# Supplemental Online Content

Abdul-Aziz MH, Hammond NE, Brett SJ, et al. Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock: A Systematic Review and Meta-Analysis. *JAMA*. Published online June 12, 2024. doi:10.1001/jama.2024.9803

This supplementary material has been provided by the authors to give readers additional information about their work.

**eAppendix 1: Study protocol**

URL: https://www.medrxiv.org/content/10.1101/2023.05.15.23289889v1

## Introduction

### Rationale

Patients who develop sepsis and septic shock often require treatment in an intensive care unit (ICU) and face high morbidity and mortality rates (1). There is an urgent need to define strategies and interventions that can improve morbidity and mortality, as well as to reduce significant healthcare resource utilisation associated with sepsis management. Source control of the infection, along with early and appropriate antibiotic administration are central to the management of critically ill patients with sepsis (2). However, administering appropriate antibiotic therapy can be challenging in the ICU for a variety of reasons. Physiological changes can occur from pharmacological interventions such as the administration of fluid therapy, and the natural course of sepsis may also alter antibiotic pharmacokinetics in critically ill patients (3). In addition, pathogens isolated in the ICU are commonly less susceptible to common antibiotics than those in other environments (4). Conventional antibiotic dosing rarely considers these issues and therefore, has a higher likelihood to fail in this patient population (5-7).

The beta-lactam class of antibiotics are widely used to treat patients with sepsis or septic shock in the ICU due to their wide spectrum of antibiotic activity and favourable safety profile (8, 9). Beta-lactam antibiotics display “time-dependent” bactericidal activity, which is optimal when the duration of time (T) that the free drug concentration remains at least 40 – 70% of the time above the minimum inhibitory concentration (MIC) during a dosing interval ($fT_{>MIC}$ or 40 – 70% $fT_{>MIC}$) (10). However, recent data suggest that patients may benefit from higher (e.g., 2 – 5 x MIC) (11) and longer (e.g., 100% $fT_{>MIC}$) (7, 12) beta-lactam antibiotic exposures than those described in earlier pre-clinical infection models (13). Therefore, administration via prolonged infusion (infusion duration ≥2 hours or greater) is theoretically advantageous compared to standard intermittent infusion, which is characterized by high peaks followed by low concentrations for longer periods of the dosing interval.

*In vitro* and *in vivo* pharmacokinetic/pharmacodynamic data show that prolonged infusions more consistently achieve effective beta-lactam antibiotic exposure associated with maximal bacterial killing than intermittent infusion (14, 15). Clinical studies reporting patient outcomes with prolonged infusion of beta-lactam antibiotics have varied, ranging from no significant effect (16-26), to significant improvements in patient mortality (27, 28), clinical cure (29, 30), microbiological cure (31), length of ICU and/or hospital stay (32, 33), and duration of mechanical ventilation (29). Most meta-analyses have included heterogenous patient populations (34-38), including those in whom a difference in effect between prolonged and intermittent infusions is unlikely (e.g., non-critically ill patients), or studies with other important methodological shortcomings (39).

Two large multicentre randomized controlled trials (RCTs) comparing prolonged versus intermittent infusion of beta-lactam antibiotics in critically ill patients with sepsis or septic shock are due to be published in 2023: (1) the Beta-Lactam InfusioN Group (BLING) III Study, which aims to recruit 7000 ICU patients across Australia, Belgium, France, Malaysia, New Zealand, Sweden and the United Kingdom (40), and (2) the continuous infusion versus intermittent administration of MERopenem in criticallY ill patients (MERCY) Study, which aims to recruit 300 ICU patients across Croatia and Italy (41). To provide context for clinicians to interpret the results of these studies in light of the larger body of evidence, we plan to perform a systematic review and meta-analysis to assess whether in critically ill patients with sepsis or septic shock, a prolonged infusion of beta-lactam antibiotic compared to standard intermittent bolus dosing is associated with reduced 90-day all-cause mortality, as well as assessing the effect on other prespecified secondary outcomes.

**Objective**

The primary objective is to determine whether prolonged infusion of a beta-lactam antibiotic is associated with improved all-cause 90-day mortality when compared with intermittent infusion in critically ill adult patients with sepsis or septic shock. Key secondary outcomes will include ICU mortality, ICU length of stay, clinical cure, microbiological cure, and adverse events.

**Methods and analysis**

This systematic review and meta-analysis of RCTs comparing prolonged versus intermittent beta-lactam antibiotic infusion in critically ill adult patients with sepsis or septic shock will follow reporting recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (42). This systematic review has been registered on International Prospective Register of Systematic Reviews (PROSPERO) CRD42023399434.

**Eligibility criteria**

Inclusion criteria

RCTs comparing prolonged versus intermittent infusion of one or more beta-lactam antibiotics, which meet the following criteria will be included:

- *Population*

Critically ill adult (≥18 years old) patients with sepsis or septic shock receiving care in the ICU. All conventional and current definitions of sepsis and septic shock at the time of patient recruitment will be accepted (43-45).

A study is determined to have been conducted in a critically ill population if the manuscript reported any of the following:

(1) the patients were recruited in an ICU, or
(2) the inclusion criteria described were such that the patients would normally be managed in an ICU (e.g., patients receiving invasive mechanical ventilation), or
(3) the patients were suffering from a condition that usually requires care in an ICU (e.g., severe burns of >40% total body surface area), or
(4) the patients had an average ICU length of stay of ≥2 days, or
(5) a majority of the patients received a therapy that is delivered in the ICU (e.g., invasive mechanical ventilation), or
(6) a severity of illness score which reflected a critically ill population.

ICU may include a general ICU or complex of ICUs (medical, surgical, or mixed) capable of providing close monitoring and support for critically ill patients with life-threatening conditions.

- *Intervention*

Prolonged infusion of a beta-lactam antibiotic, where “prolonged infusion” is defined as either:

- Extended infusion: intravenous drug administration for ≥2 hours during a dosing interval OR
- Continuous infusion: constant intravenous drug administration either as a sequential 6-hour, 8-hour, 12-hour or 24-hour infusion.

- *Comparator*

Intermittent infusion of a beta-lactam antibiotic where “intermittent infusion” is defined as administration of an intravenous drug infusion for <2 hours.

- *Outcomes*

Studies that report or are able to provide any of the *a priori* primary or secondary outcomes specified in this systematic review and meta-analysis.

Exclusion criteria

The following studies will be excluded:

- Retrospective cohort studies
- Trials of patients not meeting the criteria for sepsis or septic shock.

**Search strategy**

Medline (via PubMed), CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), pre-print servers (medRxiv and OSF Preprints), and clinical trials registries will be searched to identify eligible trials to be included for review. The search will be performed with no restrictions on language, publication date or publication status. We will use a combination of keywords and search terms to identify RCTs in:

- “sepsis” or “septic shock” or “systemic inflammatory response syndrome” AND
- “beta-lactam” or “carbapenem” or “cephalosporin” or “monobactam” or “penicillin” AND
- “continuous infusion” or “extended infusion” or “prolonged infusion” AND
- “critically ill” or “intensive care unit”

The search terms for this review will be created by a research librarian in collaboration with content area experts. Additionally, we will manually check the reference lists of relevant primary and review articles, as well as contacting experts in the field, to identify additional RCTs that may be eligible for inclusion. Full details of the electronic search strategy are available in the appendix.

**Study records**

Selection process

Study titles and abstracts from the search will be screened in a reference management system (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Duplicates and irrelevant studies will be excluded. Review of titles and abstracts will be independently undertaken by two reviewers. Reports identified by either reviewer that may potentially meet inclusion criteria will be obtained for full text review. Full text manuscripts of potentially eligible studies will be assessed by two reviewers independently, with disagreements resolved by consensus or resort to a third reviewer if required. The selection process will be documented and presented in a Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) flow diagram.

Data collection

Data from included studies will be extracted using a standardized data collection form. Data extraction will be performed in duplicate and any disagreements will be resolved by discussion or, if required, by referral to a third reviewer. Attempts will be made to contact corresponding authors to obtain essential additional data. Access to aggregate level data for the BLING III (40) and MERCY (41) studies prior to publication has been agreed by the respective investigators and study management committees. Data from unpublished studies will not be made public without the express prior consent of the responsible parties.

The following data will be extracted:

- Study characteristics: first author, year of publication, study period, recruiting countries, number of patients enrolled.
- Participant characteristics: age, sex, severity of illness scores at baseline, renal replacement therapy at baseline, renal replacement therapy during

study period, microbiological confirmed infection (i.e., culture-positive infection), distribution of isolated pathogens (Gram-negative versus Gram-positive organisms), and site of infection.

- Study intervention and comparator details: antibiotic, dosing regimen, and concomitant antibiotics.
- Outcomes: 90-day mortality (or closest time point before and beyond), ICU mortality, ICU and hospital length of stay, clinical cure and the definition used in the study, microbiological cure and the definition used in the study, and the number of adverse events.

**Outcomes**

Primary outcome

The primary outcome is all-cause 90-day mortality. If 90-day mortality outcomes are not reported in a study, we will use the time closest to Day 90 (before and beyond).

Secondary outcomes

Where available, the following secondary outcomes will be reported:

- ICU mortality
- ICU length of stay as reported in the original study
- Clinical cure as defined in the original study
- Microbiological cure as defined in the original study
- Adverse events as defined in the original publication

**Risk of bias**

The Cochrane Collaboration's Risk-of-Bias Tool for Randomized Trials version 2 (RoB 2) will be used to evaluate the quality of included studies. The tool will evaluate all types of bias that can affect results of RCTs covering five domains including bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. For each domain, studies will be judged to either have "low risk of bias", "some concerns" or "high risk of bias". A proposed judgement will be generated by an algorithm based on answers to the signalling questions of the tool. The risk of bias assessment will be performed by two independent assessors who were not involved in any of the included studies.

**Statistical analysis**

The meta-analysis will be based on a Bayesian (primary approach) and a frequentist (secondary approach) framework. Random-effects meta-analyses will be carried out and pooled effect estimates will be reported as Risk Ratio (RR) with 95% confidence interval (CI) or credible interval (CrI) for binary outcomes, and as Mean Difference (MD) for continuous outcomes. When median and interquartile range or range are reported, mean and standard deviation will be estimated using the method described by Wan et al (46).

For the Bayesian analysis, pooled effect estimates and posterior probabilities that prolonged infusion of beta-lactam antibiotics is associated with better outcomes compared to intermittent infusion will be generated using: (a) vague priors for the effect and heterogeneity parameters in the main analysis, and (b) weakly-informative priors in the sensitivity analysis. Normally distributed priors will be used for the effect parameters logRR and MD (e.g., a vague prior for the logRR centered at mean of 0 with a standard deviation of 2 will be used for binary outcomes), while half-normal priors will be used for the heterogeneity parameter $\tau^2$ (e.g., a vague prior of 0.5). Where applicable and appropriate, weakly informative priors for the heterogeneity parameter will be specified for different types of outcome measures (47, 48). For the frequentist analysis, the (a) Hartung-Knapp-Sidik-Jonkman method, and the (b) DerSimonian-Laird method will be employed to obtain an overall effect estimate for each outcome measure.

Quantitative heterogeneity will be assessed using $\tau^2$ and its 95% credible interval. The proportion of variation across studies due to heterogeneity rather than chance will be assessed using the $I^2$ statistic. Presence of small-study effects will be assessed through regression-based Egger's test and visual inspection of the contour-enhanced funnel plots.

Statistical analyses will be performed using Stata BE V17 for Windows (StataCorp LLC, College Station, TX) and the bayesmeta package in R (49).

Missing data

Data from “intention-to-treat” populations will be used in the analysis and an attempt to obtain missing outcome data from the original study authors will be made. There will be no imputing of values for missing data.

