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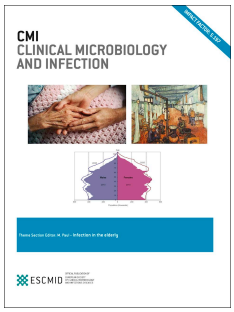

Excess resource use and cost of drug-resistant infections for six key pathogens in Europe: a systematic review and Bayesian meta-analysis

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Original article

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

(Current word count: 250)

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 1st January 1990 to 21st June 2022.

Study eligibility criteria: Resource use and cost outcomes (including excess length of stay, overall costs and other excess in/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 (MRSA) 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 5,969 screened publications, 37 were included in the review. Data were sparse and heterogeneous. Most studies estimated attributable burden, comparing resistant and susceptible pathogens (32/37). Four studies analysed the excess cost of hospitalisation attributable to 3GCREC bloodstream infections (BSIs), ranging from -€ 2,465.50 to €

6,402.81. Eight studies presented adjusted excess length of hospital stay estimates for MRSA and 3GCREC BSIs (4 each) allowing for Bayesian hierarchical analysis, estimating means of 1.26 (95% credible interval (CrI): -0.72 – 4.17) and 1.78 (95% CrI: -0.02 – 3.38) days, respectively.

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.

Keywords: Antimicrobial resistance, resource use, costs, length of stay, Bayesian meta-analysis.

Background

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

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 (GDP) – 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 to the base case scenario (no AMR) (3).

A significant barrier to understanding the true effects of AMR is the lack of evidence in health economic outcomes. Estimates of the cost of AMR will vary depending on the perspective taken (patient, healthcare 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, while costs from a healthcare 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 (OECD) 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, as well as 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 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 costs of hospital infection and AMR in hospital (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 due to external economic factors not directly influencing internal healthcare 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 (like LoS) is essential to quantify the extent of the issue, estimate justified levels of resource use for control, parameterise cost-effectiveness models to evaluate associated interventions, thus maximising the efficiency in our spending 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 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*. estimated that a similar subset of pathogens were responsible for 0.93 million of the 1.27 million deaths predicted through modelling in 2019 (1). From an economic perspective, in 2019 Zhen *et al*. conducted a systematic review to assess the economic burden of ABR

130 infections in ESKAPE organisms and found evidence they were often associated with higher
131 costs. For example, the mean total hospital costs among inpatients with methicillin-resistant
132 *S. aureus* (MRSA) was between 1.12 and 6.25 times higher than for methicillin-susceptible
133 *S. aureus* (MSSA) cases (11). The authors suggested that lack of significant differences
134 between resistant and control groups (e.g. susceptible or no infection comparators) may be
135 due to problems with study design, and particularly highlighted large heterogeneities
136 between, as well as within, countries. Due to these heterogeneities and differences in
137 outcome types, no meta-analyses were performed.

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

Methods

Search strategy and inclusion

The systematic review is structured according to PRISMA guidance 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 was 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. Additionally, only publications which utilised 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 to 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, 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, colonised, 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 ICU, non-ICU and "general" (I.e., across all wards) days where possible, Excess inpatient cost, Excess ICU cost, Excess primary care cost, 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	Studies reported in conference abstracts only, Trial registries, Editorials, letters and comments, Studies published before 1990.

	comparative studies, Non-systematic reviews – for the purpose of identifying studies only.	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.

154

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

166 In brief, selection, deduplication and assessment of agreement was conducted using
167 Covidence software (15). Data extracted and a sub-set checked: a copy of the dataset used
168 for the final meta-analyses can be found in the project repository on the EPI-Net website
169 (16). Risk of bias was conducted independently by 2 reviewers and followed a framework
170 adapted from the Joanna Briggs Institute (JBI) tools for bias assessment in cohort, case
171 control, and economics studies (see supplementary material, 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.* 2014 (see supplementary materials) (20).

Furthermore, due to 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 (EUR) (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 mean excess length of stay, in days. All analyses focused on resistant versus susceptible comparators, as there was insufficient data to conduct analyses with resistant versus 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 studies meant a fixed effects model would also not be useful.

