies comparing the costs of antibiotic-susceptible and antibiotic-resistant cases.

Methods

This systematic review followed the ‘Preferred Reporting Items for Systematic Review and Meta-Analysis’ (PRISMA) guidance (PRISMA checklist presented in Supplementary Material, Table S1) [18], and was registered at International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42023374551).

Search methods

We searched for the studies estimating the economic costs attributable to antibiotic drug-resistant CA-UTIs published from 01 January 2008 to 31 January 2023 using a combination of broad-based (and wildcard) search criteria, including terms for 1) UTI, 2) community-acquired, 3) antibiotic resistance, and 4) health-economic cost. We searched PubMed, Ovid Medline and Embase, Cochrane Review Library, and Scopus databases using the strings developed for each database (Supplementary Material, Table S2). The bibliographies of the identified studies were also reviewed.

Study selection

The study inclusion/exclusion criteria are presented in Table 1, including the patient/population, intervention, comparison and outcomes (PICO) eligibility. Two authors (NZ and MW) independently screened the titles and abstracts of the records yielded from the database search, and independently screened the full-text articles. The discrepancies during title/abstract screening and full-text screening were resolved by consulting the third author (EC). Any article comparing monetary or health-economic costs of antibiotic-resistant versus susceptible CA-UTIs through clinical trials, observational designs (e.g., cohort study, case-control study), or modelling approach was included for full-text review.

Table 1. Study inclusion/exclusion criteria

Inclusion	Exclusion
Article type	

Clinical trials Observational designs (e.g. cohort study, case-control study) Modelling approach (e.g. economic evaluation)	Abstracts without full text Studies with small samples (e.g. case reports) Studies with no primary evidence (e.g. reviews, commentaries, editorials, or letters)
Language	
English	Other languages
PICO eligibility: Population	
Humans All ages All sexes Patients with CA-UTIs	Animals Environmental studies Patients with HA-UTIs Patients with infections of other locations
PICO eligibility: Intervention/exposure	
Infected by antibiotic-susceptible bacteria Infected by antifungal-susceptible fungi	Infected by virus Infected parasites
PICO eligibility: Comparison/control	
Infected by antibiotic-non-susceptible/resistant bacteria Infected by antifungal-non-susceptible/resistant fungi	Infected by virus Infected parasites
PICO eligibility: Outcomes	
Mortality Hospital LOS Direct and indirect medical costs	Other outcomes (e.g. patient satisfaction)

Data extraction and analysis

Data were extracted from the included studies, including study identifier, authors, journal, publication year, study design, data collection period, country / region, healthcare setting, perspective (patient, health system (representing payer and / or provider), societal), patient population, number of patients, UTI diagnosis criteria, pathogen, sensitivity profile, treatment, and outcome. We synthesised the impact of ABR on health outcomes (e.g. mortality), healthcare system (e.g. hospital length of stay (LOS), medication cost), and economic system (e.g., productivity) and compared these for infections caused by resistant versus susceptible pathogens. The methods to estimate the cost-of-illness were categorised into top-down approach, for those studies that reported total costs on a population level irrespective of the specific method used to derive these costs; or bottom-up approach, for those studies that reported average costs derived from accumulating measured costs from patient samples.

A meta-analysis was performed to synthesise the reported mortality and hospital LOS using a random effect model [19]. A random effects model assumes that the true effect size of the exposure(s) varies from study to study due to the study heterogeneity. Particularly, heterogeneities in this type of analysis occurred in definitions and categories of costs across health systems, settings, and disease types, cost measurement instruments, and unit prices. Thus, a random effects model was chosen to allow aggregating cost data from different studies by circumventing this heterogeneity. When meta-analysing mortality, we estimated pooled odds ratio based on crude mortality rate [20]. When meta-analysing LOS, we applied both the transformation-based methods (i.e. estimating sample mean and standard deviation from the median and sample size) [21,22] and median-based methods (i.e., considering study-specific median differences and data distribution) [23], considering mean and variance, and median and interquartile range (IQR) were commonly used when reporting LOS, and the distribution of LOS was heavily right-tailed (e.g., not normally distributed) [24,25]. We assessed the publication bias for the mortality outcome using a funnel plot and Egger's test [26,27]. No meta-analysis was performed for economic costs due to the large variation in the resources costed and the methods used to determine the cost. To compare the reported monetary costs, the outcomes were converted into 2023 United States dollars (USD) by inflating the cost to 2023 original-currency estimates using annual inflation rates [28], then converting this into USD utilising 2023 average exchange rates [29].

Quality assessment

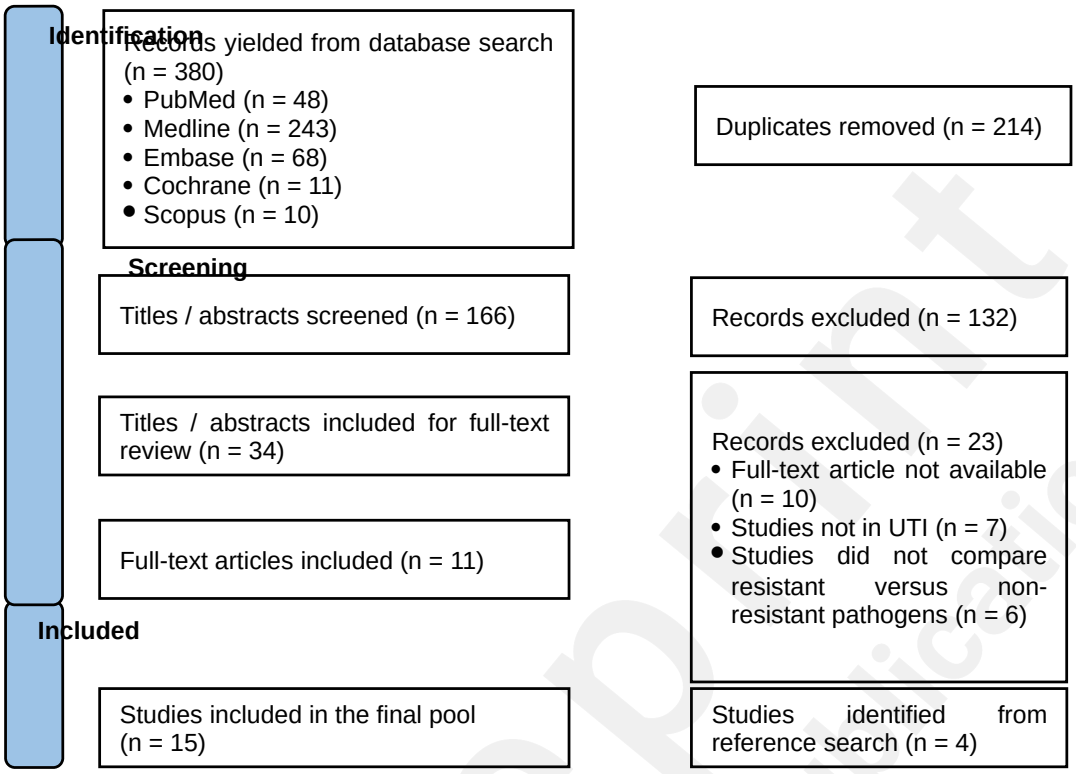
The included studies were assessed using the Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS) tool [30].

Results

Study characteristics

A total of 380 titles and abstracts were yielded from the database search. 214 duplicates were removed, and 132 abstracts were deemed irrelevant. Thirty-four (34) studies entered the full-text review, of which, 11 studies were included. Through reference search, other 4 studies were identified and included in the final study pool. Figure 1 summarised the screening process in a PRISMA flowchart.

Figure 1. PRISMA flowchart



The characteristics of the 15 identified studies are present in Table 2 [12–14,31–42]. The countries which individually produced the highest number of studies were the US (33%, 5/15) [14,34,39,40,42], followed by Spain (20%, 3/15) [13,33,41], and South Korea (13%, 2/15) [31,37]. Thirteen (87%, 13/15) studies focused on hospitalised patients [12–14,31,33–37,39–42], and 2 (13%, 2/15) studies focused on primary care patients [32,38]. Thirteen (87%, 13/15) studies included adult patients of all genders [12–14,33–42], of which, 1 study included patients aged 65 and above [33]. Chang et al and Little et al (13%, 2/15) investigated adult female patients [31,32]. All hospital-based studies had UTI diagnosed via presence of symptoms, infection biomarkers, and microbiology culture confirmation, and differentiate community-acquired cases using the 48 hours cut-off time after admission. Two (13%, 2/15) studies reported HA-UTI [14,40]. The community-based study recruited the patient with urinary tract symptoms (suspected UTI) or history of dysuria and frequency [32,38]. In total, 57,251 CA-UTI cases were reported, 47,131 UTI cases were analysed (Supplementary material, Table S3).

Table 2 Study characteristics: data collection period, patient population, and identified pathogens

Study	Country	Period	Population	Organisms identified		
				Gram-negative	Gram-positive	Fungi
Chang, 2016 [31]	South Korea	Jan 2001 - Dec 2010	Hospitalised female patients with CO-APN defined by presence of fever (>=38.0℃), pyuria (5-10 leukocytes per HPF upon urine microscopic examination), bacteriuria (>=105/ml clean voided urine or >=104/ml catheterised urine)	*Escherichia coli*		
Sozen, 2015 [12]	Turkey	Jul 2012 - Jun 2014	Hospitalised patients with positive urine culture <48 hours of admission, without hospitalisation or urological surgery during the last month	*Enterobacter aerogenes* *Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*		
Little,	UK	Apr 2002	Female patients aged 17-70 recruited from	Not reported		