Sub-group analysis

Sub-group analyses for the primary outcome will be hypothesis generating. The following patient sub-groups will be analysed if enough baseline data are available:

- Meropenem vs. piperacillin/tazobactam. It is hypothesized that improvements in patient survival will be greater in patients receiving prolonged infusion of piperacillin/tazobactam as longer % $fT_{>MIC}$ exposure is required for antibiotic efficacy when compared with meropenem.
- Culture-positive vs. culture-negative infections. Patients with microbiological confirmed infections who receive prolonged infusion of beta-lactam antibiotics is hypothesized to show greater improvements in patient survival when compared with intermittent infusion.
- Gram-positive vs. Gram-negative infections. Patients with Gram-negative infections who receive prolonged infusion of beta-lactam antibiotics is hypothesized to show greater improvements in patient survival when compared with intermittent infusion. Gram-negative microorganisms tend to have higher MICs and, in such infections, pharmacokinetic/pharmacodynamic data have consistently demonstrated that prolonged infusion of beta-lactam antibiotics is more likely to achieve higher % $fT_{>MIC}$ exposures for maximal bacterial killing.
- Renal replacement therapy vs. non-renal replacement therapy. It is hypothesized that improvements in patient survival will be greater in patients who receive prolonged infusion of beta-lactam antibiotics who are not on renal replacement therapy support. Patients receiving renal replacement therapy are likely to have reduced drug clearance leading to higher and longer % $fT_{>MIC}$ beta-lactam antibiotic exposures, regardless of which administration method is used.
- Lung infections vs. other infections. It is hypothesized that improvements in patient survival will be greater in patients with lung infections who receive prolonged infusion of beta-lactam antibiotics. An administration

method that can enhance the beta-lactam antibiotic penetration into the interstitial fluid of the infected lung tissues (where the antibiotic-bacteria interactions occur) is likely to improve patient outcomes.

- Sepsis vs. septic shock. It is hypothesized that improvements in patient survival will be greater in patients with septic shock who receive prolonged infusion of beta-lactam antibiotics. Patients with septic shock commonly develop extreme pathophysiological changes, which may reduce effective % $fT_{>MIC}$ beta-lactam exposures, and these patients are usually infected with pathogens that are less susceptible to antibiotic therapy (i.e., high MICs).
- Male vs. female sex. It is hypothesized that improvements in survival will be greater in male patients who received prolonged infusion of beta-lactam antibiotics. Critically ill male patients are more likely to demonstrate increased glomerular filtration rates leading to reduced % $fT_{>MIC}$ beta-lactam antibiotic exposures. As beta-lactam antibiotics are predominantly cleared via renal elimination, prolonged infusion dosing may confer clinical advantages by maintaining effective beta-lactam antibiotic exposures throughout the dosing interval when compared with intermittent infusion.

The credibility of any subgroup analysis will be assessed using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in meta-analyses of RCTs (50).

**Assessment of evidence**

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to evaluate the overall quality of evidence for each outcome measures (51, 52). Findings will be presented in a “Summary of findings and certainty of evidence” table. The certainty of evidence will be assessed based on five domains including the risk of bias, imprecision, inconsistency, indirectness and publication bias. For each outcome, the quality and certainty of evidence will be rated as “high”, “moderate”, “low” or “very low”.

**Patient and public involvement**

As this is a secondary analysis, patient or consumer representation was not involved in the development of this protocol.

## Ethics and dissemination

Human research ethics approval is not required as the study involves the use of existing collections of data that are de-identified. It is expected that the findings of this systematic review/meta-analysis will be presented at national and international intensive care and infectious diseases meetings. The results will be published in a peer-reviewed journal in the intensive care or infectious diseases literature. The publication will be made available on publicly accessible institutional websites. The results will not be publicly released until the main studies are published and are publicly available. Data sharing requests will be handled in accordance with The George Institute for Global Health (TGI) data sharing policy (https://www.georgeinstitute.org.au/data-sharing-policy).

## Discussion and limitation

This systematic review and meta-analysis will provide the most robust and up-to-date evidence concerning the clinical benefits of prolonged infusion versus intermittent infusion dosing of beta-lactam antibiotics in critically ill patients with sepsis or septic shock. New combined data from two large multicentre RCTs will be included to help address the uncertainty in beta-lactam antibiotic dosing strategy for ICU patients with sepsis or septic shock.

We acknowledge that there will be limitations in this systematic review and meta-analysis due to studies with heterogeneous ICU patient populations, variable illness severity, variable beta-lactam antibiotic dosing regimens, and differences in primary and secondary outcomes definitions.

## Funding

This systematic review and meta-analysis will be conducted without specific funding support. The investigators are grateful to The George Institute for Global Health and the Centre of Research Excellence – Personalising Antimicrobial Dosing to Reduce Resistance (CRE RESPOND; Australian National Health and Medical Research Council Centre of Research Excellence, APP2007007), The University of

Queensland, for providing in-kind support for this work. Naomi E. Hammond, John Myburgh and Jason A. Roberts are supported by National Health and Medical Research Council (NHMRC) Investigators Grant. Jan De Waele is supported by a Senior Clinical Investigator Fellowship from the Flanders Research Foundation (FWO). Fredrik Sjövall is supported by a grant from the Swedish Research Council.

**eAppendix 2: Electronic search strategy**

We systematically searched Medline (via PubMed), CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov, from inception to May 2, 2024. The search was performed with no restrictions on language, publication date or publication status. Combinations of search terms and keywords used in all databases are presented below:

**PubMed**

**Sepsis**

"Sepsis"[Mesh] OR "bacteremia"[mesh] OR "shock, septic"[MeSH Terms] OR "systemic inflammatory response syndrome"[MeSH Terms] OR bacteraem*[tiab] OR bacterem*[tiab] OR bacteremia[tiab] OR “blood infection*”[tiab] OR “blood stream infection*”[tiab] OR “bloodstream infection*”[tiab] OR endotoxaem*[tiab] OR endotoxem*[tiab] OR intensive care[tiab] OR sepsis[tiab] OR septic[tiab] OR septicaemia[tiab] OR septicemia[tiab] OR SIRS[tiab] OR Systemic Inflammatory Response Syndrome[tiab] OR ((bloodstream[tiab] OR "blood stream"[tiab] OR "blood-stream"[tiab]) AND infection*[tiab])

**Beta Lactams**

"beta-Lactams"[Mesh] OR "Lactams"[Mesh] OR "penicillins"[MeSH Terms] OR "cephalosporins"[MeSH Terms] OR "carbapenems"[MeSH Terms] OR "monobactams"[MeSH Terms] OR "Moxalactam"[Mesh] OR "Clavulanic Acids"[Mesh] OR "beta-lactamase inhibitors"[Pharmacological Action] OR "beta-lactamase inhibitors"[MeSH Terms] OR aztreonam*[tiab] OR benzylpenicillin*[tiab] OR beta-Lactam*[tiab] OR carbapenem*[tiab] OR cefazolin*[tiab] OR cefepime*[tiab] OR cefoperazone*[tiab] OR ceftazidime*[tiab] OR Cephalosporin*[tiab] OR clavulanic acid*[tiab] OR doripenem*[tiab] OR ertapenem[tiab] OR imipenem*[tiab] OR meropenem*[tiab] OR monobactam*[tiab] OR penicillin*[tiab] OR piperacillin*[tiab] OR sulbactam*[tiab] OR tazobactam*[tiab] OR ticarcillin*[tiab]

**Infusions**

("Administration, Intravenous"[Mesh] OR "Infusions, Intravenous"[Mesh] OR Infusion*[tiab]) AND (intermittent[tiab] OR continuous[tiab] OR extended[tiab] OR prolonged[tiab] OR "Drug Administration Schedule"[Mesh])

**Critically Ill**

"critical care"[MeSH Terms] OR "Intensive Care Units"[Mesh] OR acute care[tiab] OR critical care[tiab] OR “intensive care”[tiab] OR ICU[tiab] OR "Critical Illness"[Mesh] OR "Critically Ill*"[tiab] OR “critical care”[tiab] OR “critical illness”[tiab] OR “Intensive therapy”[tiab]

**CINAHL**

**Sepsis**

(MH "Sepsis+") OR (MH "Bacteremia") OR (MH "shock, septic+") OR (MH "systemic inflammatory response syndrome+") OR (TI bacteraem* OR AB bacteraem*) OR (TI bacterem* OR AB bacterem*) OR (TI bacteremia OR AB bacteremia) OR (TI "blood infection*" OR AB "blood infection*") OR (TI "blood stream infection*" OR AB "blood stream infection*") OR (TI "bloodstream infection*" OR AB "bloodstream infection*") OR (TI endotoxaem* OR AB endotoxaem*) OR (TI endotoxem* OR AB endotoxem*) OR (TI "intensive care" OR AB "intensive care") OR (TI sepsis OR AB sepsis) OR (TI septic OR AB septic) OR (TI septicaemia OR AB septicaemia) OR (TI septicemia OR AB septicemia) OR (TI SIRS OR AB SIRS) OR (TI "Systemic Inflammatory Response Syndrome" OR AB "Systemic Inflammatory Response Syndrome") OR (((TI bloodstream OR AB bloodstream) OR (TI "blood stream" OR AB "blood stream") OR (TI blood-stream OR AB blood-stream)) AND (TI infection* OR AB infection*))

**Beta Lactams**

(MH "Antibiotics, Lactam+") OR (MH "Penicillins+") OR (MH "Cephalosporins+") OR (MH "Carbapenems+") OR (MH "Clavulanic Acid") OR "beta-lactamase inhibitors" OR (MH "beta-lactamase inhibitors+") OR (TI aztreonam* OR AB aztreonam*) OR (TI benzylpenicillin* OR AB benzylpenicillin*) OR (TI beta-Lactam* OR AB beta-Lactam*) OR (TI carbapenem* OR AB carbapenem*) OR (TI cefazolin* OR AB cefazolin*) OR (TI cefepime* OR AB cefepime*) OR (TI cefoperazone* OR AB cefoperazone*) OR (TI ceftazidime* OR AB ceftazidime*) OR (TI Cephalosporin* OR AB Cephalosporin*) OR (TI "clavulanic acid*" OR AB "clavulanic acid*") OR (TI doripenem* OR AB doripenem*) OR (TI ertapenem OR AB ertapenem) OR (TI imipenem* OR AB imipenem*) OR (TI meropenem* OR AB meropenem*) OR (TI

monobactam* OR AB monobactam*) OR (TI penicillin* OR AB penicillin*) OR (TI piperacillin* OR AB piperacillin*) OR (TI sulbactam* OR AB sulbactam*) OR (TI tazobactam* OR AB tazobactam*) OR (TI ticarcillin* OR AB ticarcillin*)

**Infusions**

((MH "Administration, Intravenous") OR (MH "Infusions, Intravenous") OR (TI Infusion* OR AB Infusion*)) AND ((TI intermittent OR AB intermittent) OR (TI continuous OR AB continuous) OR (TI extended OR AB extended) OR (TI prolonged OR AB prolonged) OR (MH "Drug Administration Schedule"))

**Critically Ill**

(MH "Critical Care+") OR (MH "Intensive Care Units+") OR (TI "acute care" OR AB "acute care") OR (TI "critical care" OR AB "critical care") OR (TI "intensive care" OR AB "intensive care") OR (TI ICU OR AB ICU) OR (MH "Critical Illness+") OR MM "Critically Ill Patients") OR (TI "Critically Ill*" OR AB "Critically Ill*") OR (TI "critical care" OR AB "critical care") OR (TI "critical illness" OR AB "critical illness") OR (TI "Intensive therapy" OR AB "Intensive therapy")

**EMBASE**

**Sepsis**

'sepsis'/exp OR 'bacteremia'/exp OR 'septic shock'/exp OR 'systemic inflammatory response syndrome'/exp OR bacteraem*:ti,ab OR bacterem*:ti,ab OR bacteremia:ti,ab OR 'blood infection*':ti,ab OR 'blood stream infection*':ti,ab OR 'bloodstream infection*':ti,ab OR endotoxaem*:ti,ab OR endotoxem*:ti,ab OR 'intensive care':ti,ab OR sepsis:ti,ab OR septic:ti,ab OR septicaemia:ti,ab OR septicemia:ti,ab OR SIRS:ti,ab OR 'Systemic Inflammatory Response Syndrome':ti,ab OR ((bloodstream:ti,ab OR 'blood stream':ti,ab OR blood-stream:ti,ab) AND infection*:ti,ab)

**Beta Lactams**

'beta lactam'/exp OR 'lactam'/exp OR 'penicillin derivative'/exp OR 'cephalosporin derivative'/exp OR 'carbapenem derivative'/exp OR 'monobactam derivative'/exp OR 'latamoxef'/exp OR 'clavulanic acid'/exp OR 'beta-lactamase inhibitors' OR 'beta-lactamase inhibitors'/exp OR aztreonam*:ti,ab OR benzylpenicillin*:ti,ab OR beta-