To utilise 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 (S5) (22-37). Sensitivity analyses was conducted testing the effect of weak and strong informative priors of the heterogeneity parameter on the summary estimate.

Results

Study selection

The search strategy identified 5,969 references (deduplicated from 6,798 references). After title/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 Figure 2. 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; twelve case-control studies (15/37, 35%), thirteen retrospective cohort studies (13/37, 38%), ten prospective cohort studies (10/37, 29%), and two 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 twenty publications were set in a secondary / tertiary care centre (20/37, 54%), fourteen in a tertiary centre (14/37, 38%) two in a primary / tertiary care setting (2/37, 5%), and one in all settings (1/34, 3%).

Thirty-two publications compared infection due to resistant and susceptible pathogens (32/37, 86%), eleven which compared to susceptible also compared resistant infection to no infection (11/37, 32%), and seven compared susceptible infection to no infection (7/37, 19%). The infections under study were split over different acquisition sources, with fourteen publications focusing on hospital-acquired infections (14/37, 38%), seven publications not specifying the source of infections (7/37, 19%) and six publications specifying infections as hospital- and community-acquired (6/37, 16%). Furthermore, the infections that were studied were heavily weighted towards bloodstream infections (BSIs), which were analysed in twenty publications (20/37, 54%), followed by respiratory tract infections (RTIs) with nine publications (9/37, 24%), and urinary tract infections (UTIs) in five publications (5/37, 14%).

A summary of the study characteristics and results can be seen in the supplementary materials (Tables S4-6).

Of the publications selected, the types of outcomes that were reported varied widely (Figure 1). In addition, there were significant data gaps, with limited data on excess healthcare resource use due to the included target pathogens. Overall, the grid is sparse, with a maximum of six 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 two pathogen-resistance-infection combinations yielded sufficient data for these outcomes: third-generation cephalosporin resistant *E.* coli (3GCREC) and methicillin resistant *Staphylococcus aureus* (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 four and five, respectively. Whereas for 3GCREC BSIs, this was four and six, respectively.

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

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

Five studies analysed the excess total cost of hospitalisation (from a payer/provider perspective) associated with 3GCREC, versus susceptible *E. coli* infections, four of which gave estimates for BSIs which ranged from - € 2,465.50 to € 6,402.81 per case. A meta-analysis of these costs was not performed as this was deemed inappropriate, due to 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 Figures 4 and 5. For the analysis of excess length of hospital stay attributable to MRSA infections (susceptible infection comparator), five publications reported an adjusted estimate which evaluated BSIs (4), RTIs (1), SSTIs (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 to susceptible infection), the weakly informative prior resulted in a mean of 1.26 (95% CrI: -1.72 – 4.17) days, with a probability of a positive excess length of stay associated with MRSA BSIs of 92% (Figure 6).

For excess length of hospital stay attributable to 3GCREC infections (susceptible infection comparator), four publications were found which 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 weakly informative prior resulted in a mean excess length of stay (compared to susceptible infection) of 1.78 (95% CrI: -0.02 – 3.38) days, and the probability of a positive excess length of stay was 95% (Figure 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% credible interval (CrI): -0.11 – 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 S7), 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 due to MRSA consisted of four publications with a "low" risk of bias, and one paper with a "medium" risk of bias, while for 3GCREC, all four of the publications included had a "low" risk of bias.

Due to 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 costs and resource use associated with and attributable to AMR. However, out of these 37 studies, only eight studies, which focus on BSIs, could be used to create pooled estimates of AMR impact. This was due to (i) a spread of data across syndromes, outcome measures and drug-bug combinations and (ii) a lack of studies estimating outcome (in this case excess length of stay) whilst 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 and/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. Though these results are based on only 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 heterogeniety by breaking down analyses by clinical subgroups (11, 38). This study extended the work carried out by previous reviews such as Zhen *et al*., who found 32 publications across the EU, EEA, and UK regions focusing on costs associated with AMR and provided descriptive results, without a focus on pathogen-specific AMR burden estimates(11). In this study we provided an analysis using Bayesian hierarchical modelling. Bayesian analyses can provide more valid results in case of sparse data and allow generalisation of the health economic outcomes to a wider

312 population (39). We provide the first example of how this method can be applied in AMR-
313 attributable resource use estimation.