2009 [32]		- May 2003	primary care practices with suspected UTI or a history of dysuria and frequency			
Tabak, 2018 [14]	US	Jan 2013 - Sep 2015	Hospitalised adult patients with urine culture <3 days of admission, with Gram-negative pathogens isolated and tested for carbapenem susceptibility	*Acinetobacter baumannii* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli* *Klebsiella pneumoniae* *Morganella morganii* *Proteus mirabilis* *Pseudomonas aeruginosa* *Serratia marcescens*		
Madrazo, 2021 [33]	Spain	Jan 2016 - Dec 2019	Hospitalised patients aged >=65 with CA-UTI and positive urine culture	*Acinetobacter baumannii* *Enterobacter cloacae* *Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Other Enterobacteriaceae*	*Enterococcus faecalis* *Enterococcus faecium* *Enterococcus gallinarum* *Streptococcus agalactiae*	*Candida* spp
Wozniak, 2022 [35]	Australia	Jan 2012 - Sep 2016	Hospitalised patients with positive urine culture <48 hours of admission with >2 species identified (>105 CFUs/ml, 103/ml for cystitis, 104/ml for pyelonephritis)	*Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	Enterococcus faecium Staphylococcus aureus	
Zilberberg, 2017 [42]	US	2009 - 2013	Hospitalised adult patients aged >=18 with CO-UTI defined by ICD-9 code, positive urine culture and antibiotic treatment beginning <48 hours of admission and continuing for at least 3 consecutive days or until discharge	*Citrobacter freundii* *Escherichia coli* *Enterobacter aerogenes* *Enterobacter cloacae* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Morganella morganii* *Serratia marcescens* *Proteus mirabilis* *Proteus* spp *Providencia* spp		
Mark, 2021 [34]	US	Jan 2017 - Jun 2019	Hospitalised patients aged >=18 with febrile UTI defined by fever, ICD-10 code of UTI, pyelonephritis, or sepsis, urine culture (EKP species >100,000 CFUs/ml)	*Escherichia coli* *Klebsiella pneumoniae* *Proteus mirabilis*		
Kim, 2013 [37]	South Korea	Mar 2010 - Feb 2011	Hospitalised patients admitting emergency department or outpatient clinic from the community with CA-APN defined by pyuria (>=5-9 WBC/HPF), fever (>=37.8℃), and positive urine culture collected at the time of admission	*Acinetobacter baumannii* *Citrobacter* spp *Enterobacter* spp *Escherichia coli* *Klebsiella pneumoniae* *Proteus* spp *Pseudomonas aeruginosa*	*Enterococcus* spp *Staphylococcus aureus*	
François, 2016 [38]	France	Jan 2012 - Feb 2013	Female patients aged >18 recruited from GP practices with UTI symptoms and followed up for 8 weeks	*Escherichia coli*		
Cheong, 2022 [36]	Korea	Jan 2018 - Dec 2019	Hospitalised patients aged >=19 with ICD-10 code of CA-APN <48 hours of admission, defined by fever (>=37.8℃), pyuria (>=4-9 WBC/HPF), positive urine or blood culture, and symptoms or signs relevant to APN	*Citrobacter* spp *Enterobacter* spp *Escherichia coli* *Klebsiella pneumoniae* *Proteus* spp		
Macvane, 2013 [39]	US	Sep 2011 – Aug 2012	Hospitalised patients >=18 with UTI present <=48 hours of admission defined by positive urine culture (>=10,000 CFUs)	*Escherichia coli* *Klebsiella* spp		
Esteve-Palau, 2015 [13]	Spain	Aug 2010 - Jul 2013	Hospitalised patients >=18 with symptomatic CA- or CO-HA-UTI <=48 hours of admission including cystitis, pyelonephritis, acute prostatitis, and urosepsis, defined by increase of urinary frequency, urgency, dysuria, or suprapubic tenderness, a positive urine culture of Escherichia coli (>105 CFUs/ml)	*Escherichia coli*		
Rozenkiewicz, 2021 [41]	Spain	Jan 2011 – Jan 2016	Hospitalised patients >=18 with symptomatic CA-UTI (identified <=48 hours of admission and not AHA) including cystitis, pyelonephritis, acute prostatitis, urinary sepsis, and confusion state associated with UTI, defined by fever (>38℃),	*Klebsiella pneumoniae*		

			urinary urgency, polyuria, dysuria or suprapubic pain, a positive urine culture (>105 CFUs/ml)			
Cardwell, 2016 [40]	US	Jul 2013 – Sep 2013	Hospitalised patients >=18 with fever, chills, rigors, nausea or vomiting, haematuria, altered mental status, suprapubic or flank pain, costovertebral angle tenderness, urinary frequency, urgency, or dysuria, and treatment for UTI <=24 hours of admission	*Citrobacter* spp *Enterobacter* spp *Escherichia coli* *Klebsiella* spp *Morganella* spp *Proteus* spp *Providencia* spp *Pseudomonas aeruginosa* *Serratia* spp	Enterococcus spp	

Abbreviations: AHA: ambulatory healthcare-associated; APN: acute pyelonephritis; CA: community-acquired / associated; CFU: colony-forming unit; CO: community-onset; ESBL: extended spectrum beta-lactamase; General Practice: GP; HPF: high-power field; ICD: International Classification of Diseases; UTI: urinary tract infection; WBC: white blood cell.

Fourteen (93%, 14/15) studies reported the pathogens identified, of which, all reported Gram-negative bacteria (GNB) [12–14,31–42], four (29%, 4/14) reported Gram-positive bacteria (GPB) [33,35,37,40], one (7%, 1/14) reported fungi [33], three (21%, 3/14) exclusively reported UTI caused by E. coli [13,31,38], one (7%, 1/14) reported UTI caused by K. pneumoniae [41]. *E. coli*, *K. pneumoniae*, and *P. aeruginosa* are the most frequently identified organisms. Among the studies in specific antibiotic-pathogen combinations, 2 studies assessed Carbapenem-resistant organisms, specifically GNB and Enterobacteriaceae in each, respectively [14,42]. Mark et al examined *E. coli*, *K. pneumoniae*, and *Proteus mirabilis* (*P. mirabilis*) resistant to third-generation cephalosporin-resistant (3GC) [34], Sozen et al and Macvane et al examined ESBL- and/or inducible beta-lactamases (IBL)-producing GNB [12,39].

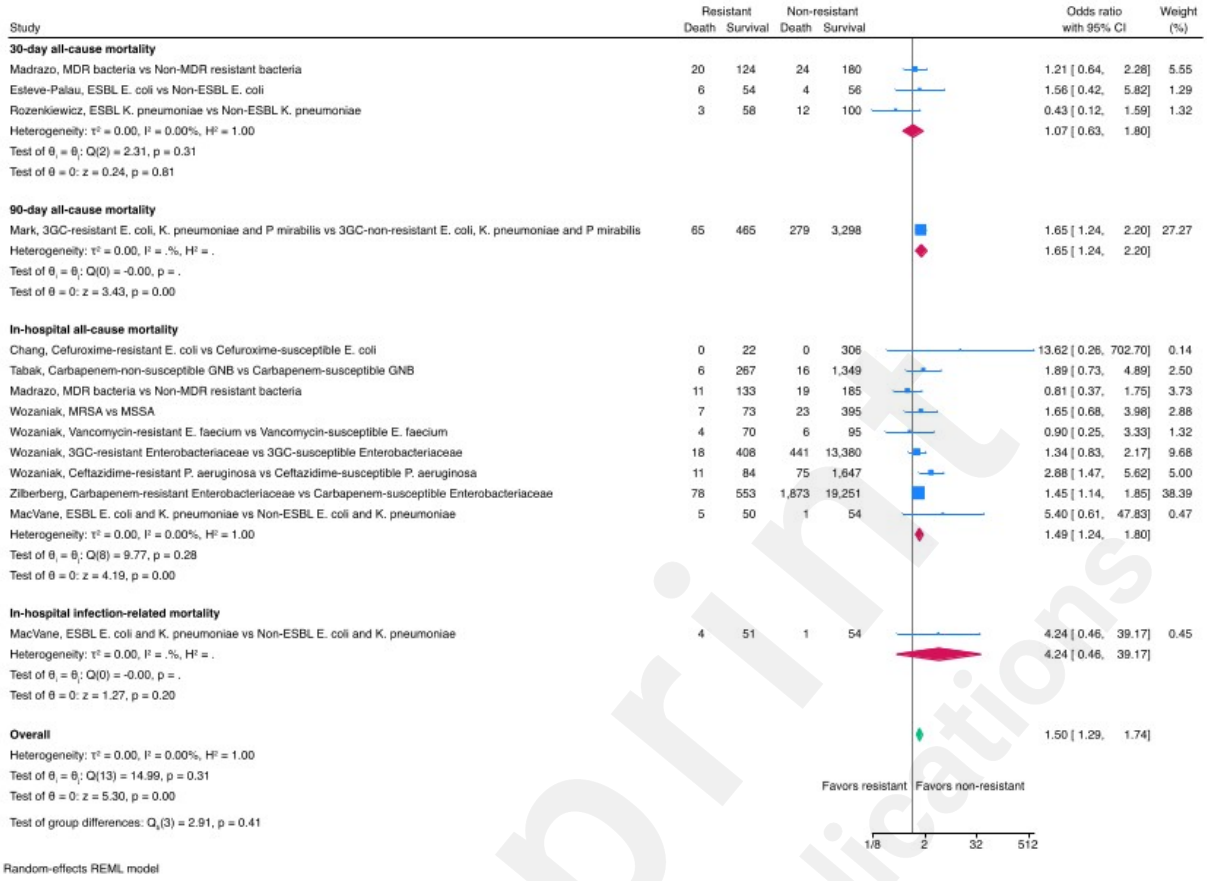
All the included studies estimated the clinical and economic outcomes from patients recruited from single or multiple health facilities. François et al provided a national-level estimate of the infection incidence and costs derived from the study cohort [38]. No study performed sensitivity analysis. The results of the quality assessment are presented in supplementary material (Supplementary material, Table S5). All studies met the minimum required score. Six (40%, 6/15) studies failed to meet the minimum required criteria [13,31,38,39,41,42].

The burden of antibiotic-resistant urinary tract infections

When quantifying the burden attributable to ABR, the included studies compared patient outcomes, health system outcomes, and economic costs of the CA-UTI cases caused by resistant pathogens against those caused by non-resistant pathogens. The most reported outcomes were mortality, hospital LOS, and economic costs due to antibiotic treatment (Supplementary material, Table S4). A health system perspective was taken by all bar 1 included studies when estimating the costs [12–14,31–42]. François et al took a society perspective and included productivity loss due to absenteeism [38]. When comparing the patients with resistant and non-resistant CA-UTIs, 4 studies matched case and control [13,14,39,42], 2 studies adjusted patient characteristics and other risk factors when reporting outcomes [34,36], other studies performed no matching or adjusting.

Twelve (12) studies reported mortality, including in-hospital all-cause mortality [14,31,33,35,39,42], in-hospital infection-related mortality [39], 30-day all-cause mortality [13,33,41], and 90-day all-cause mortality [34] (Supplementary material, Table S4(a)). Seven (7) studies reported higher crude mortality among the patients with antibiotic-resistant UTI [13,14,33–35,39,42], of which, 1 study demonstrated the statistical significance [42]. The pooled odds ratios of mortality outcomes for resistant UTIs are presented in Figure 2. Results presented odds ratios of resistant compared against non-resistant infections. The blue squares centred at the point estimate of the effect size, with horizontal lines depicting the 95% confidence interval (95% CI), and sizes of the blue squares corresponding to the patient group sizes. The overall effect sizes are represented by diamonds centred on their estimated values with the diamond width corresponding to the CI length. The random-effects model estimated an overall odds ratio of 1.50 (95% CI: 1.29, 1.74), suggesting that ABR increased the overall mortality. The subgroup analysis conducted for different mortality outcomes suggested increased odds of in-hospital all-cause mortality (Figure 2). No publication bias was detected for mortality (Supplementary material, Figure S1).