Lactam*:ti,ab OR carbapenem*:ti,ab OR cefazolin*:ti,ab OR cefepime*:ti,ab OR cefoperazone*:ti,ab OR ceftazidime*:ti,ab OR Cephalosporin*:ti,ab OR 'clavulanic acid*':ti,ab OR doripenem*:ti,ab OR ertapenem:ti,ab OR imipenem*:ti,ab OR meropenem*:ti,ab OR monobactam*:ti,ab OR penicillin*:ti,ab OR piperacillin*:ti,ab OR sulbactam*:ti,ab OR tazobactam*:ti,ab OR ticarcillin*:ti,ab

**Infusions**

('intravenous drug administration'/exp OR Infusion*:ti,ab) AND (intermittent:ti,ab OR continuous:ti,ab OR extended:ti,ab OR prolonged:ti,ab )

**Critically Ill**

'intensive care'/exp OR 'intensive care unit'/exp OR 'acute care':ti,ab OR 'critical care':ti,ab OR 'intensive care':ti,ab OR ICU:ti,ab OR 'critical illness'/exp OR 'Critically Ill*':ti,ab OR 'critical care':ti,ab OR 'critical illness':ti,ab OR 'Intensive therapy':ti,ab

**Cochrane Central Register of Controlled Trials (CENTRAL)**

**Sepsis**

[mh Sepsis] OR [mh bacteremia] OR [mh "shock, septic"] OR [mh "systemic inflammatory response syndrome"] OR bacteraem*:ti,ab OR bacterem*:ti,ab OR bacteremia:ti,ab OR ("blood" NEXT infection*):ti,ab OR ("blood stream" NEXT infection*):ti,ab OR ("bloodstream" NEXT infection*):ti,ab OR endotoxaem*:ti,ab OR endotoxem*:ti,ab OR "intensive care":ti,ab OR sepsis:ti,ab OR septic:ti,ab OR septicaemia:ti,ab OR septicemia:ti,ab OR SIRS:ti,ab OR "Systemic Inflammatory Response Syndrome":ti,ab OR ((bloodstream:ti,ab OR "blood stream":ti,ab OR blood-stream:ti,ab) AND infection*:ti,ab)

**Beta Lactams**

[mh “beta-Lactams”] OR [mh “Lactams”] OR [mh “penicillins”] OR [mh “cephalosporins”] OR [mh “carbapenems”] OR [mh “monobactams”] OR [mh “Moxalactam”] OR [mh “Clavulanic Acids”] OR "beta-lactamase inhibitors" OR [mh "beta-lactamase inhibitors"] OR aztreonam*:ti,ab OR benzylpenicillin*:ti,ab OR beta-Lactam*:ti,ab OR carbapenem*:ti,ab OR cefazolin*:ti,ab OR cefepime*:ti,ab OR cefoperazone*:ti,ab OR ceftazidime*:ti,ab OR Cephalosporin*:ti,ab OR ("clavulanic" NEXT acid*):ti,ab OR doripenem*:ti,ab OR ertapenem:ti,ab OR imipenem*:ti,ab OR

meropenem*:ti,ab OR monobactam*:ti,ab OR penicillin*:ti,ab OR piperacillin*:ti,ab OR sulbactam*:ti,ab OR tazobactam*:ti,ab OR ticarcillin*:ti,ab

**Infusions**

([mh "Administration, Intravenous"] OR [mh "Infusions, Intravenous"] OR Infusion*:ti,ab) AND (intermittent:ti,ab OR continuous:ti,ab OR extended:ti,ab OR prolonged:ti,ab OR [mh "Drug Administration Schedule"])

**Critically Ill**

[mh "critical care"] OR [mh "Intensive Care Units"] OR [mh "critical care"] OR "acute care":ti,ab OR "critical care":ti,ab OR "intensive care":ti,ab OR ICU:ti,ab OR [mh "Critical Illness"] OR ("Critically" NEXT Ill*):ti,ab OR "critical care":ti,ab OR "critical illness":ti,ab OR "Intensive therapy":ti,ab

**ClinicalTrials.gov**

condition "sepsis" intervention "Continuous infusion of beta-lactam antibiotics" OR "Extended infusion of beta-lactam" OR "prolonged infusion of beta-lactam"

condition "critically ill patients" intervention "Continuous infusion of beta-lactam antibiotics" OR "Extended infusion of beta-lactam" OR "prolonged infusion of beta-lactam"

condition "sepsis OR septic shock" intervention "Continuous infusion of beta-lactam antibiotics" OR "Extended infusion of beta-lactam" OR "prolonged infusion of beta-lactam"

**eAppendix 3: Semi-informative priors for heterogeneity parameter details**

For the Bayesian analysis, pooled effect estimates and posterior probabilities that prolonged infusion of beta-lactam antibiotics is associated with better outcomes compared to intermittent infusion will be generated using: (a) vague priors for the effect and heterogeneity parameters in the main analysis, and (b) weakly-informative priors in the sensitivity analysis. The analysis was performed using the model described in Röver et al., 2021[1]. Normally distributed priors will be used for the effect parameters logRR and MD (e.g., a vague prior for the logRR centered at mean of 0 with a standard deviation of 2 will be used for binary outcomes), while half-normal priors will be used for the heterogeneity parameter $\tau^2$ (e.g., a vague prior of 0.5). Weakly informative priors for the heterogeneity parameter have been specified for different types of outcome measures[1,2]:

- ICU mortality: log-normal distribution with a mean of -3.95 and a standard deviation of 1.34
- ICU length of stay: log-normal distribution with a mean of -2.34 and a standard deviation of 1.74
- Clinical cure: log-normal distribution with a mean of -2.06 and a standard deviation of 1.51
- Microbiological cure: log-normal distribution with a mean of -1.77 and a standard deviation of 1.52
- Adverse events: log-normal distribution with a mean of -1.87 and a standard deviation of 1.52

We define the Bayesian random effects models as follows:

$$y_i | \mu, \sigma_i, \tau \sim Normal\left(\mu, \sigma_i^2 + \tau^2\right)$$

where $y_i$ and $\sigma_i^2$ represent the natural logarithm of the risk ratio and the variance $y_i$ for the individual study $i$. The mean effect $\mu$ and the heterogeneity $\tau$ are the unknown parameters. In the Bayesian framework, we define the prior distributions as follows:

- with vague priors

    - $\mu \sim Normal(0,\ 2^2)$
    - $|\tau| \sim HalfNormal(0.5)$

- with semi-informative priors
    - $\mu \sim Normal(0,\ 2^2)$
    - $\tau \sim LogNormal(-1.975,\ 0.67)$

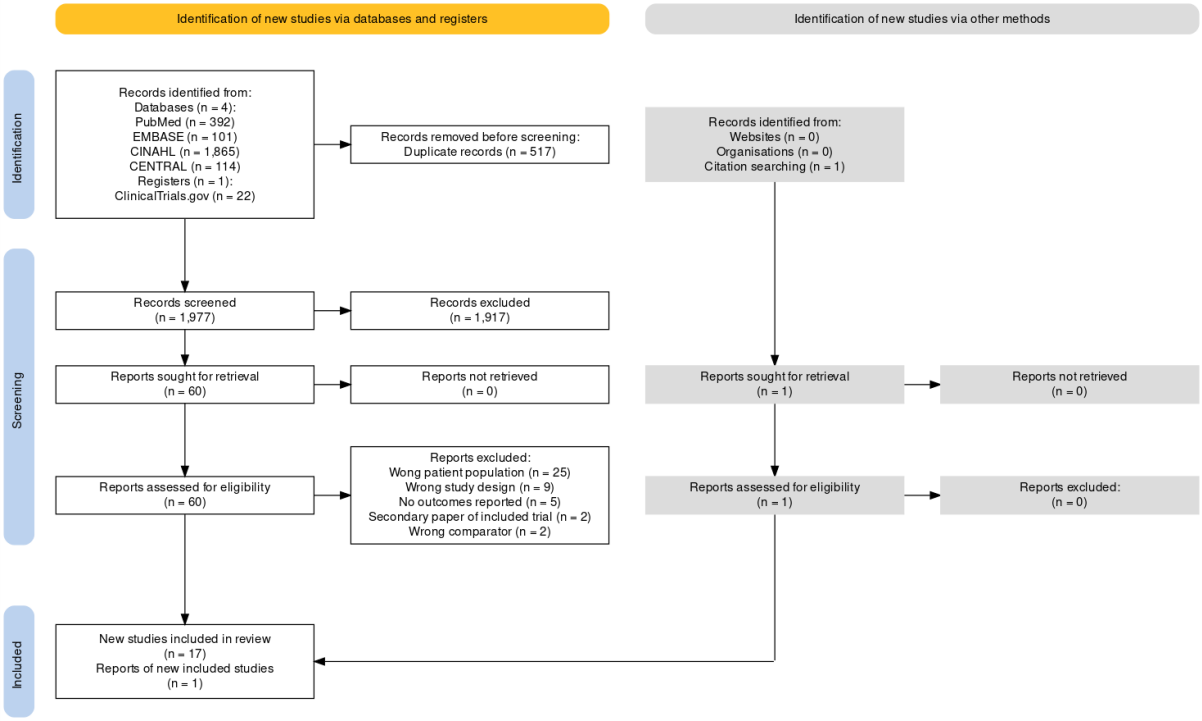
Sub-group heterogeneity was assessed by including an interaction term in the Bayesian analysis, to obtain an estimate and 95% CrI for the ratio of risk ratios (RRR), from the posterior distribution of the interaction estimate. We used a vague prior defined by a normal distribution with mean = 0 and standard deviation = 2 to define the interaction term.

**References**

1. Röver C, Bender R, Dias S, Schmid CH, Schmidli H, Sturtz S, Weber S, Friede T. On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Res Synth Methods* 2021; 12: 448-474.

2. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Stat Med* 2015; 34: 984-998.

**eFigure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of search strategy and included studies**




The PRISMA flowchart was designed using Haddaway NR, Page MJ, Pritchard CC & McGuinness LA (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimized digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230

**eTable 1: Excluded reports and reasons for exclusion**

| | Reference | Reasons for exclusion |
|---|---|---|
| **1.** | Bergogne-Berezin et al., J Antimicrob Chemother. 1984 Jul;14(1):67-73. doi: 10.1093/jac/14.1.67. | Wrong patient population – ventilated ICU patients with acute infections with chronic obstructive lung disease |
| **2.** | Thalhammer et al., J Antimicrob Chemother. 1999 Apr;43(4):523-7. doi: 10.1093/jac/43.4.523. | Wrong patient population – community or hospital-acquired infections |
| **3.** | Georges et al., Pathol Biol (Paris). 1999 May;47(5):483-5. | Secondary paper of included trial |
| **4.** | Lipman et al., J Antimicrob Chemother. 1999 Feb;43(2):309-11. doi: 10.1093/jac/43.2.309. | Wrong patient population – all ICU patients |
| **5.** | Nicolau et al., Infectious Diseases in Clinical Practice. 1999;8(1):45-49 | Wrong patient population – nosocomial pneumonia |
| **6.** | Nicolau et al., Int J Antimicrob Agents. 2001 Jun;17(6):497-504. doi: 10.1016/s0924-8579(01)00329-6. | Wrong patient population – ICU patients |
| **7.** | Cousson et al., Pathol Biol (Paris). 2005 Oct-Nov;53(8-9):546-50. doi: 10.1016/j.patbio.2005.06.002. Epub 2005 Jul 14. | Wrong patient population – ICU patients |
| **8.** | Langgartner et al., Chemotherapy. 2007;53(5):370-7. doi: 10.1159/000107725. Epub 2007 Sep 3. | Wrong patient population – suspected infection requiring antibiotic |
| **9.** | Sakka et al., Antimicrob Agents Chemother. 2007 Sep;51(9):3304-10. doi: 10.1128/AAC.01318-06. Epub 2007 Jul 9. | Wrong patient population – ICU acquired pneumonia |
| **10.** | Langgartner et al., Intensive Care Med. 2008 Jun;34(6):1091-6. doi: 10.1007/s00134-008-1034-7. Epub 2008 Feb 23. | Wrong patient population – suspected infection requiring antibiotic |
| **11.** | De Jongh et al., J Antimicrob Chemother. 2008 Feb;61(2):382-8. doi: 10.1093/jac/dkm467. Epub 2007 Dec 10. | Wrong patient population – nosocomial infection |
| **12.** | Merchant et al., Clin Ther. 2008 Apr;30(4):717-33. doi: 10.1016/j.clinthera.2008.04.001. | Wrong patient population – ventilator-associated pneumonia |
| **13.** | Roberts et al., Crit Care Med. 2009 Mar;37(3):926-33. doi: 10.1097/CCM.0b013e3181968e44. | Secondary paper of included trial |
| **14.** | Breilh et al., Minerva Anestesiol. 2011 Nov;77(11):1058-62. Epub 2011 May 11. | Wrong study design – not randomized |