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

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

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

334 The higher frequency of studies reporting MRSA and drug-resistant *E. coli* BSI outcomes
335 is perhaps unsurprising given the relative prevalence of these pathogen-resistance-infection
336 combinations in Europe (44). However, drug-resistant pathogens causing the largest
337 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 due to 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 ECDC and the WHO emphasises 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 the fact that, while 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 healthcare systems varying greatly across Europe (46). One approach to address this would be for studies to report resource use (e.g., type/number of diagnostics, treatments, other types of interventions, hospital readmissions, 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$ 1,020 respectively (47).

Similarly, no data was available from non-hospital settings. Cost outcomes from infections in hospital 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 healthcare utilisation 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, like 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. While 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 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, where 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 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/abstract screening for 100 publications showed 100% inter-reviewer agreement. The JBI 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 due to the subjectivity that is required in analysing the studies.

Conclusion

This review summarises the current evidence on the cost and resource use impact of resistant infections but yielded 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 to 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, whilst providing impact estimates by antibiotic, syndrome, and patient characteristic subgroups. These data are needed to appropriately parameterise cost-effectiveness models to efficiently tackle ABR.

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Availability of data and materials

Extracted data from included studies are provided in the [Additional file 1] associated with this manuscript, the subset of data used for the meta-analyses can be accessed via the Epi-NET website (16).

Competing interests

Venanzio Vella, Lorenzo Argente, Johannes Eberhard Schmidt, and Andrea Palladino are employees of GSK, VV, JES, and AP own GSK shares. Jeroen Geurtsen is an employee of Janssen, and owns stocks of Johnson & Johnson.

Figures and tables

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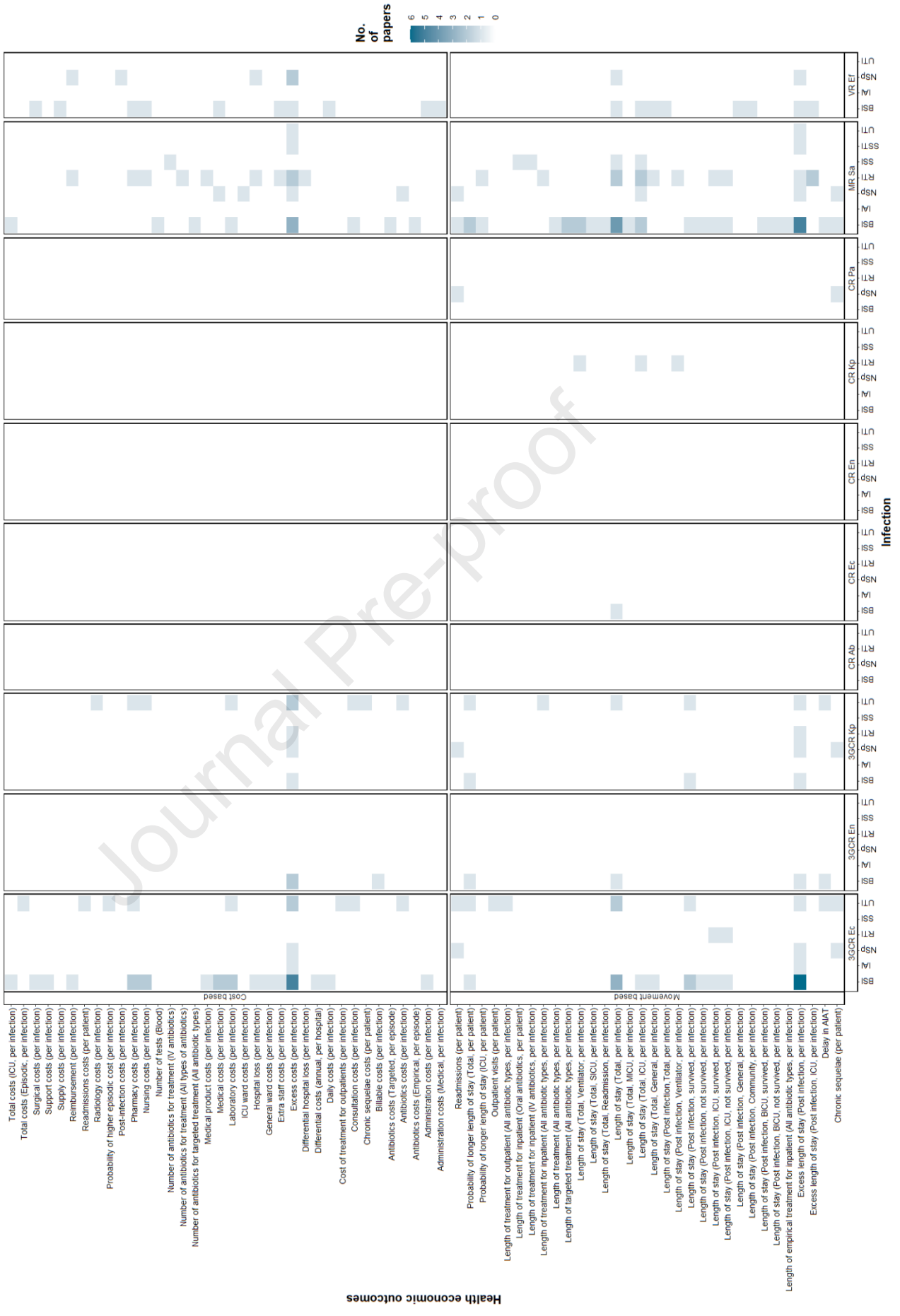