Figure 2. Pooled mortality of urinary tract infections



All 13 hospital-based studies reported LOS [12–14,31,33–37,39–42], among which, 11 reported significantly higher LOS associated with antibiotic-resistant UTIs (Supplementary material, Table S4(b)) [12–14,33–37,39,41,42]. Cardwell et al reported higher LOS among the patients with clinical failure due to inappropriate antibiotic therapies for resistant infections [40]. The meta-analysis of studies reported LOS in mean and SD estimated a pooled excess LOS of 2.45 days (95% CI: 0.51 – 4.39) (Figure 3(a)). The meta-analysis of studies reported LOS in median and IQR estimated a pooled excess LOS ranged from the lowest value of 1.50 days (95% CI: 0.71, 4.00) estimated by the median of the differences of medians (MDM) method to the highest value of 2.00 days (95% CI: 0.85, 3.15) estimated by the linear quantile mixed models (LQMM) method (Figure 3(a)).

Figure 3(a). Pooled mean difference in length of stay of urinary tract infections

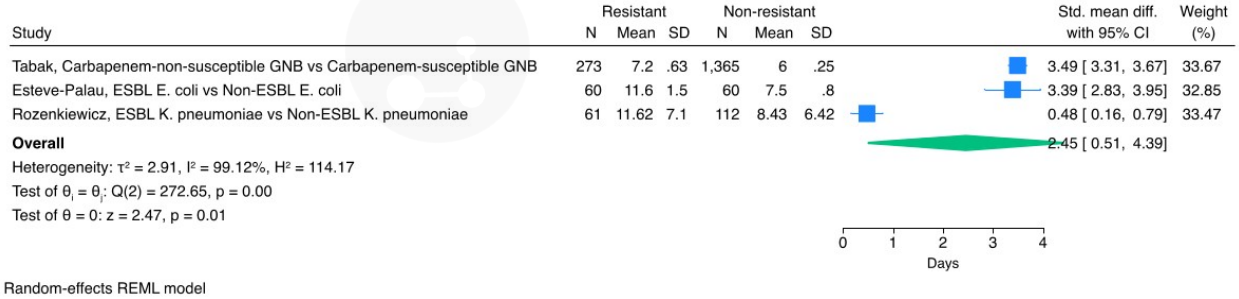
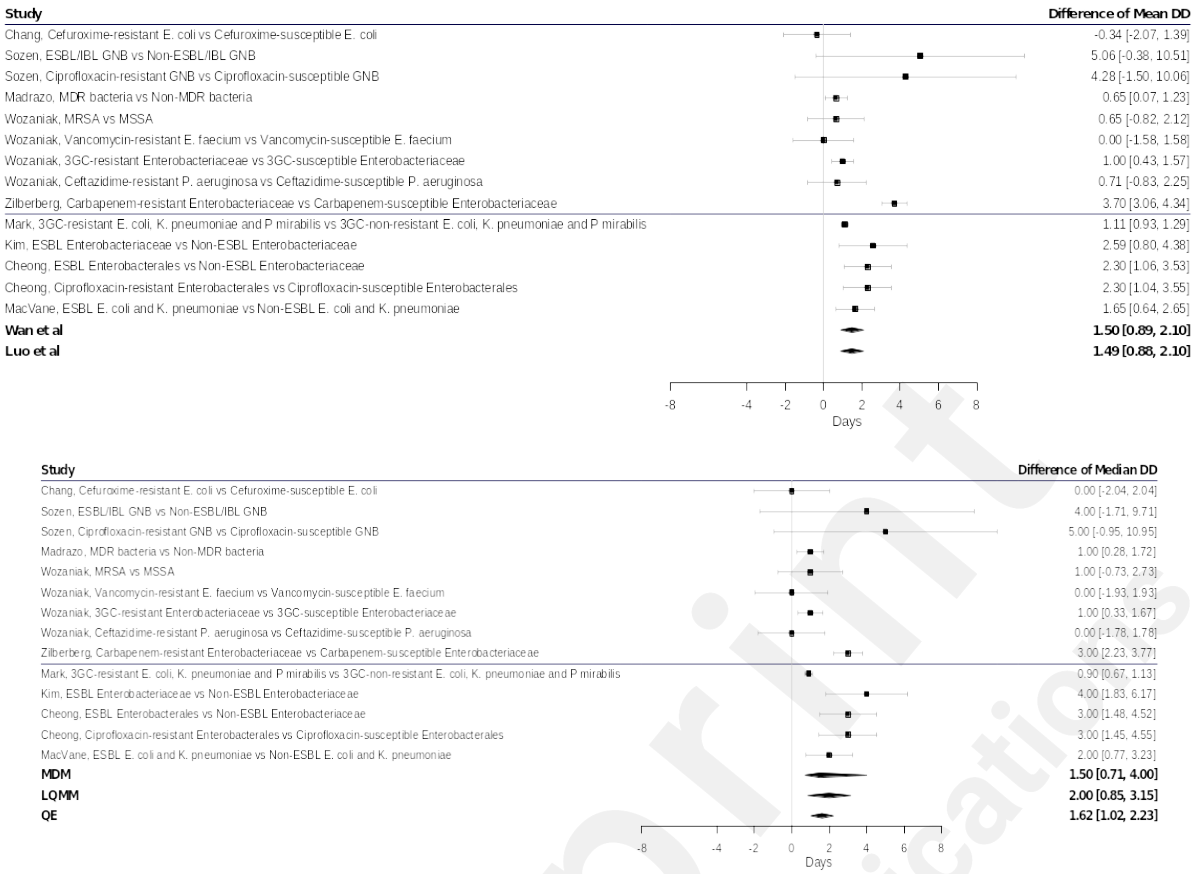
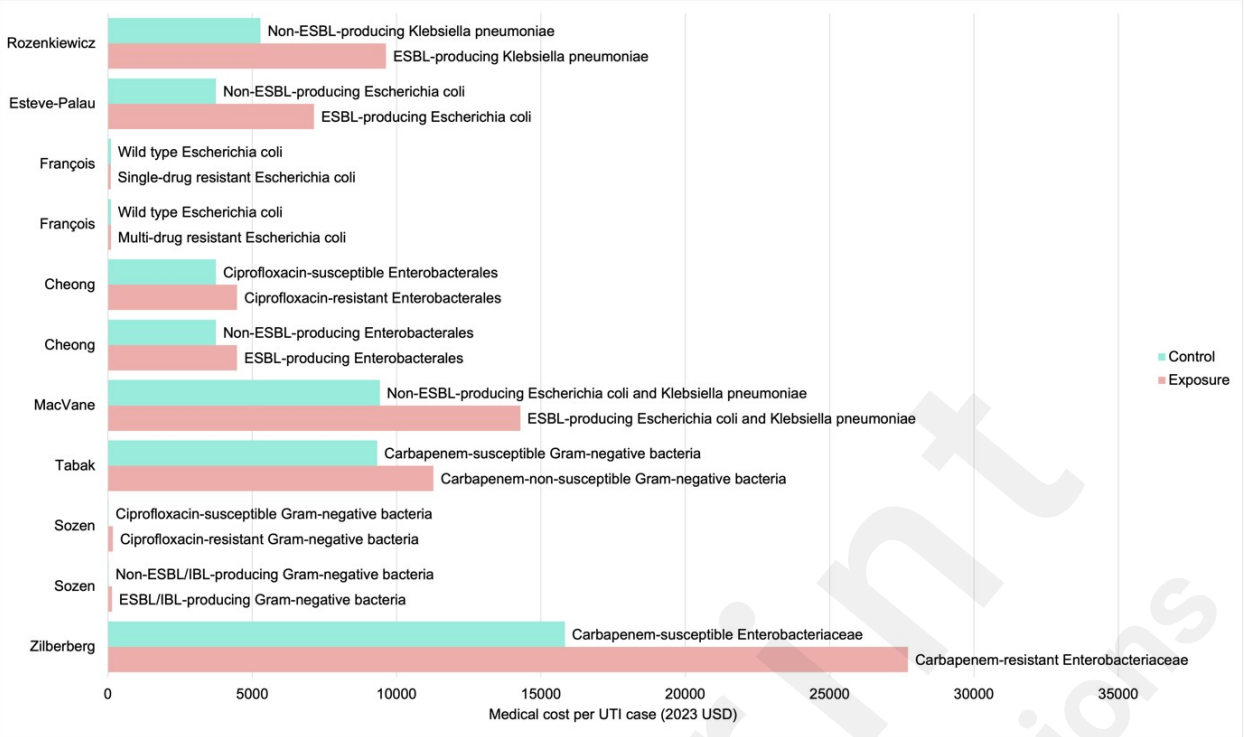


Figure 3(b). Pooled median difference in length of stay of urinary tract infections



Eight (8) studies reported costs in monetary terms (Supplementary material, Table S4(c)) [12–14,36,38,39,41,42], including 5 that reported costs in USD [12,14,36,39,42], and 3 reported costs in Euros [13,38,41]. None of the included studies discounted the costs. Considering only two studies explicitly stated the year of which the costs were adjusted to [12,38], the end year of data collection period was used to convert the reported costs into 2023 USD. Eight (8) studies reported direct medical costs incurred in secondary care, including emergency department costs [13,34], and additionally OPAT costs in one study [13,34]. All these 8 studies reported higher medical costs spent treating patients with resistant UTI in hospitals. The highest excess cost was observed in UTI caused by Carbapenem-resistant Enterobacteriaceae [42]. François et al reported costs incurred in primary care, specifically, the costs of GP visits due to UTI symptoms. The primary care costs of single- or multi-drug resistant *E. coli* UTI were not significantly higher than those caused by susceptible *E. coli*.

Figure 4. Medical cost of antibiotic-resistant urinary tract infections



Discussion

This review concluded that there is an economic burden attributable to ABR in CA-UTIs, including the costs of patients, health systems, and at societal level. The review included 15 studies, over-represented by the research from high-income countries, hospital settings, and infections caused by *E. coli* and *K. pneumoniae*. All studies were cross-sectional with limited patient sample size. No sensitivity analysis was performed to quantify the level of uncertainty in the results. The meta-analysis provided pooled estimates of odds ratio of mortality and mean difference in hospital LOS. The reported variation in economic costs were also synthesised.

