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Systematic review

Excess resource use and cost of drug-resistant infections for six key pathogens in Europe: a systematic review and Bayesian meta-analysis☆

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ABSTRACT

Background: Quantifying the resource use and cost of antimicrobial resistance establishes the magnitude of the problem and drives action.
Objectives: Assessment of resource use and cost associated with infections with six key drug-resistant pathogens in Europe.
Methods: A systematic review and Bayesian meta-analysis.
Data sources: MEDLINE (Ovid), Embase (Ovid), Econlit databases, and grey literature for the period 1 January 1990, to 21 June 2022.
Study eligibility criteria: Resource use and cost outcomes (including excess length of stay, overall costs, and other excess in or outpatient costs) were compared between patients with defined antibiotic-resistant infections caused by carbapenem-resistant (CR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, CR or third-generation cephalosporin *Escherichia coli* (3GCREC) and *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium*, and patients with drug-susceptible or no infection.
Participants: All patients diagnosed with drug-resistant bloodstream infections (BSIs).
Interventions: NA.
Assessment of risk of bias: An adapted version of the Joanna Briggs Institute assessment tool, incorporating case-control, cohort, and economic assessment frameworks.
Methods of data synthesis: Hierarchical Bayesian meta-analyses were used to assess pathogen-specific resource use estimates.
Results: Of 5969 screened publications, 37 were included in the review. Data were sparse and heterogeneous. Most studies estimated the attributable burden by, comparing resistant and susceptible pathogens (32/37). Four studies analysed the excess cost of hospitalization attributable to 3GCREC BSIs, ranging from -€ 2465.50 to € 6402.81. Eight studies presented adjusted excess length of hospital stay estimates for methicillin-resistant *S. aureus* and 3GCREC BSIs (4 each) allowing for Bayesian hierarchical analysis, estimating means of 1.26 (95% credible interval [CrI], −0.72 to 4.17) and 1.78 (95% CrI, −0.02 to 3.38) days, respectively.

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Conclusions: Evidence on most cost and resource use outcomes and across most pathogen-resistance combinations was severely lacking. Given the importance of this evidence for rational policymaking, further research is urgently needed. **Rhys Kingston, Clin Microbiol Infect 2024;30:S26**

Background

Antimicrobial resistance (AMR) can be described as an underappreciated danger of our time, threatening the advances in modern society that antibiotics, antivirals, and antifungals have achieved. Murray et al. [1] estimated that globally, in 2019, 1.27 million deaths were attributable to antibiotic-resistant (ABR) pathogens. However, consideration of the death outcome alone leads to an underestimation of the total economic consequences of ABR infections. Murray et al. [1] also estimated that 47.9 million disability adjusted life-years, or the loss of the equivalent of one full year of health, were due to AMR, of which 275 000 were years lived in disability. Similarly, Cassini et al. [2] conducted a modelling analysis for the European Economic Area, which suggested that in 2015 alone, 874 541 disability adjusted life-years were lost due to ABR pathogens, of which 129 954 were years lived in disability.

Economically, future rises in AMR may present a significant challenge to how the modern global economy functions. The World Bank reported that under a high AMR scenario the global economy would contract by an estimated 3.2% and lose 3.8% of gross domestic product—a magnitude of effect that is comparable to the 2008 financial crisis [3]. They also predict that by 2050, under the same scenario, global health expenditure could increase by $1.2 trillion, representing an 8% increase compared with the base case scenario (no AMR) [3].

A significant barrier to understanding the true effects of AMR is the lack of evidence in health and economic outcomes. Estimates of the cost of AMR will vary depending on the perspective taken (patient, health care provider, and societal or economic costs), with different outcomes relevant to each [4]. Costs from a patient perspective may focus on costs associated with excess mortality, whereas costs from a health care provider perspective may consider costs of excess hospital bed days, and wider societal or economic costs may consider productivity losses or impact on gross domestic product. To estimate cost components across perspectives, large amounts of data, from different settings and sources, are required. The Organisation for Economic Cooperation and Development released its Stemming the Superbug Tide in 2018, which helped provide insights in possible AMR health expenditure [5]. However, there is a need for empirical data, and sharing of such data, to improve the evidence-base for action in tackling AMR.

Excess hospital costs associated with resistant hospital infections are driven by the length of hospital stay (LoS) of infected patients and therefore can be represented by bed-day costs, (LoS) [6], with previous studies using this metric to estimate the costs of hospital infection and AMR in hospitals [7,8]. The validity of performing meta-analyses on cost estimates is debated [9], with meta-analyses of excess LoS (with users then applying a unit cost per bed-day) reducing the likelihood of cost-per-case biases because of external economic factors not directly influencing internal health care spending (such as market exchange rates). Therefore, highlighting the importance of reviewing not only direct cost estimate literature but also resource use literature that can be tailored to country-specific settings in economic evaluations. Having explicit estimates of resource use attributable to ABR (such as LoS) is essential to quantify the extent of the issue, estimate justified levels of resource use for control, parameterize cost-effectiveness models to evaluate associated interventions, thus maximising the efficiency of our spending on tackling this issue.

A further consideration is that AMR is not a single disease entity but rather covers multiple pathogens with multiple resistance patterns, which cause a variety of different infection types and all have potentially different cost consequences. In 2008, Rice [10] identified ABR pathogens that were both highly virulent and resistant—the ESKAPE pathogens. These pathogens are; *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp* [10]. Murray et al. [1] estimated that a similar sub-set of pathogens were responsible for 0.93 million of the 1.27 million deaths predicted through modelling in 2019. From an economic perspective, in 2019 Zhen et al. [11] conducted a systematic review to assess the economic burden of ABR infections in ESKAPE organisms and found evidence they were often associated with higher costs. For example, the mean total hospital costs among inpatients with methicillin-resistant *Staphylococcus. aureus* (MRSA) was between 1.12 and 6.25 times higher than for methicillin-susceptible *S. aureus* (MSSA) cases. The authors suggested that lack of significant differences between resistant and control groups (e.g. susceptible or no-infection comparators) may be due to problems with study design, and particularly highlighted large heterogeneities between, as well as within, countries. Because of these heterogeneities and differences in outcome types, no meta-analyses were performed.