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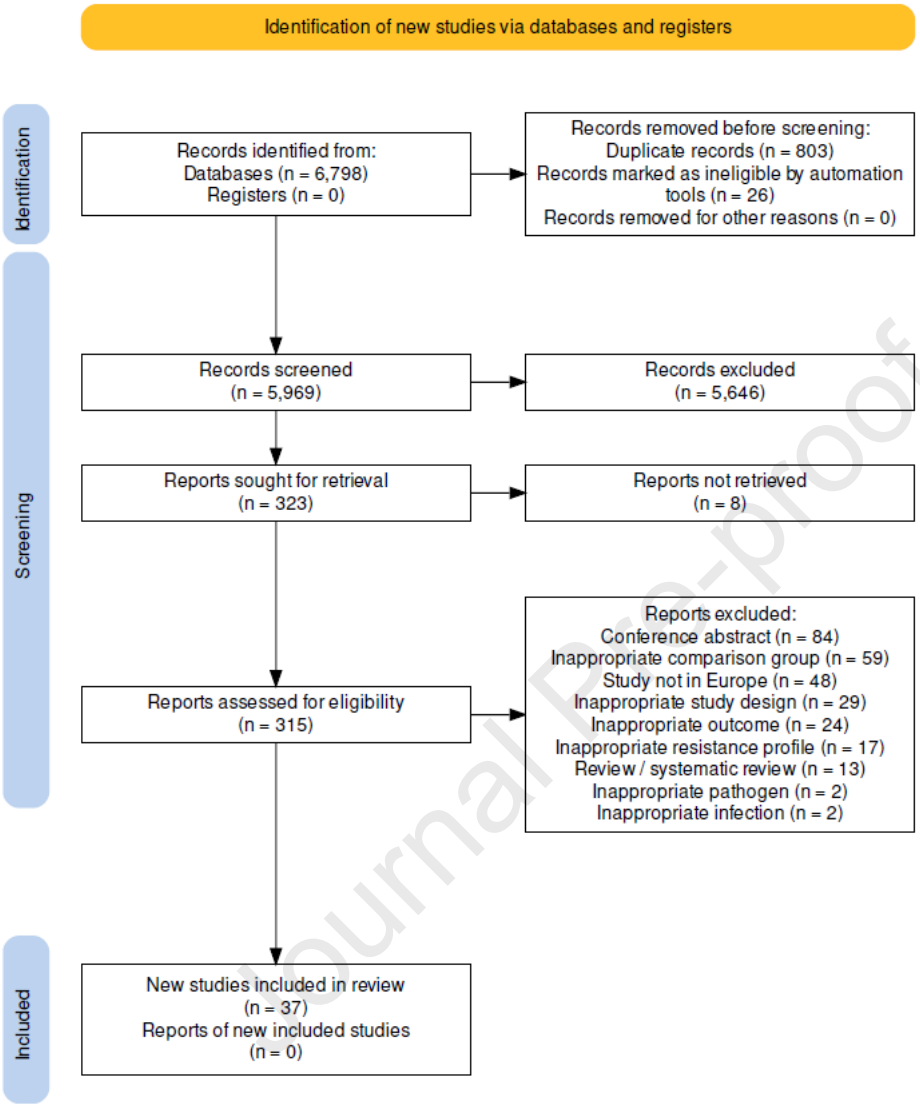