We found that no systematic review in the economic burden of ABR in CA-UTI has been previously conducted. The increased mortality among the patients with ABR CA-UTI in this review was less profound, as opposed to the existing research in other types of infections, such as bacteraemia [41–43] or healthcare-associated UTIs [44]. Overall, ABR attributes to an increased odds ratio of mortality of 1.50. The increased odds of mortality can be explained by higher risk of treatment failure and UTI complications, such as bacteraemia and sepsis. The varied types of mortality outcomes reported reduced the comparability across studies. Most of the hospital-based studies reported a longer LOS experienced by the patients in the ABR group. We used multiple modelling methods to meta-analyse hospital LOS and estimated the excess duration of hospitalisation ranged from 1.50 to 2.45 days. All the studies that captured the costs in monetary terms reported excess medical costs in the ABR group, with the highest excess medical costs of 11,884.32 USD per case of CA-UTI caused by Carbapenem-resistant Enterobacteriaceae [43–45][46]. The findings of this review highlighted the scarcity of research in quantifying the economic burden of ABR, particularly in four areas. First, besides mortality, evidence in other types of patient burden associated with ABR is lacking, such morbidity (clinical failure, time to clinical stability, secondary infections) and chronic sequelae (recurrent infections). Second, existing research has been restricted to those cases present in the hospitals, the cases managed, and the costs incurred in primary care settings were not captured. However, the pathogen distributions and treatment options varied substantially for HA- and CA-UTIs, and for CA-UTIs managed in the community and in hospitals, community-based investigation is urgently needed to generate a comprehensive understanding across the whole-health economy [43,44]. Third, the types of medical resources costed remained largely inconsistent, which further reduced the validity of the excess costs estimated. Last, all the identified studies were limited in patient cohort size and follow-up duration and lacking analysis to address uncertainty, which led to the concerns of how generalisable the results were.

This review has two limitations. First, we only searched studies published in English. Second, we did not include those studies which the primary focus was to perform economic evaluation of CA-UTI treatment or

prevention measures and included estimated costs of drug-resistant cases. These limitations provided the scope for further research.

There are pressing needs to build understanding of the economics of AMR. The evidence to provide a full economic case for interventions tackling AMR is lacking. In this review, we identified knowledge and methodological gaps in existing research particularly relevant to quantify costs associated with ABR that occurred in the community. Future research calls for cost-of-illness analysis of infections standardising therapy-pathogen combination comparators, medical resources, productivity loss, and intangible costs to be captured, and data from community sectors and low-resourced settings and countries.

Notes

Author Contributions

NZ and PA developed the concept and methodology for this research. NZ and WM undertook literature search and screening and data extraction. NZ conducted meta-analysis. NZ, WM, and EC performed quality assessment. NZ drafted the initial manuscript. NZ, EC, WM, HWA, CB, AH, and PA contributed to data interpretation, revision of the manuscript and finalisation for submission. PA is the guarantor of the study. The corresponding author attests that all listed authors meet the ICMJE criteria for authorship and that no other meeting the criteria have been omitted.

Transparency statement

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Disclaimer

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health and Social Care, or UK Health Security Agency. No generative artificial intelligence (AI) was used in any portion of the manuscript writing.

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Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files. Additional information about this review can be found on PROSPERO (Registration number CRD42023374551).

Conflicts of Interest

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest (available on request from the corresponding author).

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Supplementary Material

Table S1 PRIMSA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1: Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2: Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3: Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3: Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4: Methods – Study selection, Table 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4: Methods – Search methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 18: Supplementary Material, Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4: Methods – Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4: Methods – Data extraction and analysis
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4: Methods – Data extraction and analysis Page 18: Supplementary Material, Table S4(a)(b)(c)
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4: Methods – Data extraction and analysis Page 18: Supplementary Material, Table S3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5: Methods – Quality assessment Page 24: Supplementary Material Page 25: Table S5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4: Methods – Data extraction and analysis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 4: Methods – Data extraction and analysis
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4: Methods – Data extraction and analysis
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4: Methods – Data extraction and analysis
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4: Methods – Data extraction and analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4: Methods – Data extraction and analysis
	13f	Describe any sensitivity analyses conducted to assess robustness of the	Page 4: Methods – Data

Section and Topic	Item #	Checklist item	Location where item is reported
		synthesized results.	extraction and analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5: Methods – Quality assessment Page 24: Supplementary Material, Table S5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5: Methods – Quality assessment Page 24: Supplementary Material, Table S5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5: Results – Study characteristics, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5: Results – Study characteristics, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 6: Study characteristics, Table 2 Page 18: Supplementary Material, Table S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7: Results – Study characteristics Page 24: Supplementary Material, Table S5, Figure S1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7: Results – The burden of antibiotic-resistant urinary tract infections Page 18: Supplementary Material, Table S4(a)(b)(c)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 7: Results – The burden of antibiotic-resistant urinary tract infections
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 7: Results – The burden of antibiotic-resistant urinary tract infections, Figure 2(a)(b), Figure 3(a)(b), Figure 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7: Results – The burden of antibiotic-resistant urinary tract infections
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7: Results – The burden of antibiotic-resistant urinary tract infections, Figure 2(a)(b), Figure 3(a)(b)
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7: Results – Study characteristics Page 24: Supplementary Material, Table S5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7: Results – Study characteristics Page 24: Supplementary Material, Table S5

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 10: Discussion
	23b	Discuss any limitations of the evidence included in the review.	Page 11: Discussion
	23c	Discuss any limitations of the review processes used.	Page 11: Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11: Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2: Trial Registration Page 3: Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3: Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 3: Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 11: Notes
Competing interests	26	Declare any competing interests of review authors.	Page 11: Notes
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 11: Notes

Table S2 Database search strings

	Search terms	Results
PubMed		
1	"Community-acquired"[Title/Abstract] OR "Community-onset"[Title/Abstract] OR "general practice"[Title/Abstract] OR "primary care"[Title/Abstract]	197,781
2	"Urine"[Title/Abstract] OR "urinary tract infection"[Title/Abstract] OR "urethra infection"[Title/Abstract] OR "Urethritis"[Title/Abstract] OR "bladder infection"[Title/Abstract] OR "Cystitis"[Title/Abstract] OR "Cystalgia"[Title/Abstract] OR "Bacteriuria"[Title/Abstract] OR "Bacilluria"[Title/Abstract] OR "Pyuria"[Title/Abstract] OR "Dysuria"[Title/Abstract] OR "Pyelonephritis"[Title/Abstract] OR "Leukocyturia"[Title/Abstract]	190,676
3	"Resistant"[Title/Abstract] OR "Drug-resistant"[Title/Abstract] OR "multi drug resistant"[Title/Abstract] OR "antimicrobial resistant"[Title/Abstract] OR "antibiotic resistant"[Title/Abstract] OR "antibacterial resistant"[Title/Abstract] OR "non susceptible"[Title/Abstract]	521,035
4	“Cost” [Title/Abstract] OR “economic” [Title/Abstract] OR “burden” [Title/Abstract] OR “mortality” [Title/Abstract] OR “length of stay”[Title/Abstract] OR “length of hospitali*” [Title/Abstract] OR “duration of stay” [Title/Abstract] OR “duration of hospitali*” [Title/Abstract] OR “productivity”[Title/Abstract]	1,989,673
5	#1 AND #2 AND #3 AND #4	72
6	Limit #5 to English only	72
7	Limit #6 to human only	56
8	Limit #7 to 2018/1/1 - 2023/1/31	48
MEDLINE		
1	("Community-acquired" or "Community-onset" or "General practice" or "Primary care").at,ab.	498,525
2	(Urine or "Urinary tract infection" or Urethra or "infection Urethritis" or "Bladder infection" or Cystitis or Cystalgia or Bacteriuria or Bacilluria or Pyuria or Dysuria or Pyelonephritis or Leukocyturia).at,ab.	873,465
3	(Resistant or Drug-resistant or Multi-drug resistant or Antimicrobial resistant or Antibiotic resistant or Antibacterial resistant or Non susceptible).at,ab.	1,378,867
4	(Cost or economic or burden or mortality or “length of stay” or “length of hospitali*” or “duration of stay” or “duration of hospitali*” or productivity).at,ab.	5,685,370
5	1 and 2 and 3 and 4	277
6	Limit 5 to English language	271
7	Limit 6 to human	256
8	Limit 7 to dt=20120101-20230131 [January 1st, 2012 to January 31st, 2023]	243
Embase		
1	("Community-acquired" or "Community-onset" or "General practice" or "Primary care").at,ab.	219,111
2	(Urine or "Urinary tract infection" or Urethra or "infection Urethritis" or "Bladder infection" or Cystitis or Cystalgia or Bacteriuria or Bacilluria or Pyuria or Dysuria or Pyelonephritis or Leukocyturia).at,ab.	453,850
3	(Resistant or Drug-resistant or Multi-drug resistant or Antimicrobial resistant or Antibiotic resistant or Antibacterial resistant or Non susceptible).at,ab.	641,820
4	(cost or economic or burden or mortality or length of stay or length of hospitali* or	2,720,943

	duration of stay or duration of hospitali* or productivity).at,ab.	
5	1 and 2 and 3 and 4	123
6	Limit 5 to English language	119
7	Limit 6 to human	117
8	Limit 7 to dd=20120101-20230131 [January 1st, 2012 to January 31st, 2023]	68
Cochrane		
1	("Community-acquired" or "Community-onset" or "General practice" or "Primary care"):ti,ab	26,496
2	(Urine or "Urinary tract infection" or Urethra or "infection Urethritis" or "Bladder infection" or Cystitis or Cystalgia or Bacteriuria or Bacilluria or Pyuria or Dysuria or Pyelonephritis or Leukocyturia):ti,ab	40,746
3	(Resistant or Drug-resistant or Multi-drug resistant or Antimicrobial resistant or Antibiotic resistant or Antibacterial resistant or Non susceptible):ti,ab	26,112
4	(cost or economic or burden or mortality or length of stay or length of hospitali* or duration of stay or duration of hospitali* or productivity):ti,ab	190,072
5	#1 and #2 and #3 and #4	15
6	#5 with Cochrane Library publication date from Jan 2012 to Jan 2023	11
Scopus		
1	TITLE-ABS ("community-acquired" OR "community-onset" OR "general practice" OR "primary care")	225,402
2	TITLE-ABS (urine OR "Urinary tract infection" OR urethra OR "infection Urethritis" OR "Bladder infection" OR cystitis OR cystalgia OR bacteriuria OR bacilluria OR pyuria OR dysuria OR pyelonephritis OR leukocyturia)	421,005
3	TITLE-ABS (resistant OR "Drug-resistant" OR "Multi-drug resistant" OR "Antimicrobial resistant" OR "Antibiotic resistant" OR "Antibacterial resistant" OR "Non susceptible")	786,611
4	TITLE-ABS (cost OR economic OR burden OR mortality OR length of stay OR length of hospitali* OR duration of stay OR duration of hospitali* OR productivity)	34,989
5	#1 AND #2 AND #3 AND #4	13
6	Language (English)	13
7	((PUBYEAR > 2012) AND (PUBYEAR < 2023))	10