The objective of this systematic review was to determine the resource use and cost impact attributable to drug-resistant infections (compared with susceptible infections) and associated with drug-resistant infections (compared with no infection), with a focus on *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Escherichia coli,* across infection types.

Methods

Search strategy and inclusion

The systematic review is structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (for the PRISMA checklist, please see Table S1) and is registered with PROSPERO (registration number PROSPERO CRD42022331400), with details on search strategy and inclusion criteria available [12–14]. Ethical approval was not required as all data were extracted from publicly available sources. For the inclusion and exclusion criteria applied for the narrative review (please see Table 1) [12]. No language exclusion criteria were applied. In addition, only publications that used statistical techniques attempting to account for time dependency bias and/or adjustment for potential confounding factors were included in the meta-analyses.

Table 1
Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	Patients in European settings. Patients of all ages diagnosed with one of the above-mentioned infections caused by one of the pathogens of interest expressing one of the resistance mechanisms of interest (or being a control for a relevant resistant exposure, e.g. an antibiotic susceptible urinary tract infection in a case-control study being compared with those with a resistant infection respectively). Patients diagnosed with infections in hospital, community, and long-term care settings.	Patients with primary infections in; central nervous system, genital system, pelvic infections, head, and neck infections Patients with specific primary infections; endocarditis, upper respiratory tract infections, lung abscess. Patients with bacterial infections not included in the list of pathogens of interest, poly-microbial infections except for intra-abdominal infections, fungal infections, parasitic infections, viral infections, mycobacterial infections, sexually transmitted diseases, and zoonotic infections.
Exposure	The exposures of interest are the resistance patterns of the included pathogens. For two pathogens more than one resistance pattern will be included. Susceptible, intermediate, colonized, and resistant interpretations from studies will be accepted, as long as these are based on accepted guidelines (EUCAST, CLSI). Resistance will include both resistant and intermediate categories. Multi-drug resistance profiles will be assessed only if the specific resistance of interest is explicitly included in the definition and required to be resistant in all isolates. Infection types included were bloodstream infections (BSIs), urinary tract infections (UTIs), lower respiratory tract infections (LRTIs), skin and soft tissue infections (SSTIs), surgical site infections (SSIs), and intra-abdominal infections (IAIs).	Studies which did not specify the infections included.
Outcomes	Excess length of inpatient stay (days), stratified by intensive care unit (ICU), non-ICU and general (i.e. across all wards) days where possible, excess inpatient cost, excess ICU cost, excess primary care cost, and excess outpatient cost.	NA
Study Design	Observational cohort studies (prospective or retrospective), observational case-control studies (prospective or retrospective), systematic reviews and meta-analyses—for the purpose of identifying studies only, non-randomized comparative studies, non-systematic reviews—for the purpose of identifying studies only.	Studies reported in conference abstracts only, trial registries, editorials, letters and comments. Studies published before 1990. If a study cannot be accessed through journal subscription, the author will be contacted. Abstracts will not be used as the only data sources, and if only abstracts are available during the extraction process, these studies will be excluded.

The literature search included published studies during the period of 1 January 1990 to 21 June 2022 from MEDLINE (Ovid), Embase (Ovid), and Econlit databases. Grey literature was also searched, including that of the WHO, the Centers for Disease Control and Prevention, and the European Centre for Disease Prevention and Control. Additional publications were gathered from the references of fully screened publications, systematic reviews, and articles from the sister review of health outcomes. When full text was unavailable, the paper was marked as excluded. Studies that were considered included prospective, or retrospective cohort studies, case-control studies, and non-randomized studies. The search strategy can be found in the supplementary material (Table S2), along with full details of the selection process, data extraction and quality, risk of bias and publication bias assessments.

In brief, selection, duplication and assessment of agreement were conducted using Covidence software [15]. Data extracted and a sub-set checked: a copy of the dataset used for the final meta-analyses can be found in the project repository on the EPI-Net website [16]. Risk of bias was conducted independently by 2 reviewers and followed a framework adapted from the Joanna Briggs Institute tools for bias assessment in cohort, case-control, and economics studies (Table S3) [17–19].

Data analysis

Data preparation

Where data were not provided in a mean ± standard deviation format (e.g. only a median and interquartile range were provided), these were estimated using formulas provided by Wan et al. [20] (see supplementary materials).

Furthermore, because of the inflation of costs over time, all costs that were extracted were inflated to their equivalent value in 2021 using the consumer price index for the EU and then converted to Euros [21].

Statistical analysis and modelling

The summary mean difference and respective standard errors of the study estimates were produced for further analysis. Pooling of estimates was done per drug-resistant pathogen-infection combination across all settings, types of infection acquisition, age groups, gender, and all other potential variables. Pooled effect measures included the mean excess length of stay, in days. All analyses focused on resistant versus susceptible comparators because there was insufficient data to conduct analyses with resistant vs. no-infection comparators. The heterogeneity among the included studies would ordinarily lead to a frequentist random effects analysis; furthermore, the extremely low sample size of the studies meant a fixed effects model would also not be useful.

To use the small amount of data collected, a Bayesian hierarchical model for meta-analysis using an informative prior was used. This is an alternative to the standard frequentist interpretation of the random effects meta-analysis. A detailed description of methods and further specifications of model runs are provided in the supplementary materials (S4) [22–37]. Sensitivity analyses were conducted to test the effect of weak and strong informative priors of the heterogeneity parameter on the summary estimate.

Results

Study selection

The search strategy identified 5969 references (deduplicated from 6798 references). After title or abstract screening, 323 publications were selected for full-text review. Ultimately, 37 publications were included in the review. The PRISMA flow diagram can be

seen in Fig. 1. The most frequent exclusion reasons included: conference abstracts (n = 84), inappropriate comparison group (n = 58), and the study not being conducted in Europe (n = 48).