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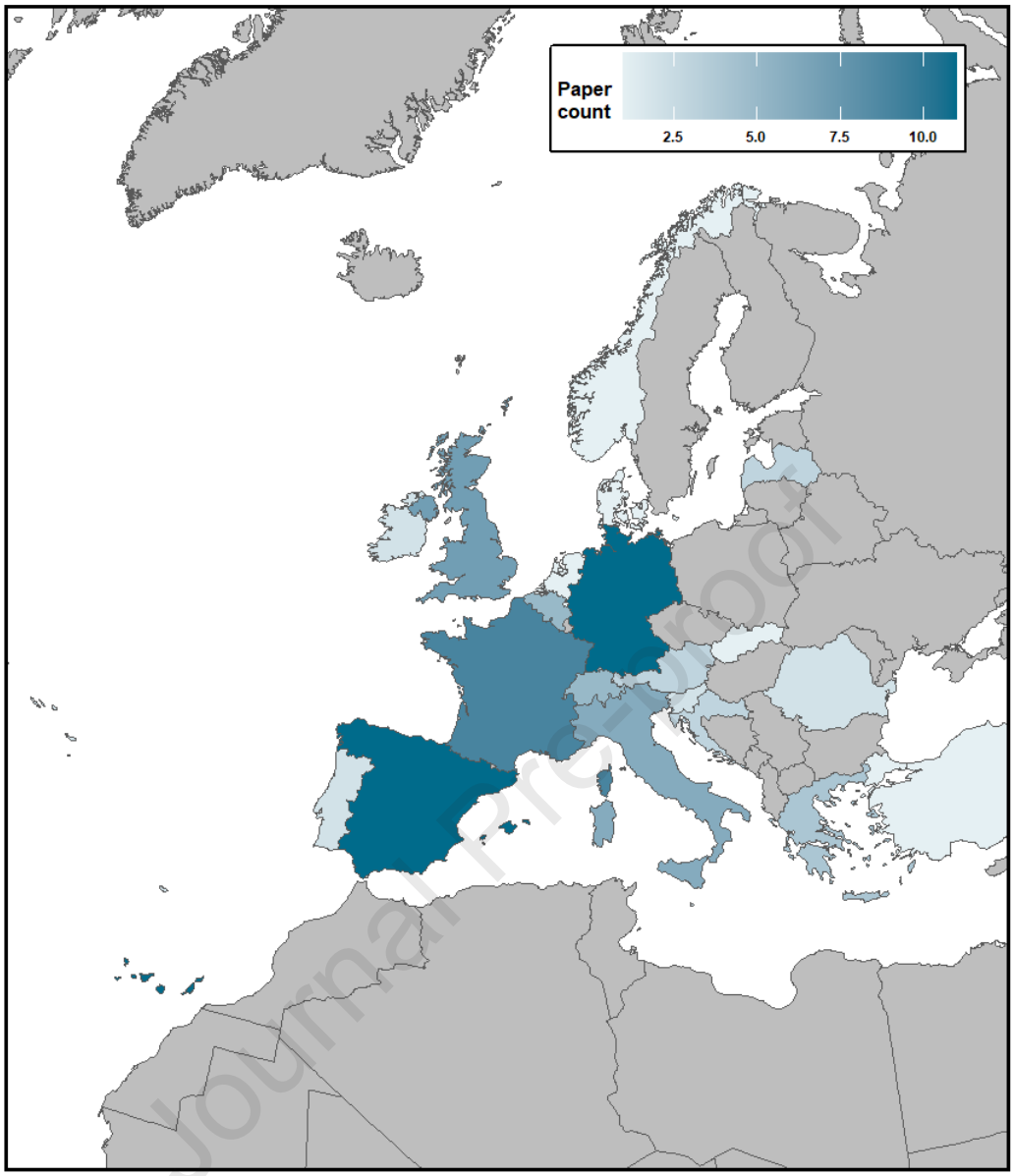