Table S3 Study characteristics: urinary tract infection criteria, incidence, and causative pathogens

	Study	UTI (n)	Further inclusion / exclusion criteria	UTI analysed (n)	Causative pathogens (n, %)		
					Escherichia coli	Klebsiella species	Pseudomonas aeruginosa
1	Chang	328		328	328		
2	Sozen	82		82	69	10	3
3	Little	839	With mid-stream urine specimen, symptoms and duration, and antibiotic resistance status available	511	Not reported		
4	Tabak	7171	Propensity score matched carbapenem susceptible (C-S) and carbapenem non-susceptible (C-NS) cases	1638 (273 C-NS vs 1365 C-S)	335	Not reported	397
5	Madrazo	388		388	219	52	28
6	Wozniak	16,737		16,737	14,247 Enterobacteriaceae (Escherichia coli and Klebsiella spp)		1,817
7	Zilberberg	21,755	Matched carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-susceptible Enterobacteriaceae (CSE) cases	21,755 (631 CRE vs 21,124 CSE)	Not reported		
8	Mark	5922	Caused by EKP pathogens (Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis)	4113	Not reported		
9	Kim	557		557	497	18	6
10	François	460	Confirmed by positive culture	345	267	Not reported	
11	Cheong	241	Caused by Enterobacteriales	241	217 (90.0%)	13 (5.4%)	Not reported
12	MacVane	2345	Matched ESBL-producing and non-ESBL producing cases	55	44	8	
13	Esteve-Palau	120		120	120		
14	Rozenkiewicz	173		173		173	
15	Cardwell	133	Confirmed by positive culture	88	51	10	Not reported

Table S4(a) Reported mortality

Study	Comparator		Infection		Mortality		Crude mortality rate (%)		
	Exposure	Control	Exposure (n)	Control (n)	Exposure (n)	Control (n)	Exposure (%)	Control (%)	p-value
In-hospital all-cause mortality									
Chang	Cefuroxime-resistant E. coli	Cefuroxime-susceptible E. coli	22	306	0	0	0.0%	0.0%	-
Tabak	Carbapenem-non-susceptible GNB	Carbapenem-susceptible GNB	273	1365	6	16	2.2%	1.2%	-
Madrazo	MDR	Non-MDR	144	204	11	19	7.6%	9.3%	0.699
Wozaniak	MRSA	MSSA	80	418	7	23	8.8%	5.5%	-
Wozaniak	Vancomycin-resistant E. faecium	Vancomycin-susceptible E. faecium	74	101	4	6	5.4%	5.9%	-
Wozaniak	3GC-resistant Enterobacteriaceae	3GC-susceptible Enterobacteriaceae	426	13,821	18	441	4.2%	3.2%	-
Wozaniak	Ceftazidime-resistant P. aeruginosa	Ceftazidime-susceptible P. aeruginosa	95	1,722	11	75	11.6%	4.4%	-
Zilberberg	Carbapenem-resistant Enterobacteriaceae	Carbapenem-susceptible Enterobacteriaceae	631	21,124	78	1,873	12.4%	8.9%	0.002
MacVane	ESBL-producing EK	Non-ESBL-producing EK	55	55	5	1	9.1%	1.8%	0.21
In-hospital infection-related mortality									
MacVane	ESBL-producing EK	Non-ESBL-producing EK	55	55	4	1	7.3%	1.8%	0.37
30-day all-cause mortality									
Madrazo	MDR	Non-MDR	144	204	20	24	13.9%	11.8%	0.624
Esteve-Palau	ESBL-producing E. coli*	Non-ESBL-producing E. coli	60	60	6	4	10.0%	6.7%	0.74
Rozenkiewicz	ESBL-producing K. pneumoniae*	Non-ESBL-producing K. pneumoniae	61	112	3	12	4.9%	10.7%	0.263
90-day all-cause mortality									
Mark	3GC-resistant EKP	3GC-non-resistant EKP	530	3,577	65	279	12.3%	7.8%	-

*Reported with HCA-UTI and CA-UTI combined

Abbreviations: GNB: Gram-negative bacteria; MDR: multi-drug resistant; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-susceptible Staphylococcus aureus; 3GC: third-generation cephalosporin; ESBL: Extended Spectrum Beta-Lactamase; E. coli: Escherichia coli; E. faecium: Enterococcus faecium; P. aeruginosa: Pseudomonas aeruginosa; K. pneumoniae: Klebsiella pneumoniae; EK: Escherichia coli and Klebsiella species; EKP: Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis.

Table S4(b) Reported hospital length of stay (LOS)

Study	Comparator		Infection		Hospital LOS		
	Exposure	Control	Exposure (n)	Control (n)	Exposure (days) (median, IQR)	Control (days) (median, IQR)	p-value
Chang	Cefuroxime-resistant E. coli	Cefuroxime-susceptible E. coli	22	306	10 (8 - 13)	10 (8 - 14)	0.319
Sozen	ESBL/IBL positive GNB	ESBL/IBL negative GNB	45	43	9 (3 - 24)	5 (2 - 14)	0.001
Sozen	Ciprofloxacin-resistant GNB	Ciprofloxacin-susceptible GNB	48	40	9 (3 - 24)	4 (2 - 17)	0.001
Tabak	Carbapenem-non-susceptible GNB	Carbapenem-susceptible GNB	273	1365	Mean: 7.2	Mean: 6.0	< 0.001
Madrazo	MDR	Non-MDR	144	208	6 (4 - 8)	5 (4 - 7)	0.029
Wozaniak	MRSA	MSSA	80	418	6.5 (4 - 12.3)	6 (3 - 12)	-
Wozaniak	Vancomycin-resistant E. faecium	Vancomycin-susceptible E. faecium	74	101	6.5 (4 - 10.7)	7 (4 - 11)	-
Wozaniak	3GC-resistant Enterobacteriaceae	3GC-susceptible Enterobacteriaceae	426	13,821	6 (3 - 11)	5 (3 - 9)	-
Wozaniak	Ceftazidime-resistant P. aeruginosa	Ceftazidime-susceptible P. aeruginosa	95	1,722	6 (3 - 12.5)	6 (3 - 11)	-
Zilberberg	Carbapenem-resistant Enterobacteriaceae	Carbapenem-susceptible Enterobacteriaceae	631	21,124	10 (6 - 17) Mean (SD): 14.6 (15.9)	7 (4 - 11) Mean (SD): 9.0 (9.4)	< 0.001
Mark	3GC-resistant EKP	3GC-non-resistant EKP	530	3,577	88.8h (64.8 - 132.0) Mean (SD): 115.4 (117.8)	67.2h (45.6 - 93.6) Mean (SD): 87.1 (98.6)	-
Kim	ESBL-producing Enterobacteriaceae	Non-ESBL-producing Enterobacteriaceae	46	480	10.5 (5.8 - 14.3)	7 (6 - 10)	0.012
Cheong	ESBL-producing Enterobacterales	Non-ESBL-producing Enterobacterales	75	166	11 (8 - 14)	8 (6 - 12)	< 0.001
Cheong	Ciprofloxacin-resistant Enterobacterales	Ciprofloxacin-susceptible Enterobacterales	87	154	11 (7 - 14)	8 (6 - 11)	< 0.001
MacVane	ESBL-producing EK	Non-ESBL-producing EK	55	55	6 (4 - 8)	4 (3 - 6)	0.02
Esteve-Palau	ESBL-producing E. coli**	Non-ESBL-producing E. coli	60	60	Mean (SD): 11.6 (1.5)	Mean (SD): 7.5 (0.8)	0.02
Rozenkiewicz	ESBL-producing K. pneumoniae**	Non-ESBL-producing K. pneumoniae	61	112	Mean (SD): 11.62 (7.1)	Mean (SD): 8.43 (6.42)	0.003
Cardwell	CA-UTI with appropriate empirical therapy	CA-UTI with inappropriate empirical therapy	Not reported	Not reported	4 (3-6)***	3 (4-10)***	0.79

**Reported with HCA-UTI and CA-UTI combined

Abbreviations: GNB: Gram-negative bacteria; MDR: multi-drug resistant; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-susceptible Staphylococcus aureus; 3GC: third-generation cephalosporin; ESBL: Extended Spectrum Beta-Lactamase; E. coli: Escherichia coli; E. faecium: Enterococcus faecium; P. aeruginosa: Pseudomonas aeruginosa; K. pneumoniae: Klebsiella pneumoniae; EK: Escherichia coli and Klebsiella species; CA-UTI: community-acquired urinary tract infection.