| | | |
|---|---|---|
| **15.** | Fahimi et al., Indian J Crit Care Med. 2012 Jul;16(3):141-7. doi: 10.4103/0972-5229.102083. | Wrong study design – quasi-experimental design |
| **16.** | Lu et al., Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2013 Aug;25(8):479-83. doi: 10.3760/cma.j.issn.2095-4352.2013.08.008. | Wrong patient population – hospital-acquired pneumonia |
| **17.** | Mathew et al., Therapeutic Drug Monitoring. 2016 Oct;38(5):593-9. doi: 10.1097/FTD.0000000000000323. | Wrong study design – not randomized |
| **18.** | Wang et al., Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2014 Sep;26(9):644-9. doi: 10.3760/cma.j.issn.2095-4352.2014.09.008. | Wrong patient population – hospital-acquired pneumonia |
| **19.** | Frippiat et al., J Antimicrob Chemother. 2015 Jan;70(1):207-16. doi: 10.1093/jac/dku354. Epub 2014 Sep 12. | Wrong patient population – hospital-acquired pneumonia |
| **20.** | Da Silva et al., Critical Care (2017) 21:2 Supplement 1. | No outcomes of interest – no results |
| **21.** | Fan et al., Pharmacotherapy. 2017 Jan;37(1):109-119. doi: 10.1002/phar.1875. Epub 2017 Jan 6. | Wrong patient population – bacterial infection or neutropenic fever |
| **22.** | Ammar et al., Saudi J Anaesth. 2018 Jan-Mar;12(1):89-94. doi: 10.4103/sja.SJA_148_17. | Wrong patient population – ventilator-associated pneumonia |
| **23.** | Pilmis et al., Eur J Clin Microbiol Infect Dis. 2019 Aug;38(8):1457-1461. doi: 10.1007/s10096-019-03573-4. Epub 2019 May 9. | Wrong study design – prospective multicentre cohort study |
| **24.** | Abdalalim et al., QJM (2020) 113: Supplement 1 (i31). | No outcomes of interest – no results |
| **25.** | Farokhi et al., Onkologia i Radioterapia. 2020;14(3):001-005 | No outcomes of interest |
| **26.** | Ruiz et al., Dose Response. 2020 Jan 29;18(1):1559325819885790. doi: 10.1177/1559325819885790. | Wrong study design – dosing simulation study |
| **27.** | Ruiz et al., European Journal of Hospital Pharmacy (2020) 27: Supplement 1 (A71-A72). | Wrong study design – dosing simulation study |
| **28.** | De Souza et al., Clinical Pharmacology in Drug Development (2021) 10: Supplement 1 (64). | Wrong study design – not randomized |
| **29.** | Morales et al., International Journal of Antimicrobial Agents (2021) 58 Supplement 1 Article Number: 21002831. | Wrong study design – no comparator |
| **30.** | Wunderink et al., Lancet Infect Dis. 2021 Feb;21(2):213-225. doi: 10.1016/S1473-3099(20)30731-3. Epub 2020 Oct 12. | Wrong comparator – both prolonged infusions |

| | | |
|---|---|---|
| **31.** | Naiim et al., Sci Rep. 2022 Jun 27;12(1):10882. doi: 10.1038/s41598-022-12861-7. | Wrong patient population – ICU patients with bacterial infections (i.e. not sepsis) |
| **32.** | Winiszewski et al., J Crit Care. 2022 Feb; 67:141-146. doi: 10.1016/j.jcrc.2021.10.023. Epub 2021 Nov 9. | Wrong study design – no comparator |
| **33.** | Maranchick et al., Ther Drug Monit. 2024 2024 Feb 1;46(1):95-101. doi: 10.1097/FTD.0000000000001144. Epub 2023 Nov 15. | Wrong patient population – severe pneumonia |
| **34.** | NCT00752882 (2007), Source: https://clinicaltrials.gov/show/NCT00752882 | Wrong patient population – cerebrospinal lesion and pneumopathy |
| **35.** | NCT00891423 (2009), Source: https://clinicaltrials.gov/show/NCT00891423 | Wrong patient population – all ICU patients |
| **36.** | EUCTR2010-021050-20-BE (2010), Source: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2010-021050-20-BE | Wrong comparator – both prolonged infusions |
| **37.** | NCT01600768 (2012), Source: https://clinicaltrials.gov/show/NCT01600768 | Wrong patient population – all ICU patients |
| **38.** | EUCTR2016-002796-10-ES (2016), Source: https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2016-002796-10-ES | Wrong patient population – not sepsis or septic shock |
| **39.** | NCT03246360 (2017), Source: https://clinicaltrials.gov/show/NCT03246360 | Wrong patient population – Staphylococcus spp. Joint infections |
| **40.** | NCT03581370 (2018), Source: https://clinicaltrials.gov/show/NCT03581370 | Wrong patient population – ventilator-associated pneumonia |
| **41.** | NCT05024565 (2021), Source: https://clinicaltrials.gov/show/NCT05024565 | No outcomes of interest – no results yet |
| **42.** | NCT05655091 (2022), Source: https://clinicaltrials.gov/show/NCT05655091 | Wrong patient population – complicated S. aureus infection, not ICU population |
| **43.** | NCT05681442 (2022), Source: https://clinicaltrials.gov/show/NCT05681442 | No outcomes of interest – no results yet |

**eTable 2: Microbiological characteristics and beta-lactam antibiotic dosing regimen details of included randomized controlled trials**