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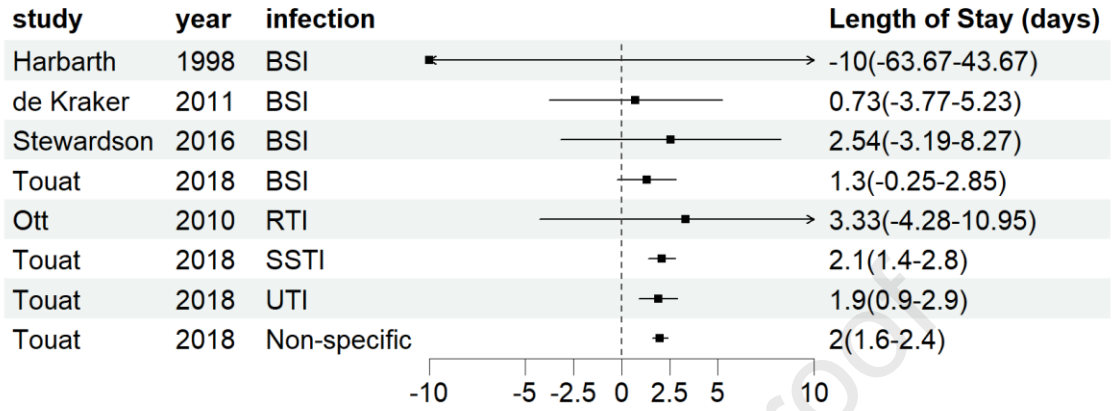

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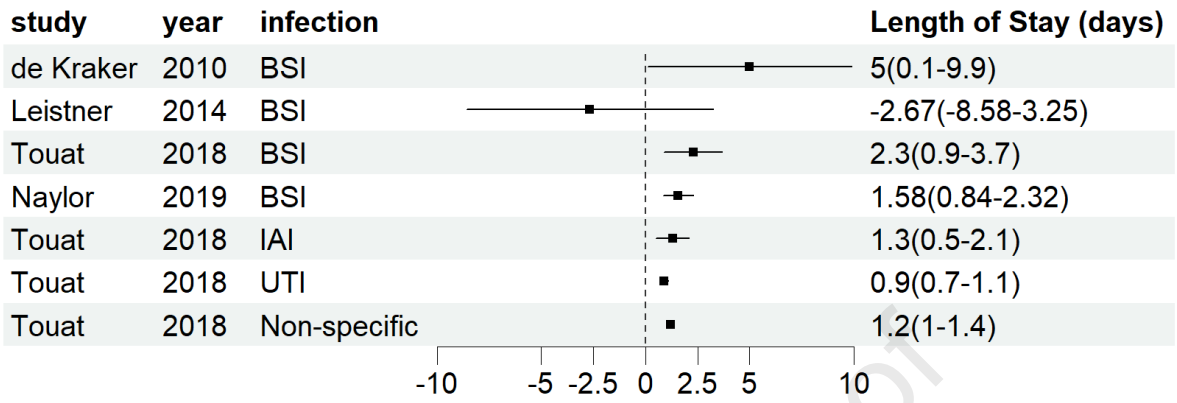