Table S4(c) Reported economic costs

Study	Comparator		Infection		Costed items	Cost			Year to convert from
	Exposure	Control	Exposure (n)	Control (n)		Exposure (mean, 95 % CI)	Control (mean, 95 % CI)	p-value	
Sozen	ESBL/IBL positive GNB	ESBL/IBL negative GNB	45	43	Antibiotic treatment	Median (IQR): $110.6 (5.5-505.2)	Median (IQR): $19.8 (6.5-384.2)	0.001	2014
Sozen	Ciprofloxacin-resistant GNB	Ciprofloxacin-susceptible GNB	48	40	Antibiotic treatment	Median (IQR): $135.1 (5.5 - 505.2)	Median (IQR): $19.8 (6.56 - 234.6)	0.001	2014
Tabak	Carbapenem-non-susceptible GNB	Carbapenem-susceptible GNB	273	1,365	Unspecified	$8,743	$7,231, p < 0.001	< 0.001	2015
Zilberberg	Carbapenem-resistant Enterobacteriaceae	Carbapenem-susceptible Enterobacteriaceae	631	21,124	Unspecified	$33,400 (SD: 37,662) Median (IQR): 21,154 (12,687 - 39,374, p < 0.001)	$19,036 (SD: 24,494) Median (IQR): 12,082 (7,104 - 21,822, p < 0.001)	< 0.001	2013
Cheong	ESBL-producing Enterobacterales	Non-ESBL-producing Enterobacterales	75	166	Consultation fee Hospitalisation expenditures Meal	Median (IQR): $3,730.2 (2,928.9 - 5,692.4)	Median (IQR): $3,119.3 (2,099.3 - 4,829.9)	0.001	2019
Cheong	Ciprofloxacin-resistant Enterobacterales	Ciprofloxacin-susceptible Enterobacterales	87	154	Cost for medication Procedure or operation Laboratory examination Radiologic examination Others	Median (IQR): $3,730.2 (2,524.4 - 5,937.7)	Median (IQR): $3,119.3 (2,148.3 - 4,578.5)	0.005	2019
MacVane	ESBL-producing EK	Non-ESBL-producing EK	55	55	Bed cost Antibiotic treatment	Median (IQR): $10,741 (6,846 - 15,819)	Median (IQR): $7,083 (5,667 - 11,652)	0.02	2012
François	MDR E. coli*	Wild (susceptible) E. coli*	98,504	222,933	Physician visits Diagnostic tests	€74.49 (30.87 - 118.11)	€74.76 (57.61 - 91.91)	0.99	2013
François	SDR E. coli*	Wild (susceptible) E. coli*	197,009	222,933	Prescription drugs Hospitalizations Loss of productivity due to absenteeism	€67.44 (43.93 - 90.95)	€74.76 (57.61 - 91.9)	0.63	2013
Esteve-Palau	ESBL-producing E. coli**	Non-ESBL-producing E. coli	60	60	Hospitalisation cost - Pharmacy - Antibiotic treatment - Laboratory - Inter consultations OPAT	Median (IQR): €4,980 (2,783 - 8,465)	Median (IQR): €2,612 (1,810 - 4,318)	<0.001	2013
Rozenkiewicz	ESBL-producing K. pneumoniae**	Non-ESBL-producing K. pneumoniae	61	112	Hospitalisation cost - Pharmacy - Antibiotic treatment - Nursery - Laboratory - Radiology - Inter consultations Emergency room visits	Median (IQR): €6,718 (3,322 - 9,611)	Median (IQR): €3,688 (1,783 - 4,141), p < 0.001	<0.001	2015

*Estimated at national level in France: The number of visits to general practices for suspected UTIs was estimated to be 823,073 among over the age of 18 years in 2012 (95 % CI: 623,614–1,040,532). Among these clinical UTIs, 626,046 (95 % CI: 465,196–786,896) were confirmed by positive urine cultures, and 518,446 (95 % CI: 381,981–654,911) of these UTIs were due to E. coli. Among the E. coli-positive urine cultures, 38 % (95 % CI: 31–45 %) were resistant to at least one antibiotic (SDR, n = 197,009), and 19 % (15–24 %) were multi-resistant (MDR, n = 98,504). The number of wild type (susceptible) E. coli was estimated to be 222,932.

Abbreviations: ESBL: Extended Spectrum Beta-Lactamase; IBL: Inducible Beta-Lactamases; GNB: Gram-negative bacteria; EK: Escherichia coli and Klebsiella species; E. coli: Escherichia coli; K. pneumoniae: Klebsiella pneumoniae; MDR: multi-drug resistant; SDR: single-drug resistant; OPAT: outpatient parenteral antimicrobial therapy

Table S5 Quality assessment results

The criteria for controlled before / after (CBA) study, controlled interrupted time-series (ITS) study, non-controlled ITS / BA study, and qualitative study are not presented as no such study design was identified in this review.

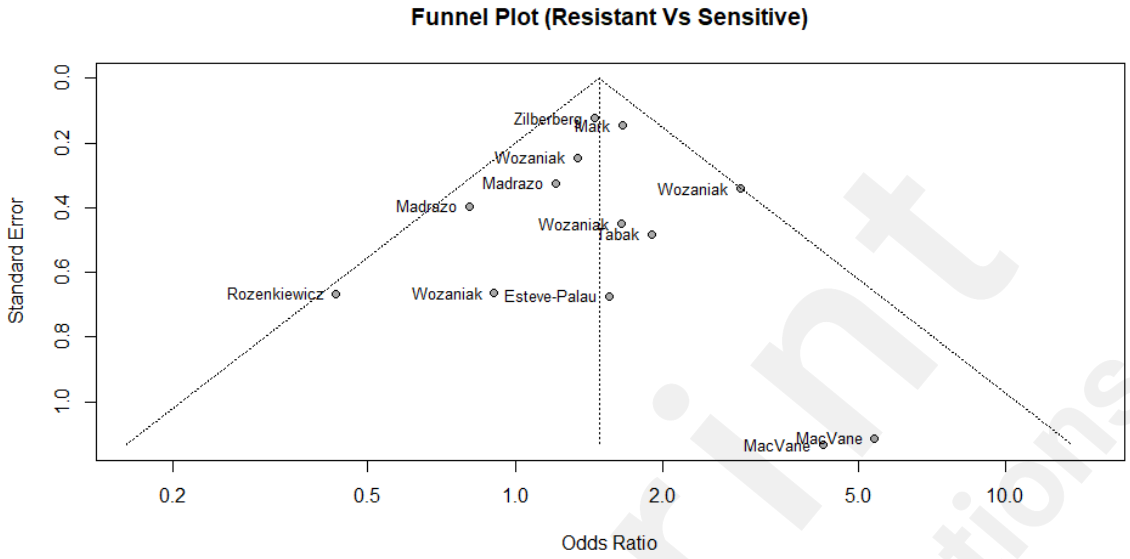
Study details	Study type	Methodology																			Overall			
		All	RCT & CRCT					Cohort Studies				All studies (quantitative and qualitative)												
		1	2	3	4	5	6	18	18	19	20	25	26	27	28	29	30	31	32	33	34	Final score	Minimum criteria met?	Minimum score met?	Related to aims of review?
Madrazo	Cohort	2						2	2	2	2	2		2	2	2	2	2	2	2	2	28	Yes	Yes	Yes
Mark	Cohort	2						2	2	2	2	2		2	2	2	2	2	2	2	2	28	Yes	Yes	Yes
Sozen	Cohort	2						2	2	2	2	2		2	2	1	0	0	0	2	1	20	Yes	Yes	Yes
Tabak	Cohort/case control	2						2	2	2	2	2		2	2	2	2	2	1	1	26	Yes	Yes	Yes	
Wozniak	Cohort/case control	2						2	2	2	2	2		2	2	1	2	2	2	2	2	27	Yes	Yes	Yes
Chang	Cohort/case control	2						2	2	2	2	2		2	2	1	2	0	2	1	1	23	No	Yes	Yes
Cheong	Cohort/case control	2						2	2	2	2	2		2	2	2	2	0	2	0	2	24	Yes	Yes	Yes
François	Cohort	2						1	1	2	2	2		2	2	0	2	2	2	1	2	23	No	Yes	Yes
Kim	Cohort/case control	2						2	2	2	2	1		2	2	2	2	0	2	1	1	23	Yes	Yes	Yes
Little	RCT	2	2	2	1	2	2					0	2	2	2	2	2	2	2	1	1	27	Yes	Yes	Yes
Cardwell	Cohort	2						2	2	2	2	2		2	2	2	2	2	2	2	1	27	Yes	Yes	Yes
Esteve-Palau	Cohort/case control	2						2	2	2	2	2		2	2	1	2	2	2	2	2	27	No	Yes	Yes
MacVane	Cohort/case control	2						2	2	2	2	2		2	2	1	2	2	2	2	2	27	No	Yes	Yes
Rozenkiewicz	Cohort	2						2	2	2	2	2		2	2	1	2	1	2	2	2	26	No	Yes	Yes
Zilberberg	Cohort	2						2	2	2	2	2		2	2	1	2	2	2	2	2	27	No	Yes	Yes
		(Criteria ID) Scoring system: Yes = 2 points; Unclear = 1 point; No = 0 points																						

Criteria

1. Clearly stated aims?
2. Sequence generation
3. Allocation concealment
4. Blinding
5. Follow-up of professionals
6. Follow-up of patients or episodes of care
18. Comparability of groups (2E)
    Comparability of outcomes (3G)
19. Sufficient follow-up period
20. Protection against information bias (5B)
21. Appropriate qualitative methodology?
22. Appropriate Study Design?
23. Sampling and Recruitment appropriate?
24. Data collection appropriate?
25. Blinded assessment of primary outcome measures? (protection against detection bias) (3E)
26. Intervention unlikely to affect data collection?
27. Reliable primary outcome measures? (3F)
28. Free of selective outcome reporting(7A)
29. Incomplete outcome data addressed? (4C)
30. Analysis sufficiently rigorous/ free of bias?
31. Limitations addressed?
32. Conclusions clear & justified?
33. Free of other risk of bias? Threats to internal/external validity? Researcher bias/reflexivity?
34. Ethical issues addressed?

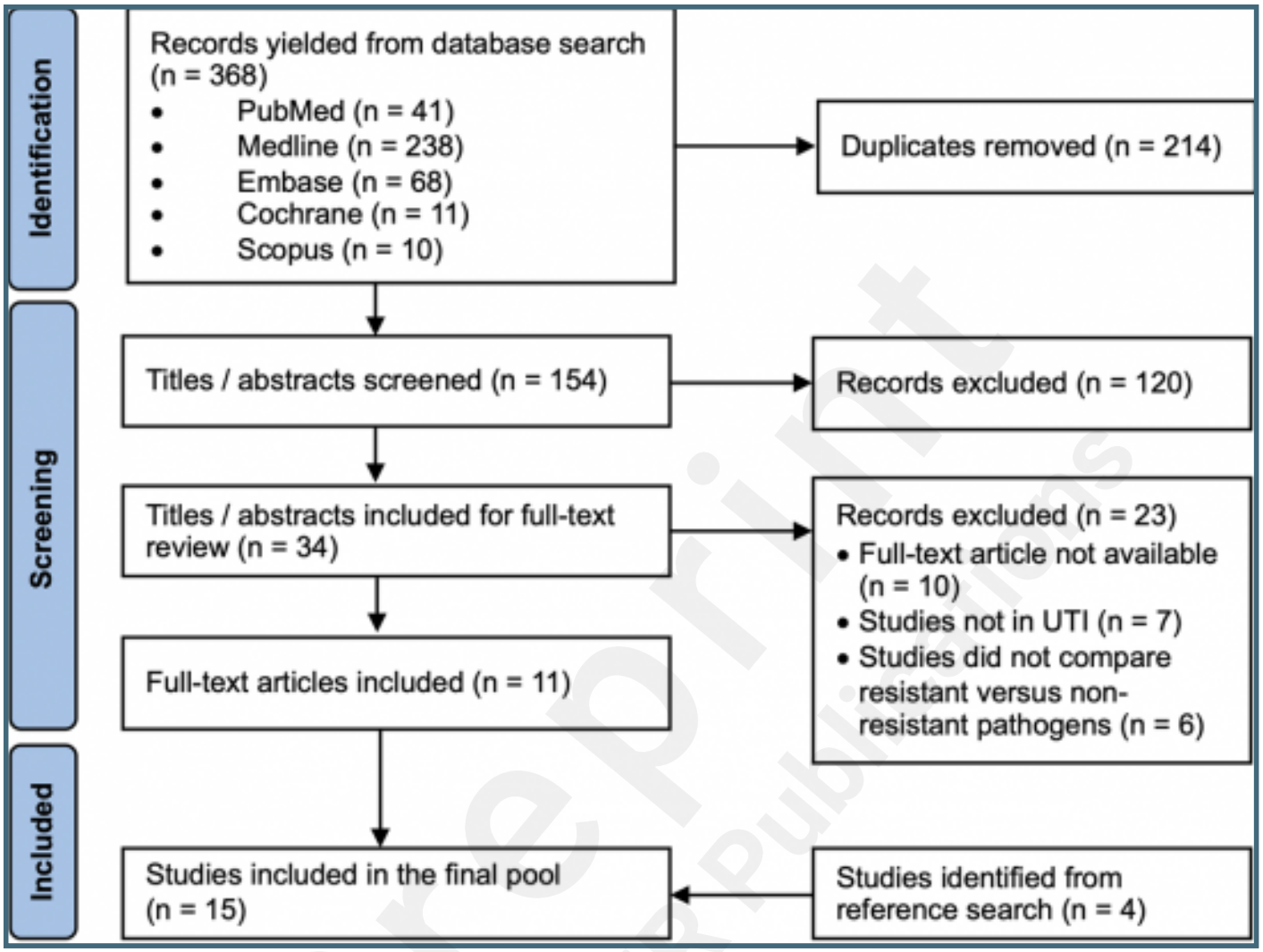
Figure S1: Funnel plot for publication bias in mortality