| Reference | Site of infection, n (%) | | | Confirmed infection, n (%) | | Gram-negative organisms, n (%) | | Beta-lactam antibiotic | Dosing regimens | | Same dosing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Site | Prolong | Intermit | Prolong | Intermit | Prolong | Intermit | | Prolong | Intermit | |
| **Georges et al,[34] 2005** | Lung | 21 (80.8) | 20 (83.3) | 36 | 30 | NR | NR | Cefepime | 2 g (over 720 mins) q 12 hrs | 2 g (over 30 mins) q 12 hrs | YES |
| | Blood | 5 (19.2) | 18 (16.7) | | | | | | | | |
| **Rafati et al,[35] 2006** | Lung | 9 (45) | 9 (45) | 10[a] | 10[a] | 10 | 10 | Piperacillin | 2 g LD then 8 g (over 1440 mins) q 24 hrs | 3 g (over 30 mins) q 6 hrs | NO |
| | Intra-abdominal | 4 (20) | 4 (20) | | | | | | | | |
| | Blood | 1 (5) | 1 (5) | | | | | | | | |
| | Urinary tract | 4 (20) | 3 (15) | | | | | | | | |
| | Operation site | 2 (10) | 4 (20) | | | | | | | | |
| **Roberts et al,[36] 2007** | Lung | 28 (97) | 28 (100) | 22[b] | 28[b] | 11 | 20 | Ceftriaxone | D1: 0.5 g LD then 2 g (over 1440 mins) q 24 hrs<br>D2: 2 g (over 1440 mins) q 24 hrs | D1: 0.5 g LD then 2 g (over 30 mins) q 24 hrs<br>D2: 2 g q 24 hrs | YES |
| | Intra-abdominal | 1 (3) | 0 (0) | | | | | | | | |
| **Roberts et al,[37] 2009** | Lung | 2 (40) | 3 (60) | 7[b] | 9[b] | 3 | 6 | Meropenem | D1: 0.5 g LD then 1 g (over 480 mins) q 8 hrs<br>D2: 1 g (over 480 mins) q 8 hrs | D1: 1.5 g LD then 1 g (over 3 mins) q 8 hrs<br>D2: 1 g (over 3 mins) q 8 hrs | YES |
| | Intra-abdominal | 2 (40) | 1 (20) | | | | | | | | |
| | Blood | 1 | 1 | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (20) | (20) | | | | | | | | |
| **Reference** | **Site of infection, n (%)** | | | **Confirmed infection, n (%)** | | **Gram-negative organisms, n (%)** | | **Beta-lactam antibiotic** | **Dosing regimens** | | **Same dosing** |
| **Roberts et al,[38] 2010** | NR | NR | NR | 5[b] | 12[b] | 1 | 6 | Pip-taz | D1: 4.5 g LD then 9 g (over 1440 mins) q 24 hrs<br>D2: 13.5 g (over 1440 mins) q 24 hrs | 4.5 g (over 20 mins) q 6 or 8 hrs | NO |
| **Chytra et al,[39] 2012** | Lung | 66 (55) | 61 (50.8) | 96 (80)[c] | 102 (85)[c] | 96 (80) | 102 (85) | Meropenem | 2 g LD then 4 g q 24 hrs (1 g over 360 mins) | 2 g (over 30 mins) q 8 hrs | NO |
| | Intra-abdominal | 23 (19.2) | 31 (25.8) | | | | | | | | |
| | Blood | 10 (8.3) | 11 (19.2) | | | | | | | | |
| | Urinary tract | 11 (9.2) | 6 (5.0) | | | | | | | | |
| | Skin/skin structure | 5 (4.2) | 6 (5.0) | | | | | | | | |
| | CNS | 3 (2.5) | 2 (1.6) | | | | | | | | |
| | Other sources | 2 (1.6) | 1 (0.8) | | | | | | | | |
| | Unknown | 0 (0.0) | 2 (1.6) | | | | | | | | |
| **Dulhunty et al,[40] 2013** | Lung | 14 (36.8) | 16 (43.2) | 12 (40.0)[d] | 16 (53.3)[d] | 7 (58.3) | 12 (75.0) | Meropenem | 3 g (3.0 – 3.8)[e] | 3 g (3.0 – 3.0)[e] | YES |
| | Intra-abdominal | 6 (15.8) | 7 (18.9) | | | | | Pip-taz | 13.5 g (13.5 – 13.5)[e] | 13.5 g (11.3 – 13.5)[e] | |
| | Blood | 7 (18.4) | 7 (18.9) | | | | | Tic-clav | Range: 12.4 – 13.5 g | 12.4 g | |
| | Urinary tract | 3 (7.9) | 2 (5.4) | | | | | | | | |
| | Skin/skin structure | 3 (7.9) | 2 (5.4) | | | | | | | | |
| | CNS | 2 (5.3) | 0 (0.0) | | | | | | | | |
| | Unknown | 1 | 0 | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | (2.6) | (0.0) | | | | | | | | |
| **Reference** | **Site of infection, n (%)** | | | **Confirmed infection, n (%)** | | **Gram-negative organisms, n (%)** | | **Beta-lactam antibiotic** | **Dosing regimens** | | **Same dosing** |
| **Dulhunty et al,[41] 2015** | Lung | 115 (54.2) | 120 (54.5) | 40 (18.9)[d] | 43 (19.5)[d] | 29 (72.5) | 31 (72.1) | Meropenem | 3 g (2.0 – 3.0)[e] | 3 g (2.0 – 3.0)[e] | YES |
| | Intra-abdominal | 53 (25.0) | 57 (25.9) | | | | | Pip-taz | 13.5 g (13.5 – 13.5)[e] | 13.5 (13.5 – 13.5)[e] | |
| | Blood | 17 (8.0) | 18 (8.2) | | | | | Tic-clav | 12.4 g | 12.4 g | |
| | Urinary tract | 16 (7.5) | 18 (8.2) | | | | | | | | |
| | Skin/skin structure | 13 (6.1) | 18 (8.2) | | | | | | | | |
| | Other sources | 22 (10.4) | 12 (5.5) | | | | | | | | |
| | Unknown | 14 (6.6) | 14 (6.4) | | | | | | | | |
| **Jamal et al,[42] 2015** | NR | NR | NR | NR | NR | NR | NR | Meropenem | D1: 1 g LD then 1 g (over 480 mins) q 8 hrs<br>D2: 1 g (over 480 mins) q 8 hrs | D1: 2 g LD then 1 g (over 30 mins) q 8 hrs<br>D2: 1 g (over 30 mins) q 8 hrs | YES |
| **Jamal et al,[43] 2015** | NR | NR | NR | NR | NR | NR | NR | Pip-taz | D1: 2.25 g LD then 9 g (over 1440 mins) q 24 hrs<br>D2: 9 g (over 1440 mins) q 24 hrs | D1: 4.5 g LD then 2.25 g (over 30 mins) q 6 hrs<br>D2: 2.25 g (over 30 mins) q 6 hrs | YES |
| **Abdul-Aziz et al,[44] 2016** | Lung | 46 (66) | 36 (51) | 48 (69)[b] | 56 (80)[b] | 49 (80) | 52 (68) | Cefepime | D1: 2 g LD then 2 g (over 480 mins) q 8 hrs<br>D2: 2 g (over 480 mins) q 8 hrs | 2 g (over 30 mins) q 8 hrs | NO |
| | Intra-abdominal | 11 (16) | 15 (21) | | | | | Meropenem | D1: 1 g LD then 1 g (over 480 mins) q 8 hrs<br>D2: 1 g (over 480 mins) q 8 hrs | 1 g (over 30 mins) q 8 hrs | |
| | Blood | 4 (6) | 6 (9) | | | | | Pip-taz | D1: 4.5 g LD then 4.5 g (over 360 mins) q 6 hrs | 4.5 g (over 30 mins) q 6 hrs | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | D2: 4.5 g (over 360 mins) q 6 hrs | | |
| | Urinary tract | 2 (3) | 3 (4) | | | | | | | | |
| | Skin/skin structure | 6 (9) | 7 (10) | | | | | | | | |
| | CNS | 1 (1) | 3 (4) | | | | | | | | |
| **Reference** | **Site of infection, n (%)** | | | **Confirmed infection, n (%)** | | **Gram-negative organisms, n (%)** | | **Beta-lactam antibiotic** | **Dosing regimens** | | **Same dosing** |
| **Zhao et al,[45] 2017** | Lung | 9 (36) | 10 (40) | 22 (88)[f] | 21 (84)[f] | NR | NR | Meropenem | D1: 0.5 g LD then 1 g (over 480 mins) q 8 hrs<br>D2: 1 g (over 480 mins) q 8 hrs | D1: 1.5 g LD then 1 g (over 30 mins) q 8 hrs<br>D2: 1 g (over 30 mins) q 8 hrs | YES |
| | Intra-abdominal | 14 (56) | 13 (52) | | | | | | | | |
| | Blood | 5 (20) | 3 (12) | | | | | | | | |
| | Urinary tract | 1 (4) | 2 (8) | | | | | | | | |
| | Wound | 1 (4) | 0 (0) | | | | | | | | |
| | CNS | 0 (0) | 1 (4) | | | | | | | | |
| | Multiple sites | 5 (20) | 4 (16) | | | | | | | | |
| **Mirjalili et al,[46] 2023** | Lung | 8 (11.8) | 12 (17.6) | NR[g] | NR[g] | NR | NR | Amp-sul | 9 g LD then 9 g (over 240 mins) q 8 hrs[h] | 9 g LD then 9 g (over 30 mins) q 8 hrs | YES |
| | Intra-abdominal | 11 (16.2) | 3 (4.4) | | | | | | | | |
| | Blood | 20 (29.4) | 15 (22.1) | | | | | | | | |
| | Urinary tract | 3 (4.4) | 7 (10.3) | | | | | | | | |
| | Skin/skin structure | 2 (2.9) | 8 (11.8) | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | CNS | 9 (13.2) | 2 (2.9) | | | | | | | | |
| | Multiple sites | 15 (22.1) | 21 (30.9) | | | | | | | | |
| **Reference** | **Site of infection, n (%)** | | | **Confirmed infection, n (%)** | | **Gram-negative organisms, n (%)** | | **Beta-lactam antibiotic** | **Dosing regimens** | | **Same dosing** |
| **Monti et al,[14] 2023** | Lung | 96 (33.0) | 99 (33.0) | 219 (72.3)[i] | 214 (70.4)[i] | 175 (57.8) | 158 (52.0) | Meropenem | 1 g LD then 1 g (over 480 mins) q 8 hrs for CLcr >50 mL/min<br>1 g LD then 1 g (over 960 mins) q 12 hrs for CLcr <50 mL/min | D1: 1 g (over 30 – 60 mins) q 6 hrs<br>D2: 1 g (over 30 – 60 mins) q 8 hrs for CLcr >50 mL/min<br>D1: 1 g (over 30 – 60 mins) q 8 hrs<br>D2: 1 g (over 30 – 60 mins) q 12 hrs for CLcr <50 mL/min | YES |
| | Intra-abdominal | 28 (9.6) | 24 (8.1) | | | | | | | | |
| | CRBSI | 28 (9.6) | 15 (5.1) | | | | | | | | |
| | Urinary tract | 16 (5.5) | 12 (4.1) | | | | | | | | |
| | Other sources | 33 (11.0) | 35 (12.0) | | | | | | | | |
| **Khan et al,[22] 2023** | Lung | 28 | 30 | 28 (53.8) | 26 (56.5) | NR | NR | Amx-clav | 1.2 g LD then 0.6 g (over 240 mins) q 4 hrs | 1.2 g (over 30 mins) q 8 hrs | NO |
| | Intra-abdominal | 29 | 17 | | | | | Imipenem | 1 g LD then 0.5 g (over 180 mins) q 3 hrs | 1 g (over 30 mins) q 6 hrs | NO |
| | Blood | 4 | 4 | | | | | Meropenem | 1 g LD then 1 g (over 480 mins) q 8 hrs | 1 g (over 30 mins) q 8 hrs | NO |
| | Skin/skin structure | 2 | 2 | | | | | Pip-taz | 4.5 g LD then 18 g (over 1440 mins) q 24 hrs | 4.5 g (over 30 mins) q 6 hrs | NO |
| | Other sources | 1 | 5 | | | | | | | | |
| **Saad et al,[47] 2023** | Lung | 8 (26.7) | 7 (23.3) | 25 (83.3)[j] | 25 (83.3)[j] | 25 | 25 | Meropenem | 0.5 g LD then 0.5 g (over 2440 mins) q 4hrs | 1.5 g (over 30 mins) followed by 1 g (over 30 mins) q 8 hrs | YES |
| | Intra-abdominal | 4 (13.3) | 4 (13.3) | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Blood | 0 (0.0) | 1 (3.3) | | | | | | | | |
| | Urinary tract | 2 (6.7) | 2 (6.7) | | | | | | | | |
| | Soft tissue | 3 (10.0) | 3 (10.0) | | | | | | | | |
| | Central nervous system | 2 (6.7) | 2 (6.7) | | | | | | | | |
| | Nosocomial infection | 8 (26.7) | 8 (26.7) | | | | | | | | |
| | Not identified | 3 (10.0) | 3 (10.0) | | | | | | | | |
| **Alvarez-Moreno et al,[48] 2024** | Lung | 3 (25.0) | 1 (7.7) | 7 (58.3)[k] | 9 (69.2)[k] | 7 (58.3) | 9 (69.2) | Cefepime | 3 g daily | 1 g (over 30 mins) q 8 hrs | YES |
| | Urosepsis | 2 (16.6) | 5 (38.5) | | | | | | | | |
| | Catheter sepsis | 3 (25.0) | 2 (14.4) | | | | | | | | |
| | Peritonitis | 1 (8.3) | 1 (7.7) | | | | | | | | |
| | Skin and soft tissue | 1 (8.3) | 1 (7.7) | | | | | | | | |
| | Tracheobronchitis | 1 (8.3) | 1 (7.7) | | | | | | | | |
| | Surgical site infection | 1 (8.3) | 1 (7.7) | | | | | | | | |
| | Bloodstream infection | 0 (0.0) | 1 (7.7) | | | | | | | | |
| **Reference** | **Site of infection, n (%)** | | | **Confirmed infection, n (%)** | | **Gram-negative organisms, n (%)** | | **Beta-lactam antibiotic** | **Dosing regimens** | | **Same dosing** |
| **Dulhunty et al,[15] 2024** | Lung | 2048 (58.6) | 2105 (59.6) | 1682 (48.1)[l] | 1678 (47.5)[l] | 887 (58.5) | 894 (59.0) | Meropenem[m] | 20.9 g (16.7) | 20.1 g (16.7) | YES |
| | Intra-abdominal | 449 (12.8) | 416 (11.8) | | | | | Pip-taz[m] | 79.3 g (53.1) | 78.0 g (52.0) | |
| | Blood | 263 (7.5) | 284 (8.0) | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Urinary tract | 213 (6.1) | 166 (4.7) | | | | | | | | |
| | Skin/skin structure | 160 (4.6) | 161 (4.6) | | | | | | | | |
| | Gut | 98 (2.8) | 120 (3.4) | | | | | | | | |
| | CNS | 62 (1.8) | 71 (2.0) | | | | | | | | |
| | Intravenous catheter | 15 (0.4) | 18 (0.5) | | | | | | | | |
| | Endocarditis | 13 (0.4) | 3 (0.1) | | | | | | | | |
| | Other | 177 (5.1) | 189 (5.4) | | | | | | | | |

**Abbreviations:** Amp-sul, ampicillin-sulbactam; Amx-clav, amoxicillin-clavulanate; CLcr, creatinine clearance; CNS, central nervous system; CRBSI, catheter-related blood stream infection; D1, Day 1; D2, Day 2; LD, loading dose; Intermit, intermittent infusion; NR, not reported; Prolong, prolonged infusion; pip-taz, piperacillin-tazobactam; tic-clav, ticarcillin-clavulanate

* Site of infection, confirmed infection, and Gram-negative organisms are presented as counts (percentage).

[a] from 8 patients.
[b] at least one causative pathogen identified before or during the course of antibiotic treatment.
[c] at least one bacterial pathogen identified at baseline that was susceptible or intermediate susceptible to meropenem.
[d] at least one causative pathogen identified in blood culture.
[e] data presented as median (interquartile range).
[f] at least one causative pathogen identified in blood culture before study drug commencement.
[g] not specifically reported but authors reported that no organisms were identified in 20 patients.
[h] administered as an extended infusion.
[i] at least one causative pathogen identified 48 hours before or just before loading dose administration.
[j] based on routine bacterial cultures (including two sets of blood cultures) before meropenem therapy.

[k] identification of Gram-negative bacilli in at least one blood culture performed at the beginning of the study, and at days 7 and 14 of the study.
[l] at least one causative pathogen identified within 72 hours prior to randomization
[m] cumulative dose of beta-lactam antibiotic received up to Day 16 post-randomization.

**eTable 3: Definition of primary and secondary outcomes in studies**

| Reference | Primary and secondary outcomes definition | | | |
|---|---|---|---|---|
| | **Mortality** | **Clinical cure** | **Microbiological cure** | **Adverse events** |
| Georges et al,[34] 2005 | Mortality | Complete remission of the infectious signs without further administration of antibiotics on day 3 | Bacteriological cure: defined as either bacteriological eradication or presumed eradication via tracheal aspirates | NR |
| Rafati et al,[35] 2006 | Mortality at ICU discharge | NR | NR | NR |
| Roberts et al,[36] 2007 | Mortality at ICU discharge | Clinical resolution: defined as complete disappearance of all signs and symptoms related to infection | Bacteriological response: defined as either bacteriological eradication or presumed eradication based on subsequent microbiological culture results | As measured by kidney failure and clinical observations by the treating physician |
| Roberts et al,[37] 2009 | Mortality at ICU discharge | NR | NR | NR |
| Roberts et al,[38] 2010 | Mortality at ICU discharge | NR | NR | NR |
| Chytra et al,[39] 2012 | Mortality at hospital discharge | Clinical success: defined as complete or partial resolution of leucocytosis, temperature, and clinical signs and symptoms of infection assessed at the end of meropenem therapy | Microbiological success: defined as either microbiological eradication or presumed eradication at the end of meropenem therapy | Meropenem-related clinical adverse events during meropenem therapy assessed by clinical symptoms (diarrhea, rash, vomiting, seizures) and/or laboratory parameters (transaminases, alkaline phosphatase, bilirubin, thrombocytes) |
| Dulhunty et al,[40] 2013 | Mortality at hospital discharge | Clinical resolution: defined as complete disappearance of all signs and symptoms | NR | Adverse events during treatment as defined as Naranjo Scale (1981) – assessed as |