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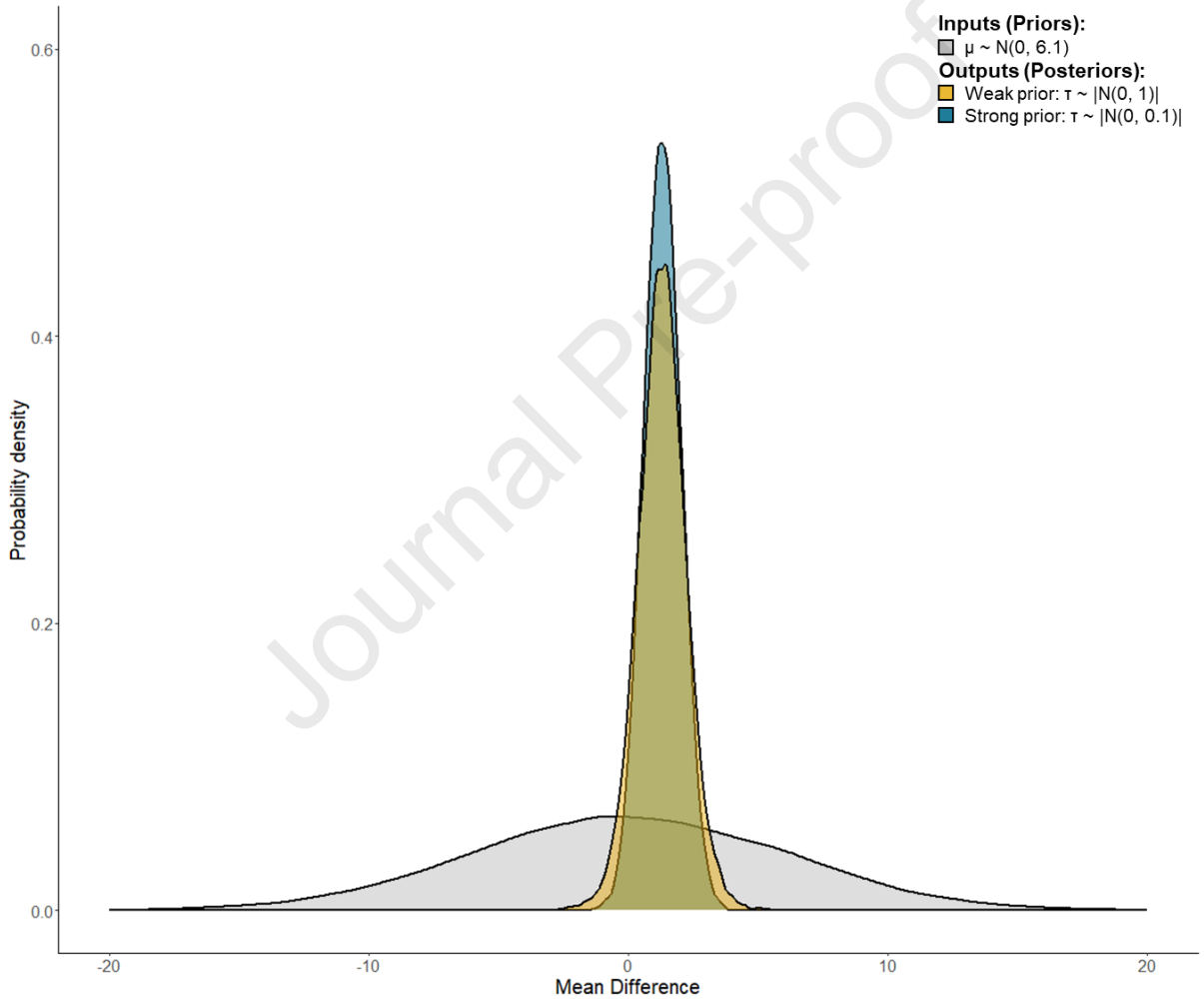