Eggar's test: p-value = 0.9699



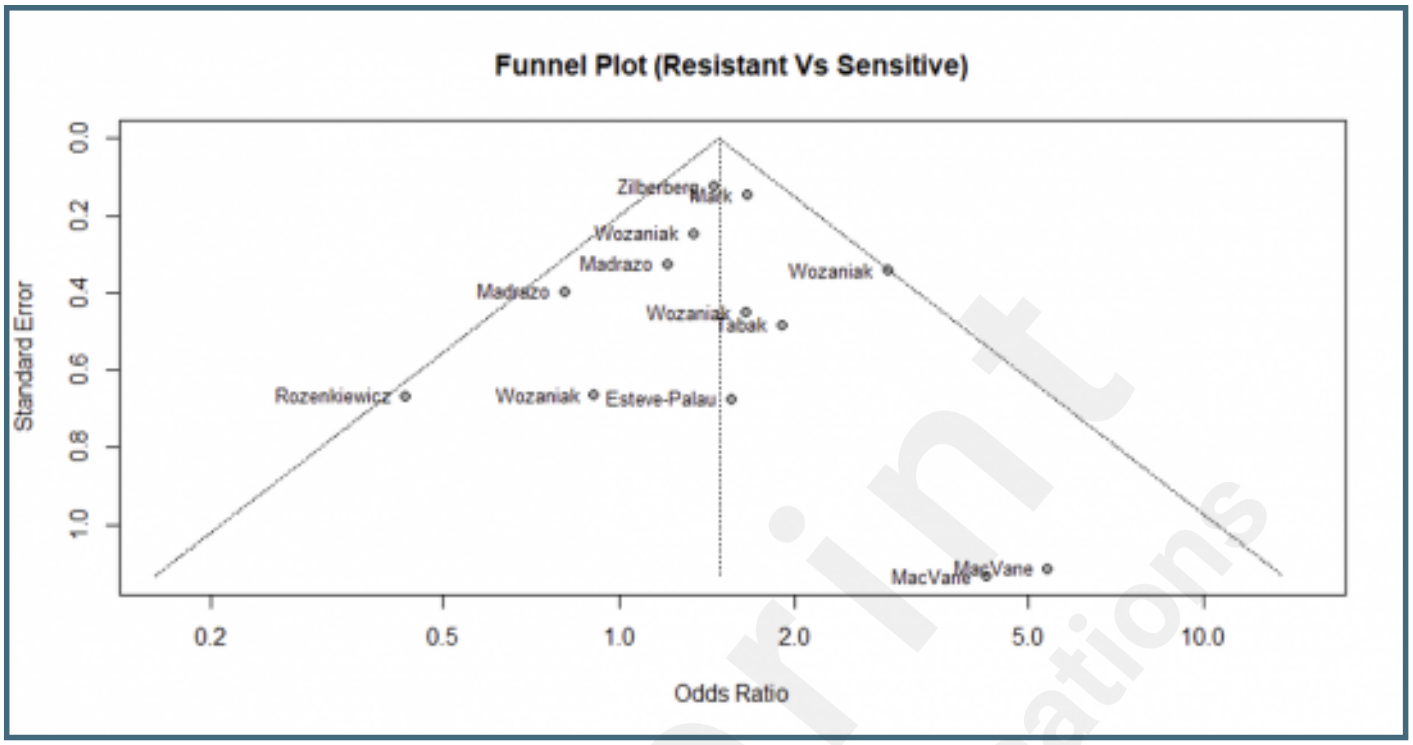
Supplementary Files

Untitled.