Study characteristics

The types of studies that were extracted were composed of; 15 case-control studies (15/37, 35%), 13 retrospective cohort studies (13/37, 38%), 10 prospective cohort studies (10/37, 29%), and 2 case-cohort studies (2/37, 6%). The median study duration, i.e. data collection period, was 36 months (IQR: 12 months–60 months). Regarding study setting, all were hospital-based, of which 20 publications were set in a secondary or tertiary care centre (20/37, 54%), 14 in a tertiary centre (14/37, 38%), 2 in a primary or tertiary care setting (2/37, 5%), and one in all settings (1/34, 3%).

Thirty-two publications compared infection because of resistant and susceptible pathogens (32/37, 86%), 11 compared with susceptible also compared resistant infection to no infection (11/37, 32%), and 7 compared susceptible infection to no infection (7/37, 19%). The infections under study were split over different acquisition sources, with 14 publications focusing on hospital-acquired infections (14/37, 38%), 7 publications not specifying the source of infections (7/37, 19%) and 6 publications specifying infections as hospital-acquired and community-acquired (6/37, 16%). Furthermore, the infections that were studied were heavily weighted toward BSIs, which were analysed in 20 publications (20/37, 54%), followed by respiratory tract infections (RTIs) with 9 publications (9/37, 24%), and urinary tract infections (UTIs) in 5 publications (5/37, 14%). A summary of the study characteristics and results can be seen in the supplementary materials (Tables S5–S7).

Of the publications selected, the types of outcomes that were reported varied widely (Fig. 2). In addition, there were significant data gaps, with limited data on excess health care resource use because of the included target pathogens. Overall, the grid is

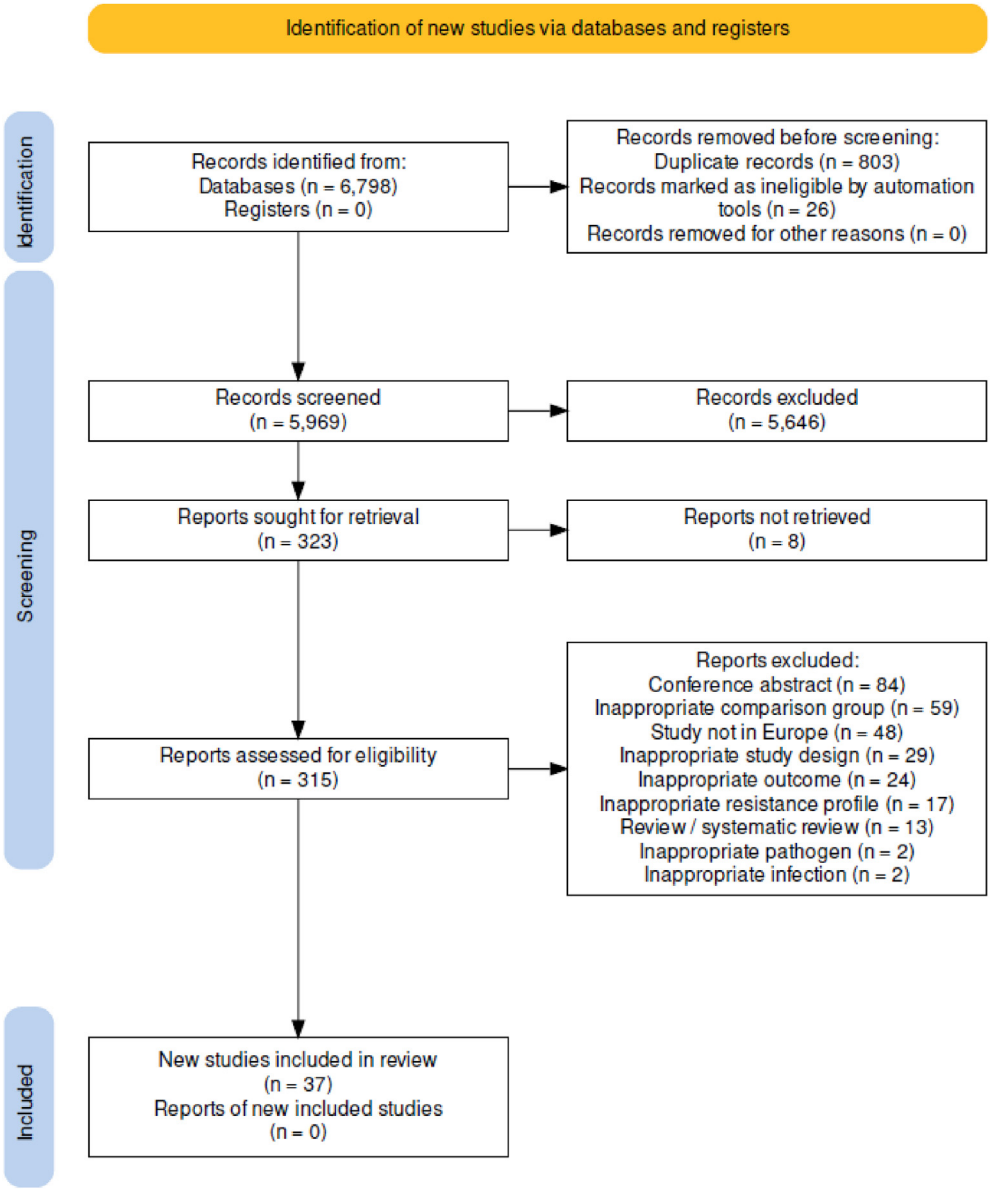

Fig. 1. PRISMA diagram of identified publications. Displays breakdown of the publications eligible at each screening stage, and the publications included in analysis.

sparse, with a maximum of 6 publications for any one outcome. Outcomes with sufficient data and adjusted estimates to enable further analysis for any of the pathogen-infection-resistance combinations were excess total costs per infection (13 publications) and excess length of stay per infection (13 publications). Only 2 pathogen-resistance-infection combinations yielded sufficient data for these outcomes: third-generation cephalosporin-resistant *E. coli* (3GCREC) and MRSA, with BSIs being the only infection type with enough data across both. For MRSA BSIs, the number of publications with adjusted and unadjusted excess length of stay estimates was 4 and 5, respectively. Whereas for 3GCREC BSIs, this was 4 and 6, respectively.