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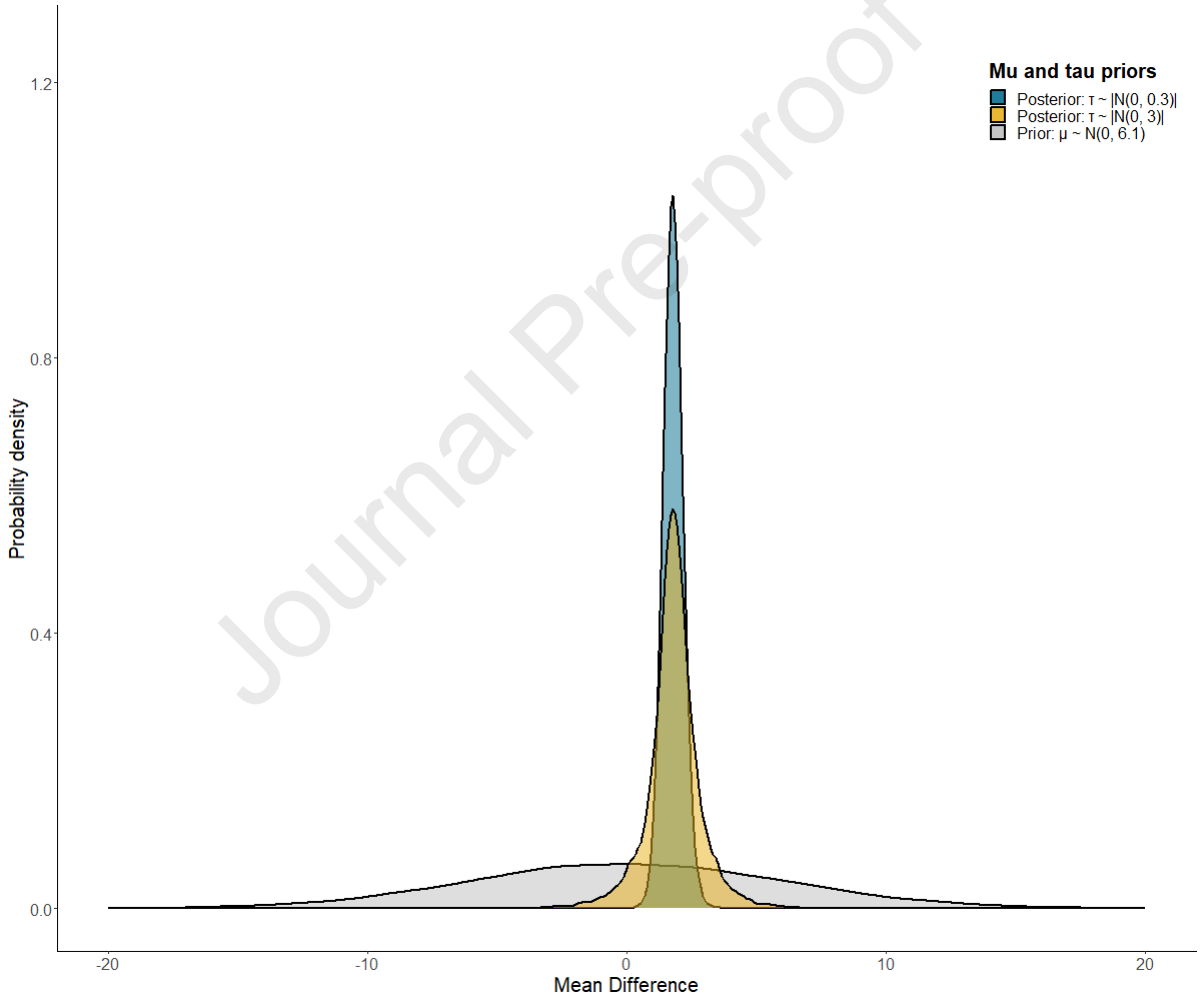

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