| | | | | |
|---|---|---|---|---|
| | | related to infection at a test-of-cure date of 7 – 14 days after study drug cessation | | "almost certainly", "probably", "possibly", or "unlikely" caused by study drug |
| **Reference** | **Primary and secondary outcomes definition** | | | |
| | **Mortality** | **Clinical cure** | **Microbiological cure** | **Adverse events** |
| Dulhunty et al,[41] 2015 | Mortality at day 90 | Clinical resolution: defined as (1) complete disappearance of all signs and symptoms related to infection 14 days post cessation of study drug OR (2) absence of any systemic inflammatory response syndrome criteria attributable to infection 14 days post cessation of study drug | NR | Adverse events during treatment as defined as Naranjo Scale (1981) – assessed as "almost certainly", "probably", "possibly", or "unlikely" caused by study drug |
| Jamal et al,[42] 2015 | Mortality at ICU discharge | NR | NR | Possible adverse events during piperacillin/tazobactam treatment as defined as Naranjo Scale (1981) – assessed as "almost certainly", "probably", "possibly", or "unlikely" caused by piperacillin/tazobactam |
| Jamal et al,[43] 2015 | Mortality at ICU discharge | NR | NR | Possible adverse events during meropenem treatment as defined as Naranjo Scale (1981) – assessed as "almost certainly", "probably", "possibly", or "unlikely" caused by meropenem |
| Abdul-Aziz et al,[44] 2016 | Mortality at day 30 | Clinical resolution: defined as complete disappearance of all signs and symptoms related to infection at 14 days after study drug cessation | NR | Adverse events during study period as defined as Naranjo Scale (1981) – assessed as "almost certainly", "probably", "possibly", or "unlikely" caused by study drug |

| Reference | Primary and secondary outcomes definition | | | |
|---|---|---|---|---|
| | **Mortality** | **Clinical cure** | **Microbiological cure** | **Adverse events** |
| Zhao et al,[45] 2017 | Mortality at ICU discharge | Clinical success: defined as complete or partial resolution of temperature, clinical signs and symptoms, and leucocytosis | Microbiological eradication based on sequential daily microbiological cultures | NR |
| Mirjalili et al,[46] 2023 | Mortality at hospital discharge | Clinical cure: defined as complete disappearance of leucocytosis, temperature, and clinical signs and symptoms of infection assessed at completion of ampicillin/sulbactam treatment | NR | Possible ampicillin/sulbactam-related clinical adverse events including skin rash, digestive tract alterations, liver and kidney dysfunction |
| Monti et al,[14] 2023 | Mortality at day 90 | NR | NR | Meropenem-related adverse events including seizures, allergic reactions, and mortality |
| Khan et al,[22] 2023 | Mortality at day 90 | Clinical cure: defined as completion of study beta-lactam antibiotic treatment course on or prior to day 14 without recommencement of antibiotic therapy within 48 hours of cessation | NR | NR |
| Saad et al,[47] 2023 | Mortality at ICU discharge | Clinical success: defined as complete or partial resolution of leucocytosis, temperature, and clinical signs and symptoms of infection assessed at the end of meropenem therapy | NR | NR |

| Reference | Primary and secondary outcomes definition | | | |
|---|---|---|---|---|
| | **Mortality** | **Clinical cure** | **Microbiological cure** | **Adverse events** |
| Alvarez-Moreno et al,[48] 2024 | Mortality at discharge | Favourable clinical response: defined as resolution of all signs and symptoms of sepsis or systemic inflammatory response syndrome (SIRS) | NR | NR |
| Dulhunty et al,[15] 2024 | Mortality at day 90 | Clinical cure: defined as completion of study beta-lactam antibiotic treatment course on or prior to day 14 without recommencement of antibiotic therapy within 48 hours of cessation | NR | Study-assigned administration method-related adverse events – assessed as "possibly", "probably" and "definitely" |

**Abbreviations:** ICU, intensive care unit; NR, not reported

**eTable 4: Unpublished outcome data obtained from study authors**

| Reference | Outcome data |
|---|---|
| Roberts et al,[36] 2007 | ▪ ICU mortality by culture-positive infection versus culture-negative infection<br>▪ ICU mortality by lung infection versus other infections<br>▪ ICU mortality by male versus female participants |
| Roberts et al,[37] 2009 | ▪ ICU mortality by culture-positive infection versus culture-negative infection<br>▪ ICU mortality by lung infection versus other infections<br>▪ ICU mortality by male versus female participants |
| Roberts et al,[38] 2010 | ▪ ICU mortality by culture-positive infection versus culture-negative infection<br>▪ ICU mortality by male versus female participants |
| Dulhunty et al,[40] 2013 | ▪ Hospital mortality by meropenem versus piperacillin/tazobactam<br>▪ Hospital mortality by culture-positive infection versus culture-negative infection<br>▪ Hospital mortality by Gram-negative infection versus Gram-positive infection<br>▪ Hospital mortality by lung infection versus other infections<br>▪ Hospital mortality by sepsis versus septic shock diagnosis<br>▪ Hospital mortality by male versus female participants |
| Dulhunty et al,[41] 2015 | ▪ ICU mortality<br>▪ 90-day mortality by meropenem versus piperacillin/tazobactam<br>▪ 90-day mortality by culture-positive infection versus culture-negative infection<br>▪ 90-day mortality by Gram-negative infection versus Gram-positive infection<br>▪ 90-day mortality by receipt of kidney replacement therapy versus no kidney replacement therapy<br>▪ 90-day mortality by lung infection versus other infections<br>▪ 90-day mortality by sepsis versus septic shock diagnosis |

| | |
|---|---|
| | ▪ 90-day mortality by male versus female participants |
| **Reference** | **Outcome data** |
| Jamal et al,[42] 2015 | ▪ ICU mortality<br>▪ ICU mortality by sepsis versus septic shock diagnosis<br>▪ ICU mortality by male versus female participants |
| Jamal et al,[43] 2015 | ▪ ICU mortality<br>▪ ICU mortality by sepsis versus septic shock diagnosis<br>▪ ICU mortality by male versus female participants |
| Abdul-Aziz et al,[44] 2016 | ▪ 30-day mortality by meropenem versus piperacillin/tazobactam<br>▪ 30-day mortality by culture-positive infection versus culture-negative infection<br>▪ 30-day mortality by Gram-negative infection versus Gram-positive infection<br>▪ 30-day mortality by lung infection versus other infections<br>▪ 30-day mortality by sepsis versus septic shock diagnosis<br>▪ 90-day mortality by male versus female participants |
| Monti et al,[14] 2023 | ▪ ICU mortality<br>▪ 90-day mortality by culture-positive infection versus culture-negative infection<br>▪ 90-day mortality by Gram-negative infection versus Gram-positive infection<br>▪ 90-day mortality by lung infection versus other infections<br>▪ 90-day mortality by sepsis versus septic shock diagnosis<br>▪ 90-day mortality by male versus female participants |
| Khan et al,[22] 2023 | ▪ 90-day mortality<br>▪ ICU mortality<br>▪ Clinical cure<br>▪ ICU length of stay<br>▪ 90-day mortality by meropenem versus piperacillin/tazobactam<br>▪ 90-day mortality by culture-positive infection versus culture-negative infection |

| | |
|---|---|
| | ▪ 90-day mortality by Gram-negative infection versus Gram-positive infection<br>▪ 90-day mortality by receipt of kidney replacement therapy versus no kidney replacement therapy<br>▪ 90-day mortality by lung infection versus other infections<br>▪ 90-day mortality by sepsis versus septic shock diagnosis<br>▪ 90-day mortality by male versus female participants |
| Dulhunty et al,[15] 2024 | ▪ 90-day mortality by culture-positive infection versus culture-negative infection<br>▪ 90-day mortality by Gram-negative infection versus Gram-positive infection<br>▪ 90-day mortality by receipt of kidney replacement therapy versus no kidney replacement therapy<br>▪ 90-day mortality by sepsis versus septic shock diagnosis |

**Abbreviations:** ICU, intensive care unit

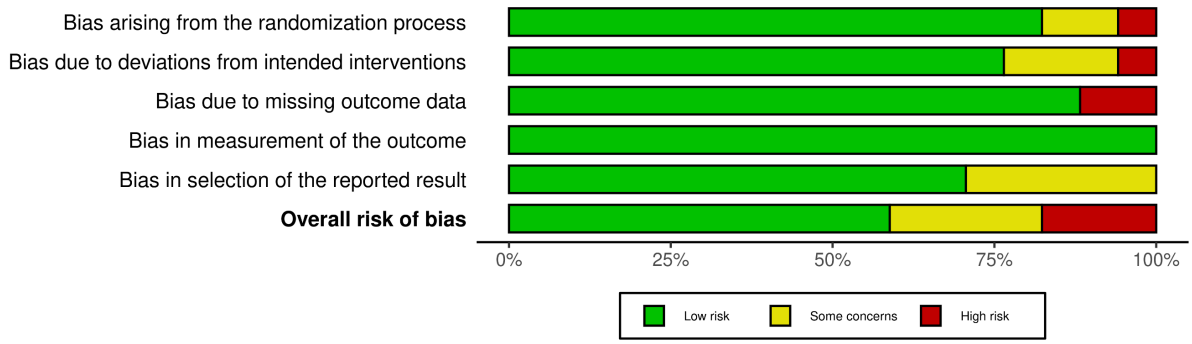
**eFigure 2: Risk of bias assessments**

Traffic light and summary plots were designed using McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1 – 7. https://doi.org/10.1002/jrsm.1411