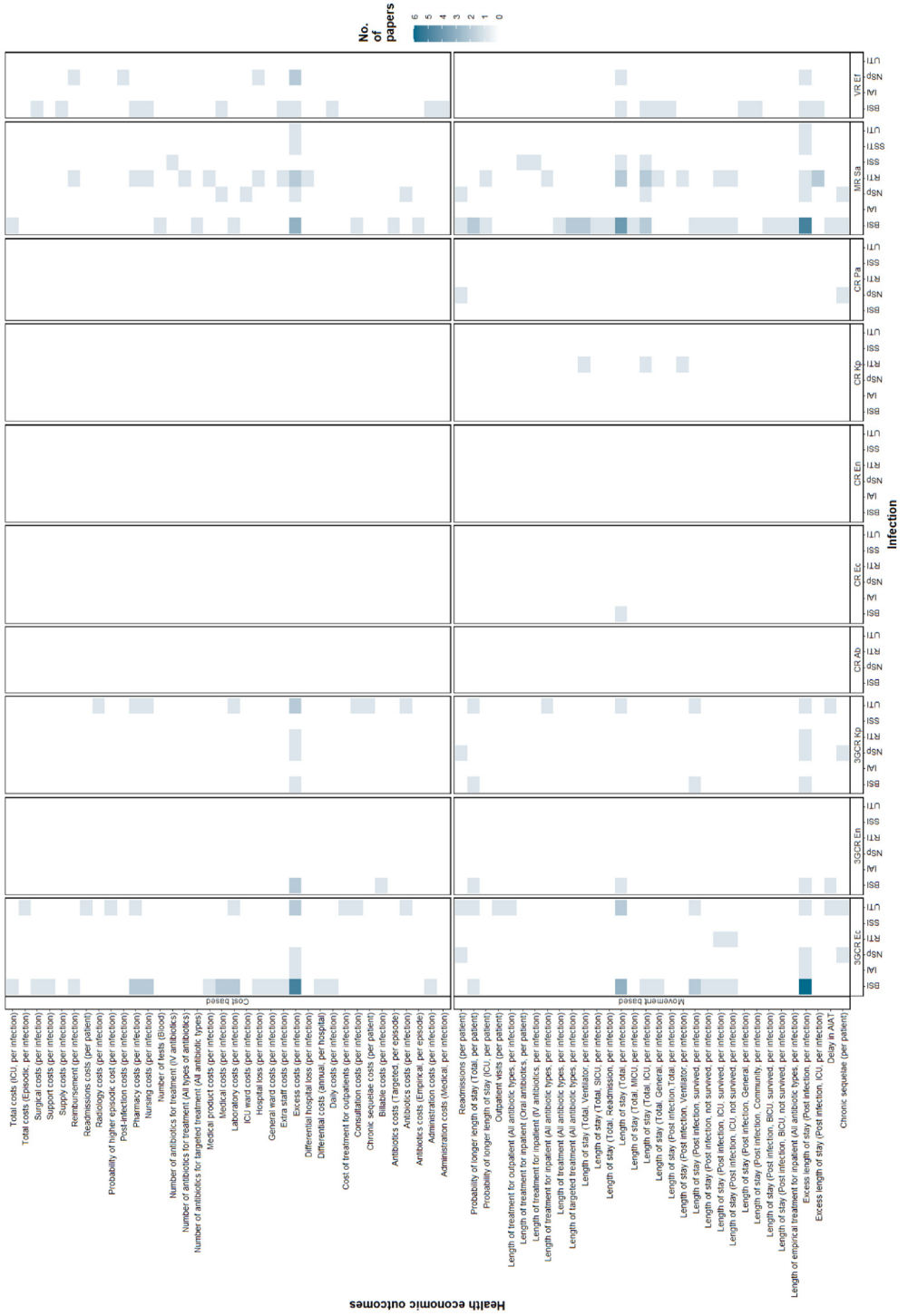

Fig. 2. Heatmap of number of studies reporting economic outcomes across resistance-pathogen-infection combinations. Dark blue indicates a higher frequency, pale blue indicates a lower frequency, white indicates no publications available. NSp, non-specific; Enterobacteriaceae, 3GCREC, third-generation cephalosporin-resistant *Escherichia coli*; 3GCRKP, third-generation cephalosporin-resistant *K. pneumonia* CRAB, carbapenem-resistant *A. baumannii*, CRE, carbapenem-resistant *Enterobacteriaceae*, CREC, carbapenem-resistant *E. coli*, CRKP, carbapenem-resistant *K. pneumoniae*, CRPA, carbapenem-resistant *P. aeruginosa*, MRSA, methicillin-resistant *S. aureus*, VREF, vancomycin-resistant *E. faecium*.

There was an uneven distribution of publications across European countries, where most of the evidence is coming from Western, Southern, and Central Europe (Fig. 3). The countries with the highest number of publications were Spain (11) and Germany (11).

Thirteen publications in total evaluated the excess costs of hospitalization (defined as the difference in costs between patients with resistant vs. susceptible infections) per episode of the disease. Of these, five evaluated the impact of MRSA, which covered BSIs (2), non-specific infections (2), RTIs (1), skin and soft tissue infections (1), and UTIs (1).

Five studies analysed the excess total cost of hospitalization (from a payer/provider perspective) associated with 3GCREC, versus susceptible *E. coli* infections, 4 of which gave estimates for BSIs which ranged from −€ 2465.50 to € 6402.81 per case. A meta-analysis of these costs was not performed as this was deemed inappropriate because of the variability in costs, their definition, and methods of estimation across studies, settings, and particularly across countries.

Bayesian meta-analysis

The excess LoS values used for the meta-analyses can be found in Figs. 4 and 5. For the analysis of excess LoS attributable to MRSA infections (susceptible infection comparator), five publications reported an adjusted estimate which evaluated BSIs (4), RTIs (1), skin and soft tissue infections (1), UTIs (1), and non-specific infections (1). For the Bayesian analysis, only the BSI publications were used for our likelihood. For the posterior distribution of the excess length of stay attributable to MRSA BSIs (compared with susceptible infection), the weakly informative prior resulted in a mean of 1.26 (95% credible interval [CrI], −1.72 to 4.17) days, with a probability of a positive excess length of stay associated with MRSA BSIs of 92% (Fig. 6).