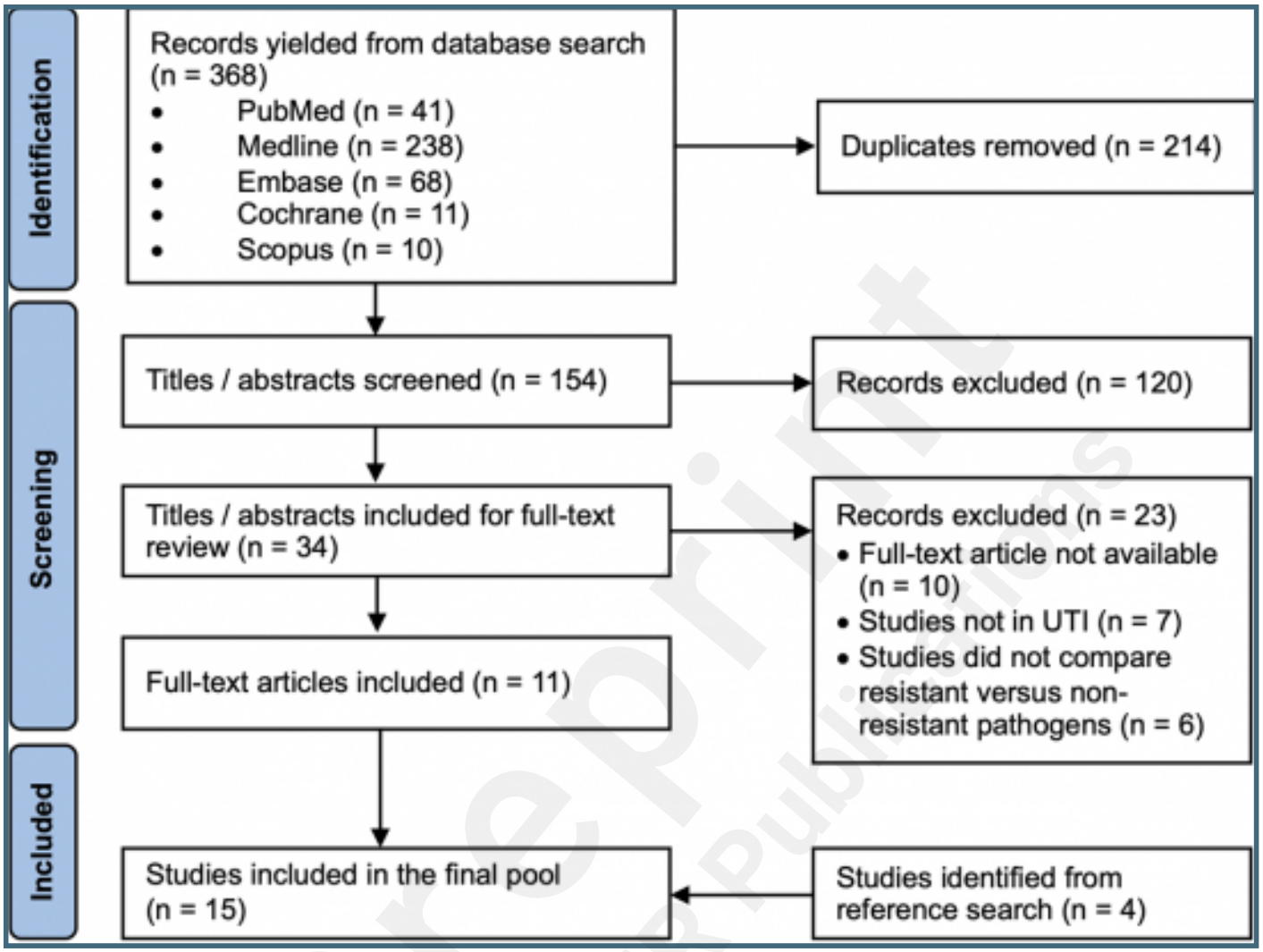


Figures

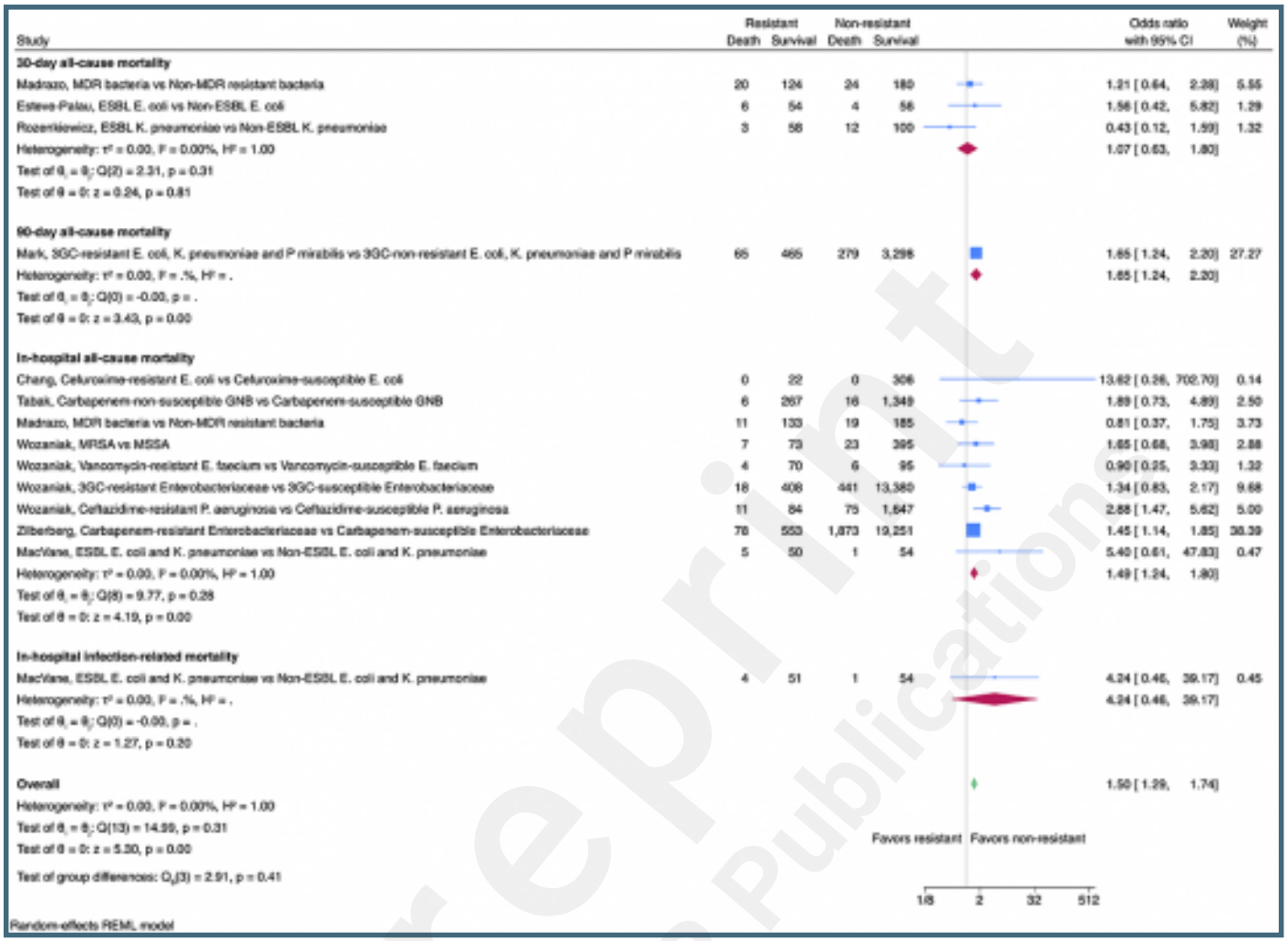
Funnel plot for publication bias in mortality.



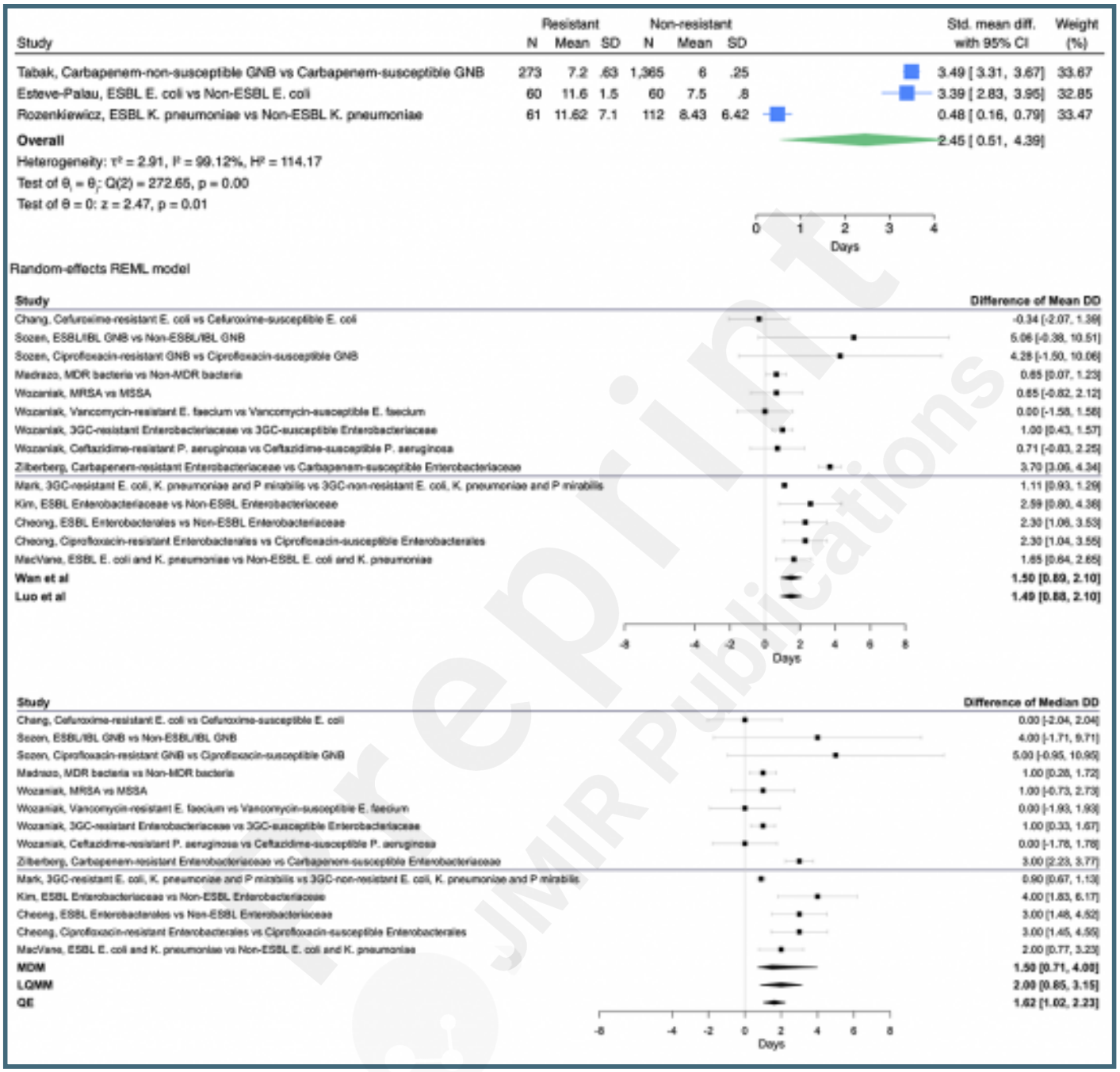
PRISMA flowchart.



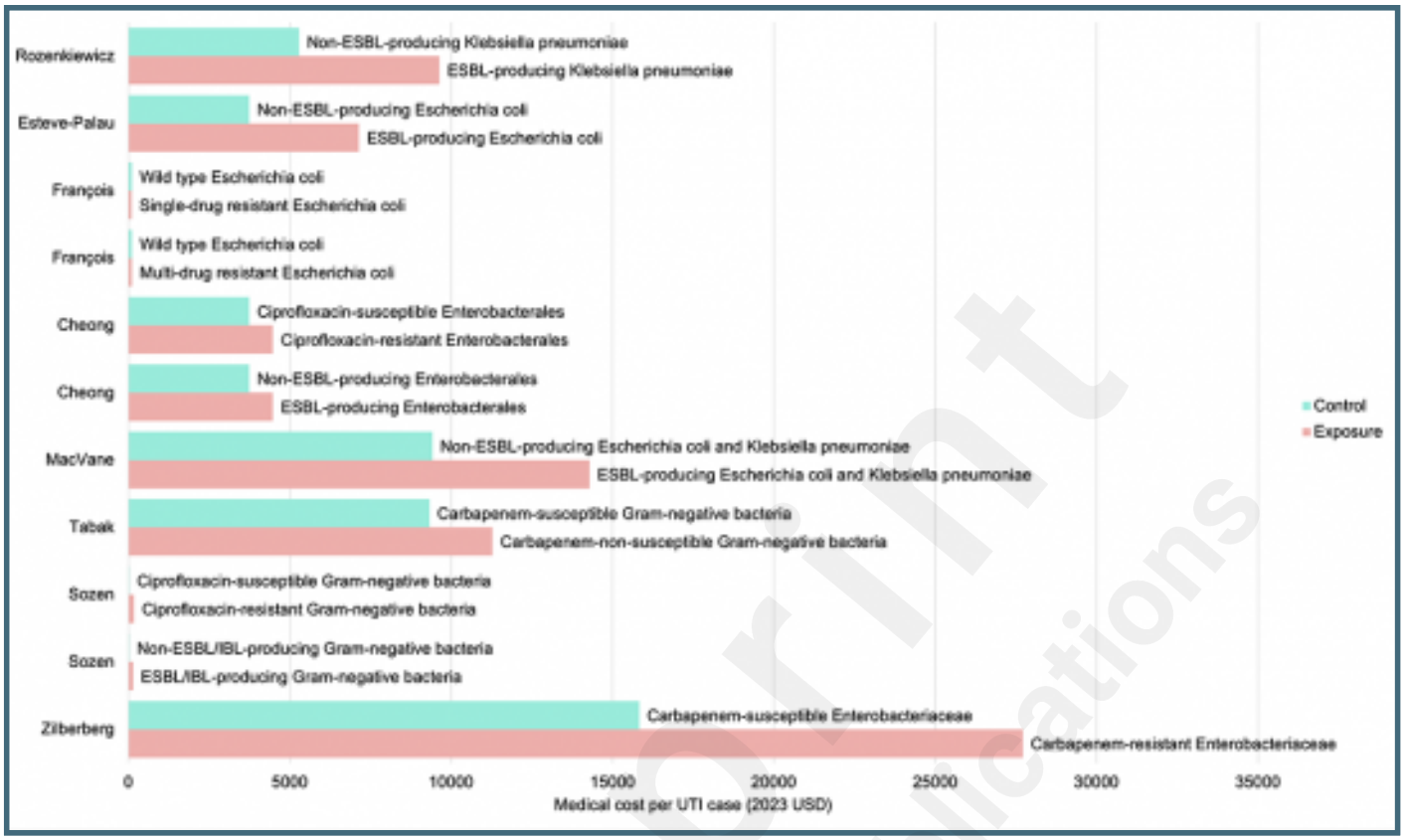
Pooled mortality of urinary tract infections by types of mortality outcomes.



(a) Pooled mean difference in length of stay of urinary tract infections, (b) Pooled median difference in length of stay of urinary tract infections.



Medical cost of antibiotic-resistant urinary tract infections.



Multimedia Appendixes

Supplementary material.
URL: http://asset.jmir.pub/assets/594cc534c6f9d04e2ee40e6dae8fe0c8.docx

CONSORT (or other) checklists

PRISMA checklist.
URL: http://asset.jmir.pub/assets/dbed4df5a5f61707395b569efc1fdb3b.pdf