**A. Primary outcome: all-cause 90-day mortality**

*Traffic light plot*

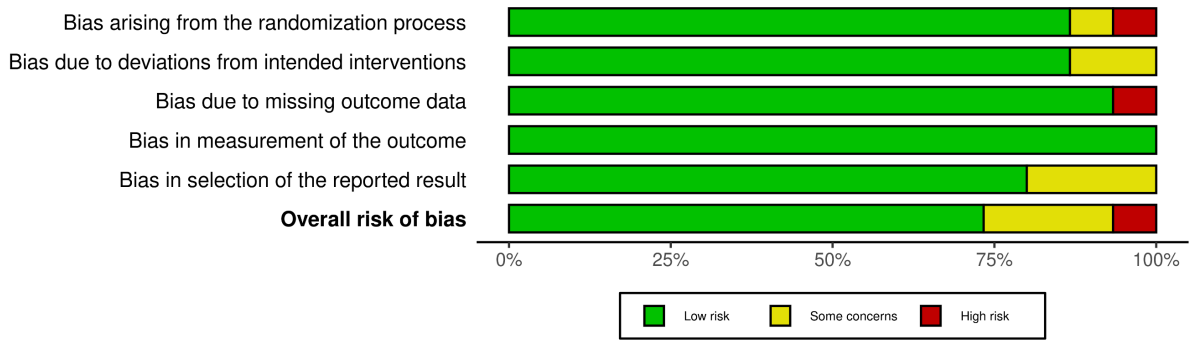
## *Summary plot*



**B. Secondary outcome: ICU mortality**

*Traffic light plot*

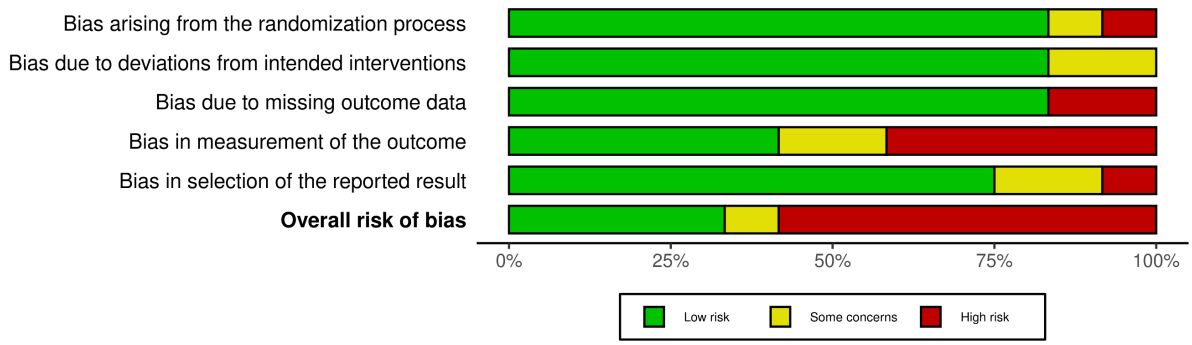
## *Summary plot*



## C. Secondary outcome: ICU length of stay

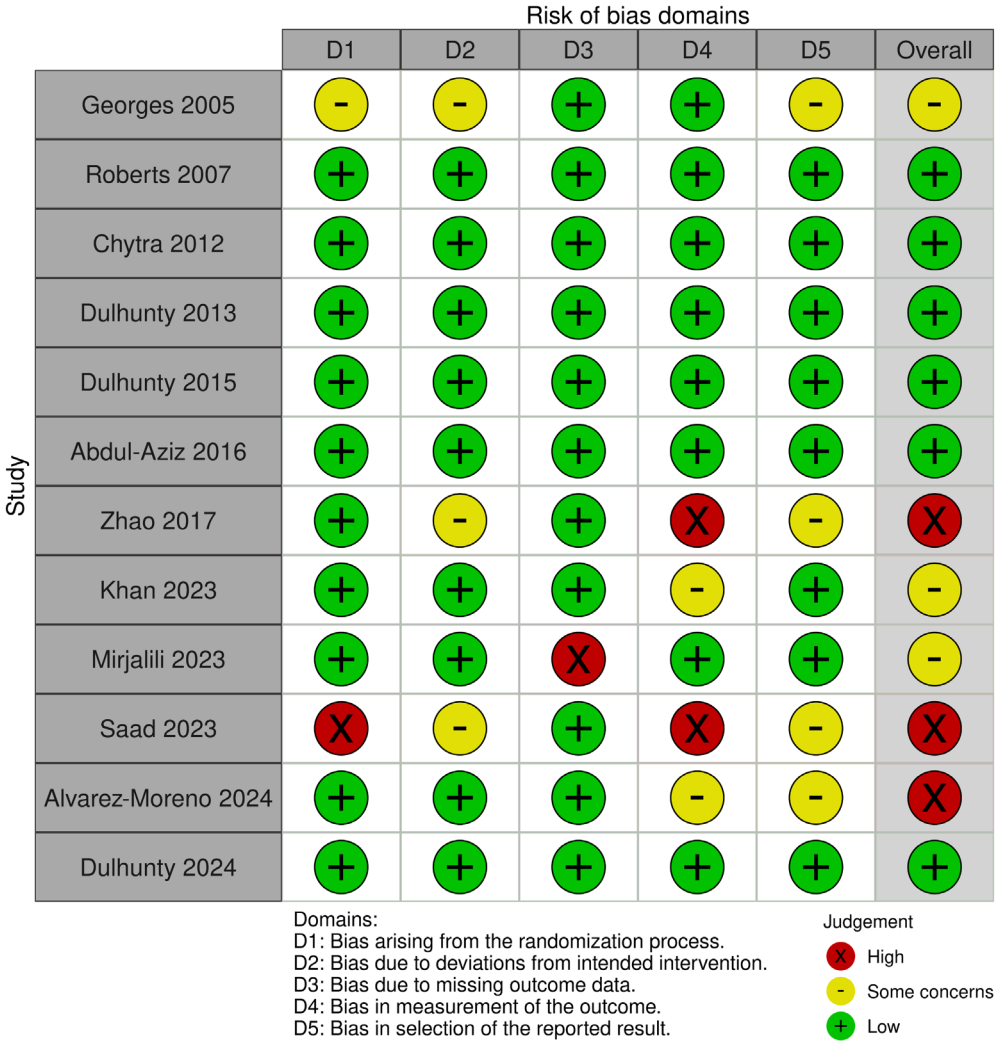
*Traffic light plot*


*Summary plot*

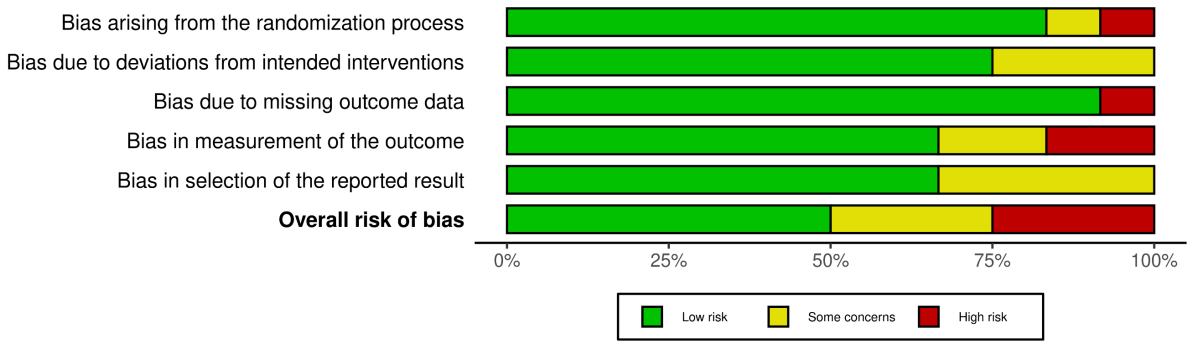


## D. Secondary outcome: clinical cure

*Traffic light plot*

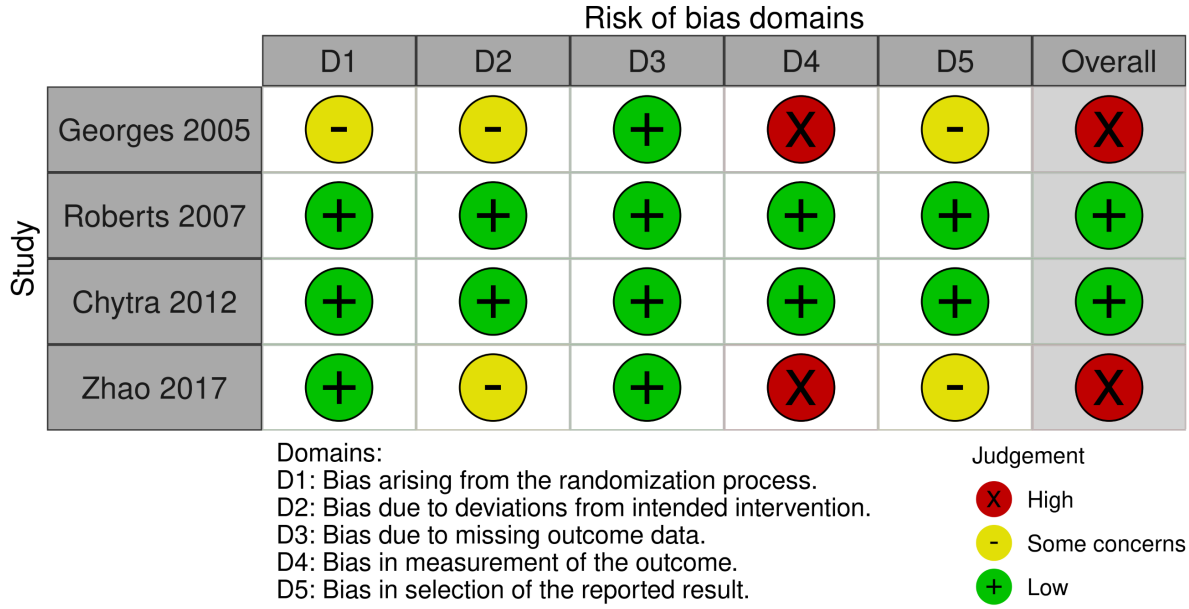



*Summary plot*

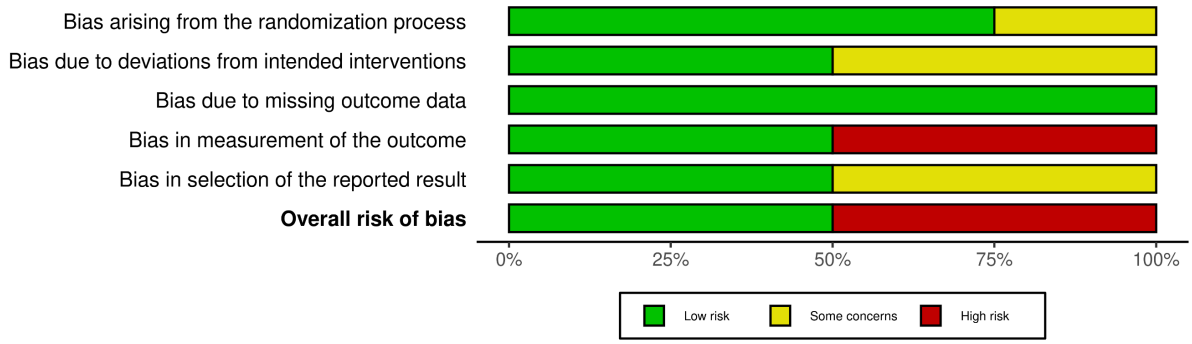


## E. Secondary outcome: microbiological cure

*Traffic light plot*

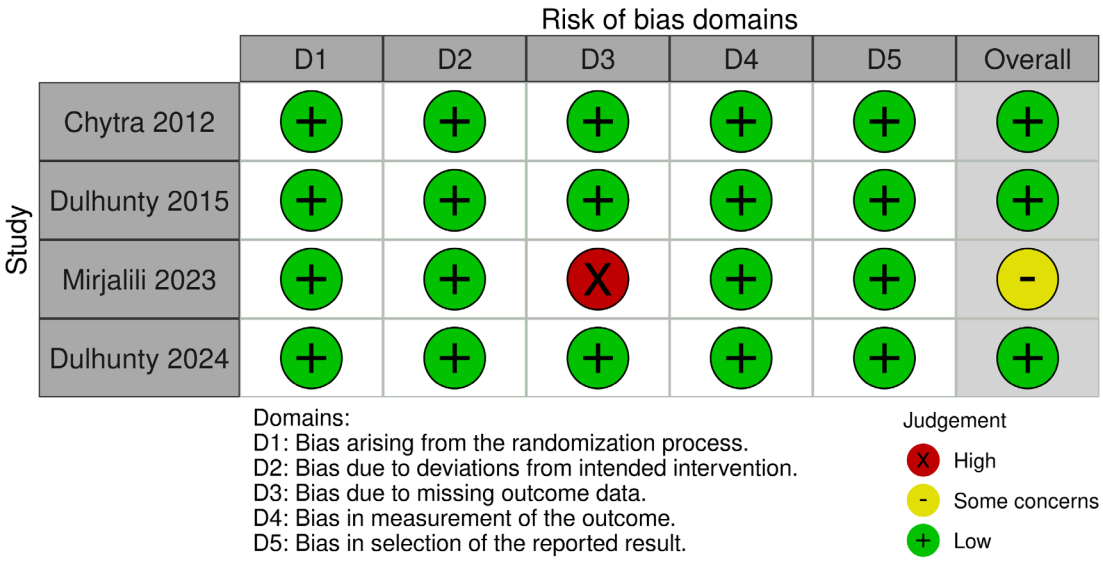



*Summary plot*

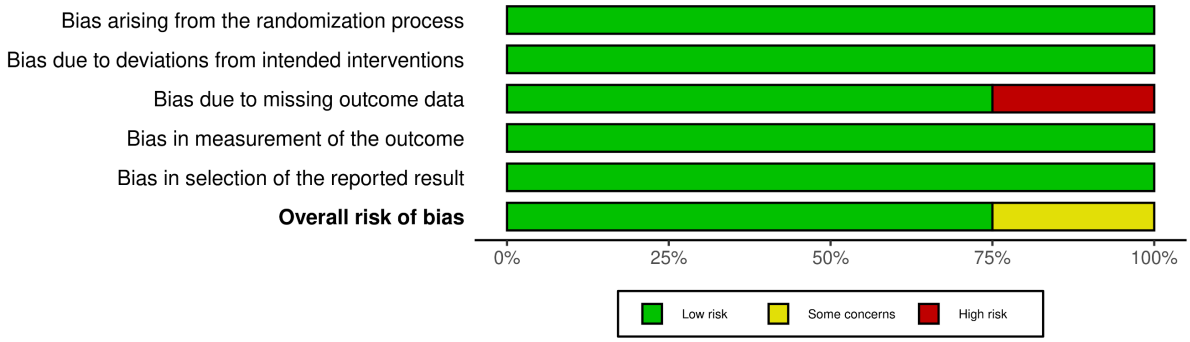


## F. Secondary outcome: adverse events

*Traffic light plot*




*Summary plot*



**eTable 5: Additional outcome statistics for the primary Bayesian model, sensitivity analyses, and secondary outcomes**

| Outcomes | RR or MD (95% CrI) | Posterior probability | Tau (95% CrI) | $I^2$ (%) | 95% prediction interval | Sub-group interaction test[a] |
|---|---|---|---|---|---|---|
| **Primary outcome** | | | | | | |
| All-cause 90-day mortality (BMA – vague priors) | 0.86 (0.72 to 0.98) | 99.1% | 0.11 (0.00 to 0.28) | 21.5 | 0.58 to 1.17 | NR |
| **Sensitivity analyses for the primary outcome** | | | | | | |
| All-cause 90-day mortality (BMA – semi-informative priors) | 0.86 (0.73 to 0.98) | 99.2% | 0.11 (0.02 to 0.23) | 23.4 | 0.62 to 1.14 | NR |
| All-cause 90-day mortality (Hartung-Knapp-Sidik-Jonkman) | 0.79 (0.66 to 0.94) | NA | NA | 78.1 | NA | NR |
| All-cause 90-day mortality (Der Simonian-Laird) | 0.91 (0.85 to 0.97) | NA | NA | 0 | NA | NR |
| **Secondary outcomes** | | | | | | |
| ICU mortality | 0.84 (0.70 to 0.97) | 99.5% | 0.10 (0.00 to 0.26) | 15.0 | 0.59 to 1.12 | NR |
| ICU length of stay (days) | -0.42 (-1.09 to 0.26) | 89.8% | 0.40 (0.00 to 0.94) | 12.9 | -1.71 to 0.88 | NR |
| Clinical cure | 1.16 (1.07 to 1.31) | 0.0% | 0.06 (0.00 to 0.19) | 25.5 | 0.96 to 1.50 | NR |
| Microbiological cure | 1.18 (0.96 to 1.48) | 4.1% | 0.08 (0.00 to 0.36) | 27.1 | 0.79 to 1.80 | NR |
| Adverse events | 0.89 (0.51 to 1.57) | 67.9% | 0.23 (0.00 to 0.72) | 21.3 | 0.35 to 2.36 | NR |
| **Sub-group analysis of the primary outcome** | | | | | | |
| Meropenem | 0.88 (0.71 to 1.04) | 94.8% | 0.10 (0.00 to 0.32) | 19.1 | 0.57 to 1.25 | 1.00[b] (0.75 to 1.29) |
| Piperacillin/tazobactam | 0.86 (0.58 to 1.10) | 92.6% | 0.18 (0.00 to 0.53) | 30.6 | 0.40 to 1.52 | |
| | | | | | | |