For the excess LoS attributable to 3GCREC infections (susceptible infection comparator), four publications were found that covered all searched for infections. BSIs had the largest number of estimates (n = 4 studies) and so were used for the analysis as our likelihood. A

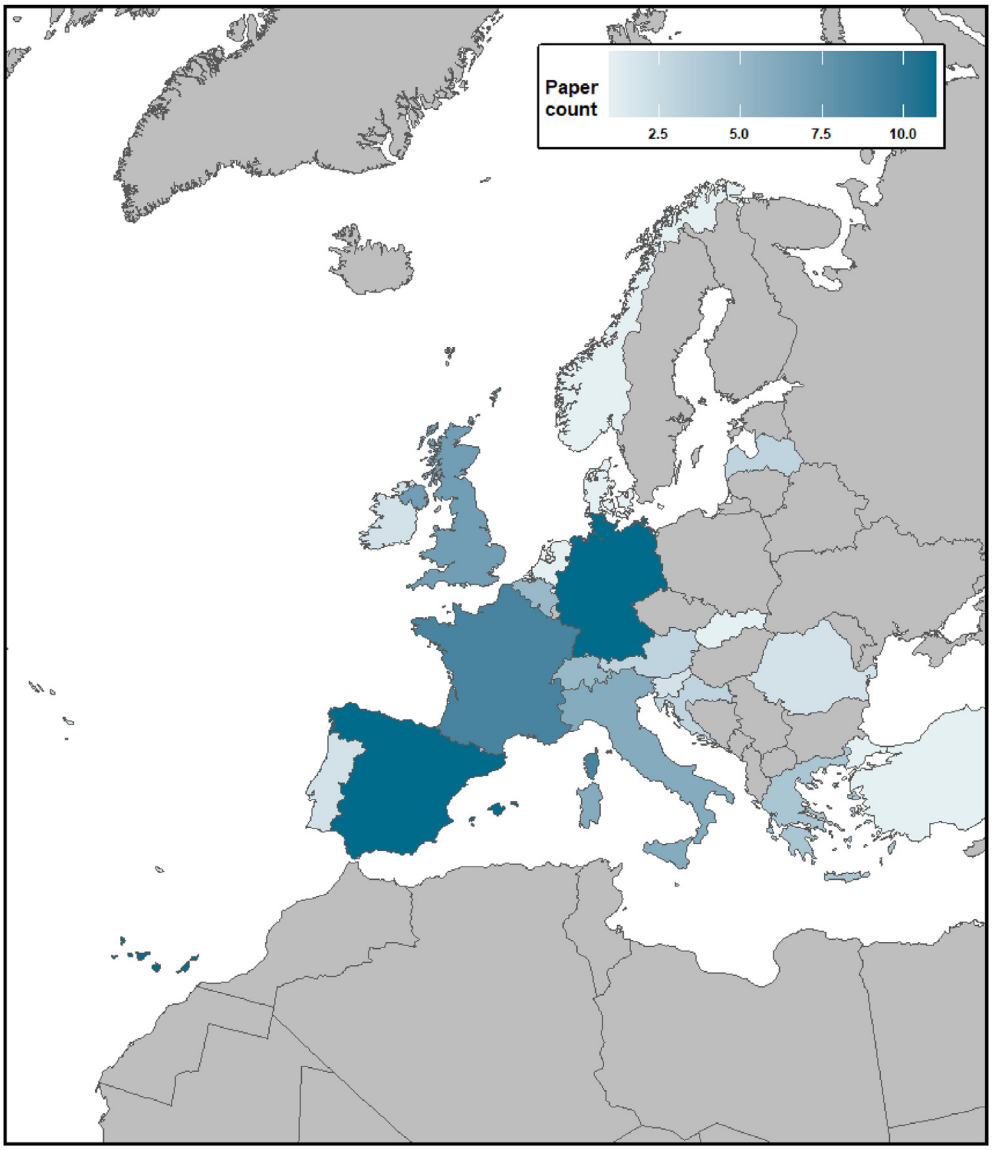

Fig. 3. Geographical spread of analysed publications across Europe. Includes all analysed pathogens, infections, and resistance patterns. Dark blue represents more publications, light blue represents fewer publications.

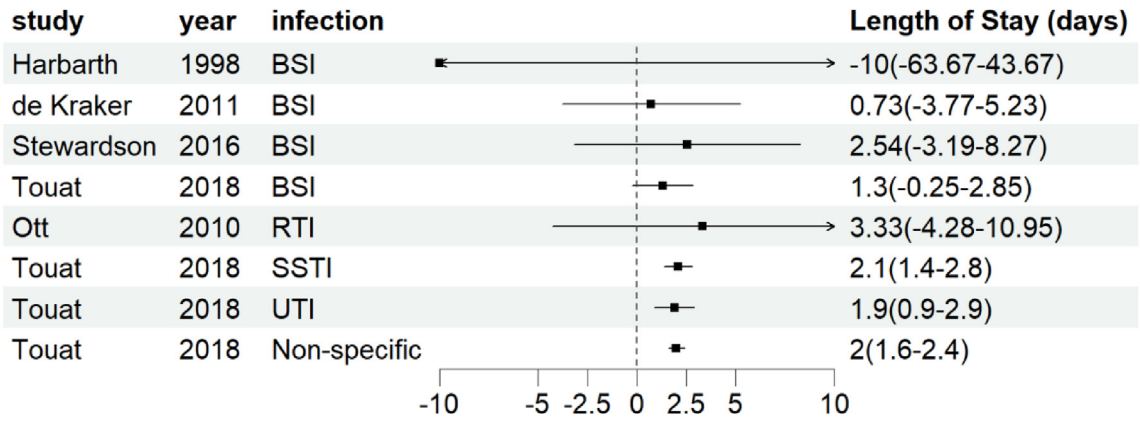

Fig. 4. Excess length of stay outcomes associated with methicillin-resistant *Staphylococcus aureus* infections compared to susceptible *S. aureus* infections.

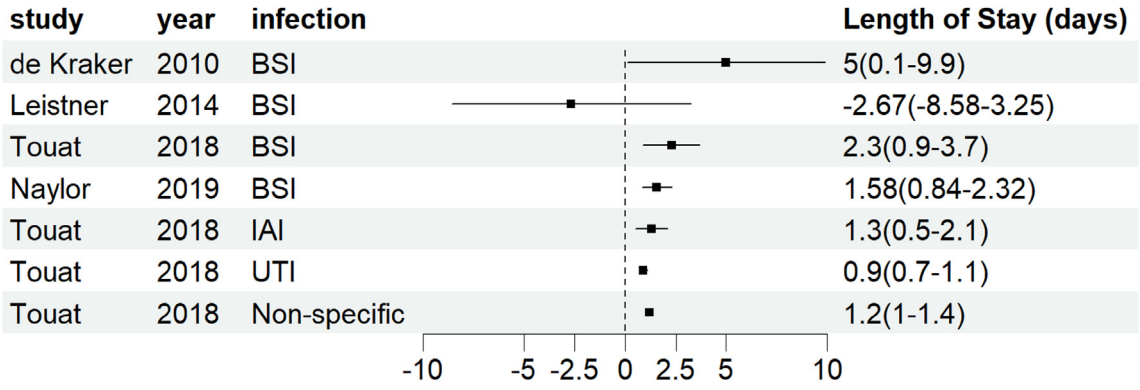

Fig. 5. Excess length of stay outcomes associated with third-generation cephalosporin-resistant *Escherichia coli* infection, compared with susceptible *E. coli* infections.

weakly informative prior resulted in a mean excess length of stay (compared with susceptible infection) of 1.78 (95% CrI, −0.02 to 3.38) days, and the probability of a positive excess length of stay was 95% (Fig. 7).

Sensitivity analysis

To assess the effect of the assumed prior values on the heterogeneity prior, weak, and strong informative priors were tested. For excess length of stay associated with MRSA BSIs, a strong informative prior resulted in a mean of 1.29 (95% CrI: −0.11 to 2.71) days and the probability of a positive excess length of stay was 97%. For excess length of stay associated with 3GCREC BSIs, a mean of 1.76 (95% CrI, 1.14–2.42) days and 100% probability of a positive excess length of stay was seen with a strong informative prior.

Assessment of bias

The risk of bias summary can be seen in the supplementary files (Table S8), separated into case-control studies and cohort studies. We identified 28 studies with a low and 9 with a medium risk of bias. For the cohort studies, loss to follow-up was the most common risk of bias (75% of publications with incomplete or poorly described follow-up). For the case-control studies, many of the outcomes were not costs e.g. length of stay estimates: excluding inappropriate questions, the most poorly answered questions included "Were confounding factors identified?" (Of which only 69% of publications were classified as yes).

The Bayesian meta-analysis on excess length of stay because of MRSA consisted of 4 publications with a low risk of bias, and one paper with a medium risk of bias, whereas for 3GCREC, all 4 of the publications included had a low risk of bias.

Because of the low number of studies included in the final Bayesian meta-analyses, a full assessment of publication bias e.g. using funnel plots, was not possible.

Discussion

This systematic review found 37 studies that estimated the costs and resource use associated with and attributable to AMR. However, out of these 37 studies, only 8 studies, which focus on BSIs, could be used to create pooled estimates of AMR impact. This was due to (a) a spread of data across syndromes, outcome measures, and drug-bug combinations, and (b) a lack of studies estimating outcome (in this case excess length of stay) while accounting for sources of confounding and bias. We therefore highlight that not only do more studies need to be conducted on resource use and cost of AMR, but that these need to use appropriate statistical techniques [4,8], across key drug-bug-syndrome exposure groups of interest, in order to fill the current research gap.

This study estimates, based on the appropriate, available evidence found through systematic review methods, that the only high probability finding was for excess length of stay associated with 3GCREC BSIs (95% probability), with MRSA BSIs having a 92% probability of incurring an excess LoS. The lack of 100% certainty of a positive associated LoS could be due to higher mortality leading to shorter stay or not enough statistical power provided within the included studies. For none of the other relevant resistant-pathogen-infection combinations were sufficient data available to reach similar conclusions. Although these results are based on only

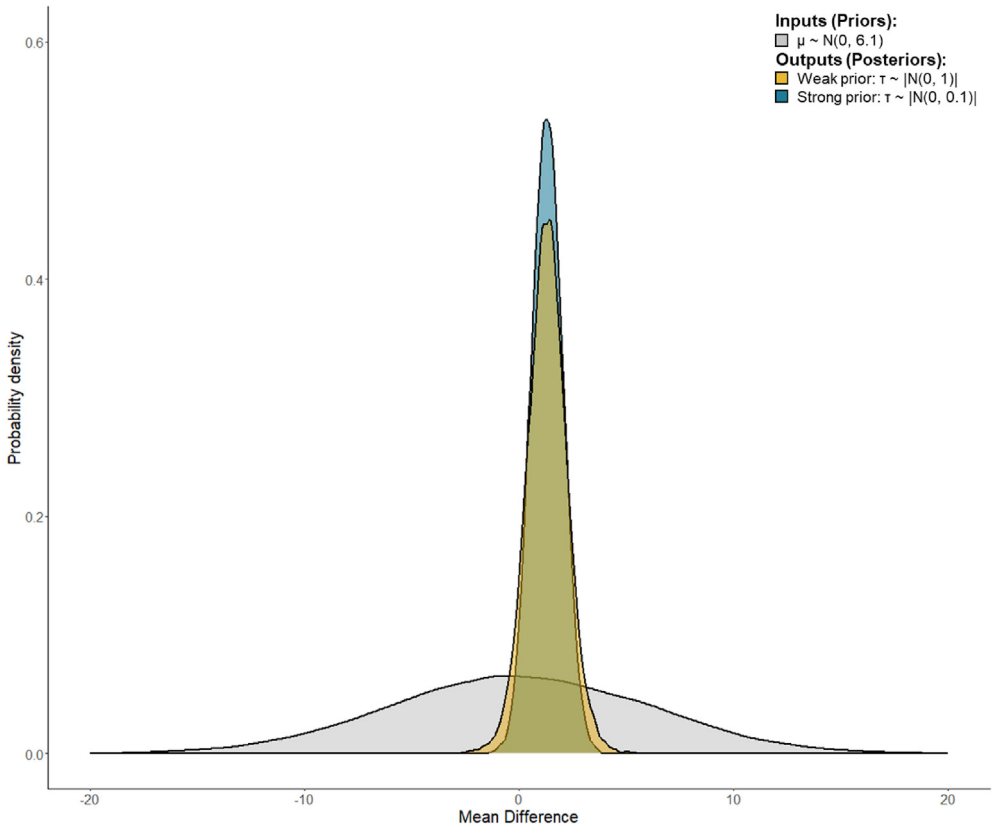

Fig. 6. Bayesian hierarchical modelling of the excess length of stay attributable to methicillin-resistant *Staphylococcus aureus* bloodstream infections (compared to susceptible infections). Grey shaded area is the probability density of a weakly informative prior on the excess length of stay (mu). Yellow shaded area is the probability density of a weakly informative prior on between group variation (tau). The blue shaded area is the probability density for a strong informative prior on the tau parameter.

a few studies that reported economic outcomes attributable to or associated with ABR, unlike previous reviews, we had stringent inclusion based on robustness of statistical methods and deal with heterogeneity by breaking down analyses by clinical subgroups [11,38]. This study extended the work carried out by previous reviews such as Zhen et al. [11], who found 32 publications across the EU, European Economic Area, and UK regions focusing on costs associated with AMR and provided descriptive results, without a focus on pathogen-specific AMR burden estimates. In this study we provided an analysis using Bayesian hierarchical modelling. Bayesian analyses can provide more valid results in cases of sparse data and allow generalization of the health economic outcomes to a wider population [39]. We provide the first example of how this method can be applied in AMR-attributable resource use estimation.

Our study estimates 1.26 (95% CrI, −1.72 to 4.17) and 1.78 (95% CrI, −0.02 to 3.38) excess LoS in days for AMR, dependent on bug-syndrome combination, this is lower that the estimated 7.4 days (95% CI, 3.4–11.4) in Poudel et al. [38] across bugs and syndromes. This is likely because of Poudel et al. [38], including studies that do not appropriately adjust for time dependency in their excess LoS estimation. The literature has consistently shown that using statistical techniques accounting for time dependency and adjusting appropriately for confounding leads to shorter excess LoS estimates [4,6,40]. In addition, Poudel et al. [38] is a global analysis, including data from countries, such as Japan, which tends to have longer average LoS values of inpatients in comparison with European countries [41].

Of the pathogen-infection-resistance combinations searched for, MRSA BSIs and 3GCREC BSIs were most frequently reported, with 9 publications (26%) identified for each.

Allel et al. [42] conducted a similar systematic literature review and meta-analysis aiming to quantify the excess mortality, LoS, ICU admission, and economic cost associated with resistant BSIs (with a sensitive infection comparator), but with a focus on low-income and middle-income countries. Again, ignoring the possible influence of confounding factors, their findings indicated that ABR BSIs were associated with substantially longer stays in hospitals and ICUs and higher mortality, resulting in increased direct medical and productivity costs. They additionally highlight the paucity of BSI data from low- and lower-middle-income countries, and performing frequentist meta-analyses with a low number of studies can result in incorrect effect estimation [43].

The higher frequency of studies reporting MRSA and drug-resistant *E. coli* BSI outcomes is perhaps unsurprising given the relative prevalence of these pathogen-resistance-infection combinations in Europe [44]. However, drug-resistant pathogens, causing the largest epidemiological burden, do not necessarily have the highest economic cost per case. Certain resistance-pathogen-infection combinations may have very high excess costs per case, for example, because of a large impact on length of ICU stay, or indeed prevalent but less severe infections (e.g. UTI) may have significant impacts on population morbidity. As such, we lack data to establish what would be the most important targets for intervention to reduce the economic burden of AMR.

A joint report by the European Centre for Disease Prevention and Control and the WHO emphasizes the growing threat due to carbapenem-resistant pathogens such as *E. coli* and *K. pneumoniae*, in which they note increases in resistant isolates in Europe [45], especially in Eastern Europe. In this study, we found no data on the economic impact of carbapenem-resistant infections and in general a lack of data from Eastern Europe. This may partly be explained by

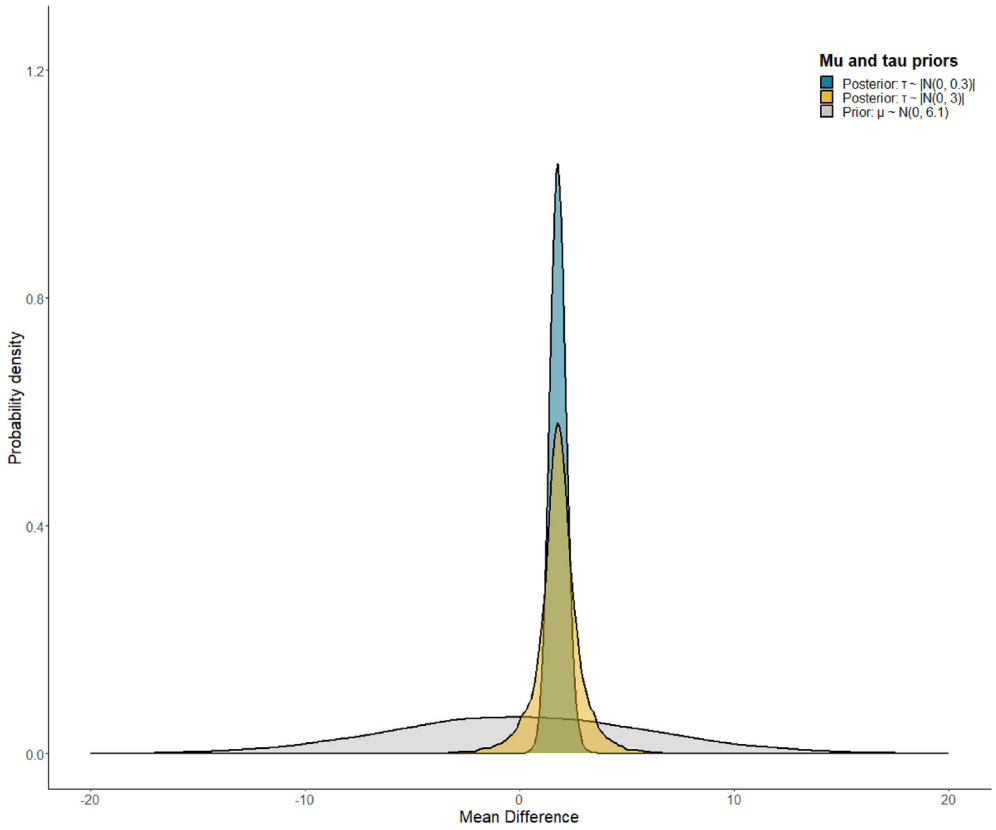

Fig. 7. Bayesian hierarchical modelling of the excess length of stay attributable to third-generation cephalosporin-resistant *Escherichia coli* bloodstream infections (compared with susceptible infections). Grey shaded area is the probability density of a weakly informative prior on the excess length of stay (mu). Yellow shaded area is the probability density of a weakly informative prior on between group variation (tau). The blue shaded area is the probability density for a strong informative prior on the tau parameter.

the fact that, although carbapenem resistance is increasing, the absolute number of infections is still relatively low.

This review highlights a striking lack of evidence across countries. Differences in cost and cost burden of resistant infections between countries are important to understand: an intervention that is cost-effective in one may not be in another, with price levels within health care systems varying greatly across Europe [46]. One approach to address this would be for studies to report resource use (e.g. type or number of diagnostics, treatments, other types of interventions, hospital readmissions, and primary care consultations) rather than costs. Arguably, these may be more useful than costs, which vary over geography and time. We would propose that estimates of resource use associated with infection, even without monetary cost values available, should be assessed in any clinical study on ABR burden. In this way, appropriate setting-specific unit costs could then be applied to such resource use estimates, thus providing improved evidence on the costs of drug-resistant infections across settings to enable tailored cost-effectiveness evaluations to be conducted. For example, using the WHO—Choice average bed-day cost in Central Europe ($255) and Western Europe ($573) (2010 International dollars) and combining this with our average excess LoS attributable to 3GCR in *E. coli* estimated in our model, gives average, excess costs per case of around I$ 450 and I$ 1020, respectively [47].

Similarly, no data were available from non-hospital settings. Cost outcomes from infections in hospitals only represent part of the burden; it is likely there is a considerable economic burden due to resistant infections in the community. Outcomes such as health care utilization for primary care and outpatient settings and cost consequences of morbidity need to be quantified, with long-term care facilities a particularly neglected area. Moreover, we found a lack of data enabling stratification for outcomes across different genders, age groups, comorbidities, such as obesity or diabetes, or other important risk groups. Such factors are important to the successful design and implementation of efficient and effective targeted interventions, such as vaccines and monoclonal antibodies. Although a potential solution is subgroup analyses, large amounts of data may be required for sufficiently powered analyses, individual patient meta-analysis is likely to be a more fruitful route. Finally, there is little evidence of comparison between resistant infections and a no-infection counterfactual, which is needed to determine the total cost of drug-resistant infections. Research in all the areas described is needed to determine optimal ABR-associated interventions across populations, pathways, and settings.

In addition to the paucity of evidence, the quality of literature reporting economic outcomes was also low. Some estimates were unadjusted for confounding factors, such as the severity of the underlying disease or comorbidities. The fact that the severity of diseases changes over time makes it particularly difficult; if this is not appropriately considered, it can result in time-varying confounding, which previous research has shown to artificially increase the excess length of stay associated with infection [48].

There are study limitations, for both the systematic review and the meta-analyses. The primary limitation being the lack of data, which in turn limited findings, resulted in high levels of uncertainty, hindered meta-analyses, and precluded full risk of bias analyses. No evidence was found for many infection types, pathogens, resistances, and settings, and so results do not represent the full extent of the burden of AMR e.g. no quantification of resource use or cost of resistant infections in non-hospital settings was possible,

whereas in reality there may be considerable burden. Therefore, highlighting the need for further evidence. Furthermore, many of the studies that were identified failed to appropriately account for sources of bias or confounding. By using only adjusted estimates for meta-analyses, grouped by drug-bug-syndrome combinations where more than one study was available, we reduced the potential pool of data further. However, this allowed for robust quantification of pooled effect estimates, considering heterogeneity of exposure groups. Despite the use of a structured and inclusive approach, we may have missed papers providing evidence relevant to our outcomes of interest. However, our approach identified a greater number of studies than similar recent reviews with a global scale. As is common to systematic literature reviews, inter-rater reliability could have influenced paper selection; however, double title or abstract screening for 100 publications showed 100% inter-reviewer agreement. The Joanna Briggs Institute criteria used for bias assessment comprised items that were difficult to assess in an objective and reproducible way and few are internally or externally validated. As such, any assessment is limited because of the subjectivity that is required in analysing the studies.

Conclusion

This review summarizes the current evidence on the cost and resource use impact of resistant infections but yields little usable evidence for many of the pathogen-resistance-infection combinations investigated. Even for those with the greatest amount of evidence, the ability to conclude with confidence that there is a net positive or negative effect of resistance is limited. The novel use of hierarchical Bayesian statistics in this review supports that there is likely a positive excess length of stay associated with 3GCREC infections when compared with susceptible *E. coli* infections. We highlight the lack of studies that adjust for confounding factors appropriately, and the lack of studies reporting on primary care and community settings, across countries, while providing impact estimates by antibiotic, syndrome, and patient characteristic subgroups. These data are needed to appropriately parameterize cost-effectiveness models to efficiently tackle ABR.

Transparency declaration

Potential conflict of interest

VV, LA, JES, and AP are employees of GSK, VV, JES, and AP own GSK shares. JG is an employee of Janssen, and owns stocks of Johnson and Johnson.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.12.013.

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