| Culture-positive infection | 0.99 (0.80 to 1.27) | 56.2% | 0.10 (0.00 to 0.40) | 20.2 | 0.64 to 1.62 | 1.13[c] (0.91 to 1.72) |
| Culture-negative infection | 0.83 (0.51 to 1.10) | 94.2% | 0.20 (0.00 to 0.68) | 41.8 | 0.32 to 1.66 | |
| | | | | | | |
| Gram-negative infection | 0.94 (0.72 to 1.19) | 74.9% | 0.10 (0.00 to 0.42) | 17.5 | 0.56 to 1.50 | 1.13[d] (0.85 to 1.79) |
| Gram-positive infection | 1.11 (0.77 to 1.92) | 24.6% | 0.22 (0.00 to 0.69) | 39.2 | 0.52 to 2.96 | |
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Kidney replacement therapy | 0.90 (0.62 to 1.23) | 81.6% | 0.15 (0.00 to 0.54) | 37.0 | 0.45 to 1.68 | 1.08[e] (0.82 to 1.53) |
| No kidney replacement therapy | 0.82 (0.65 to 0.98) | 98.7% | 0.15 (0.00 to 0.35) | 23.2 | 0.50 to 1.23 | |
| | | | | | | |
| Lung infection | 0.98 (0.76 to 1.28) | 60.1% | 0.13 (0.00 to 0.46) | 25.3 | 0.58 to 1.71 | 0.90[f] (0.64 to 1.15) |
| Other infections | 0.86 (0.62 to 1.11) | 91.5% | 0.13 (0.00 to 0.48) | 22.5 | 0.46 to 1.46 | |
| | | | | | | |
| Sepsis | 0.91 (0.65 to 1.17) | 81.4% | 0.13 (0.00 to 0.48) | 20.7 | 0.49 to 1.54 | 0.97[g] (0.75 to 1.23) |
| Septic shock | 0.89 (0.71 to 1.04) | 95.6% | 0.09 (0.00 to 0.33) | 21.4 | 0.58 to 1.25 | |
| | | | | | | |
| Male participants | 0.88 (0.71 to 1.03) | 96.4% | 0.09 (0.00 to 0.32) | 15.1 | 0.58 to 1.23 | 0.91[h] (0.71 to 1.12) |
| Female participants | 0.97 (0.75 to 1.23) | 63.6% | 0.12 (0.00 to 0.42) | 13.7 | 0.58 to 1.58 | |

**Abbreviations:** BMA, Bayesian meta-analysis; CrI, credible interval; $I^2$, heterogeneity statistic $I^2$; ICU, intensive care unit; MD, mean difference; NA, not available; NR, not relevant; RR, risk ratio

[a] The interaction terms are presented in Bayesian context using ratio of risk ratios (RRR) and their 95% credible intervals

[b] Posterior probability of ratio of risk ratios, P(RRR) <1 is 51%

[c] Posterior probability of ratio of risk ratios, P(RRR) <1 is 13%

[d] Posterior probability of ratio of risk ratios, P(RRR) <1 is 19%

[e] Posterior probability of ratio of risk ratios, P(RRR) <1 is 28%

[f] Posterior probability of ratio of risk ratios, P(RRR) <1 is 83%

[g] Posterior probability of ratio of risk ratios, P(RRR) <1 is 60%

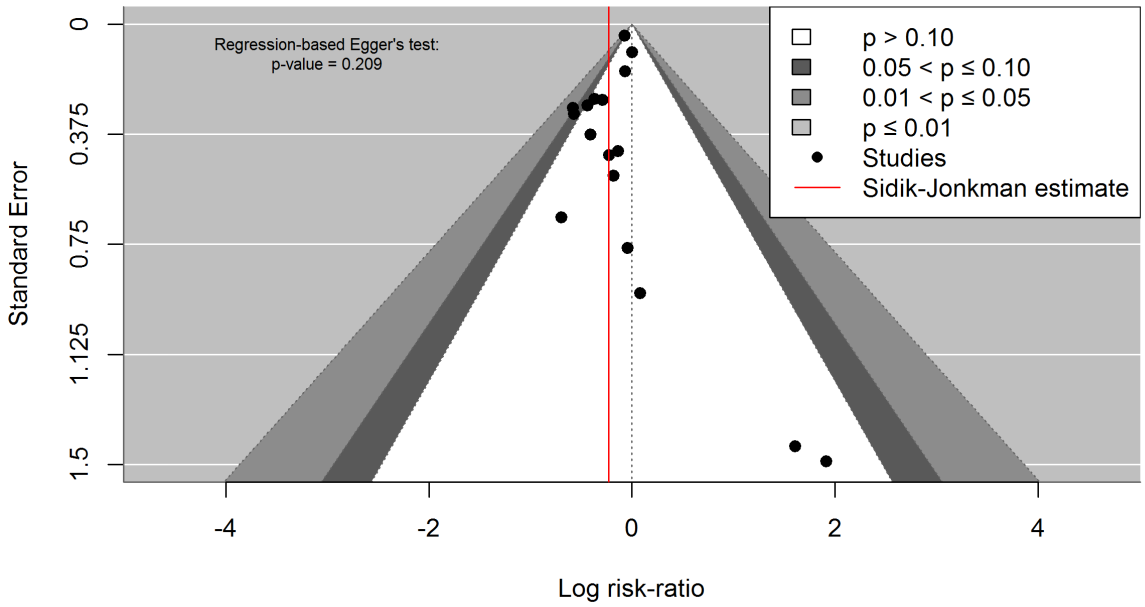
[h] Posterior probability of ratio of risk ratios, P(RRR) <1 is 82%

**eFigure 3: Funnel plots**

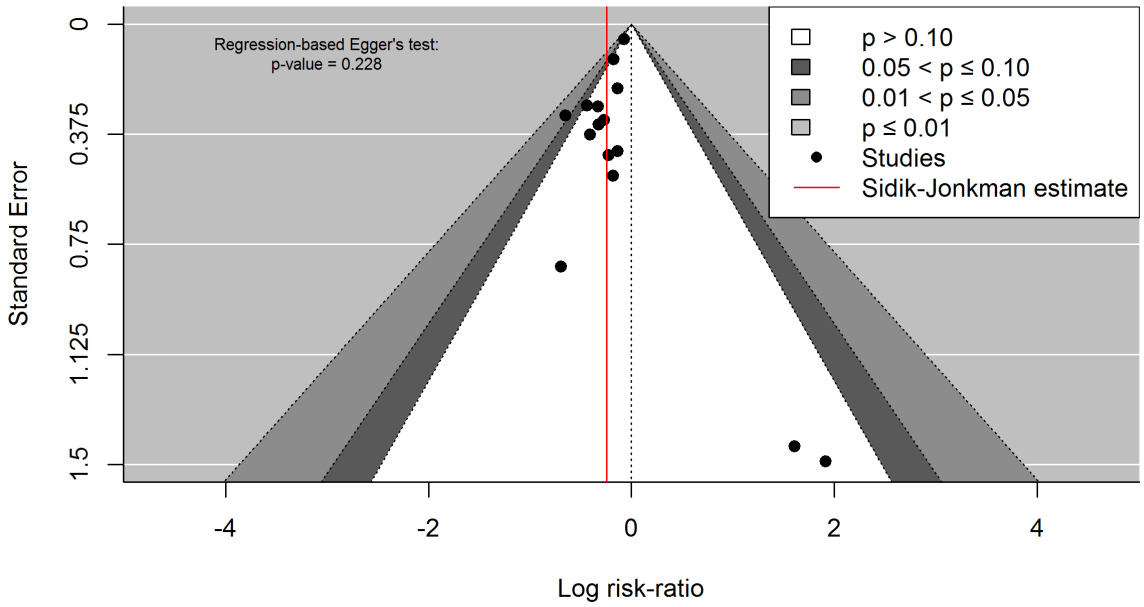
Egger test for small-study effects using random-effects model

Method: Sidik-Jonkman

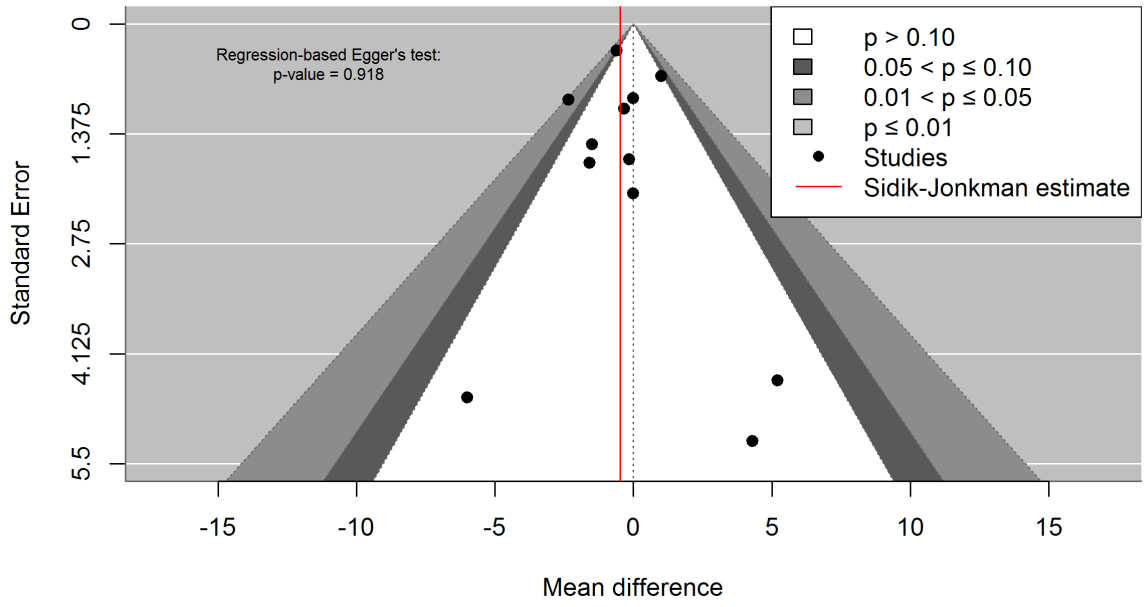
**A. <u>Primary outcome: all-cause 90-day mortality</u>**



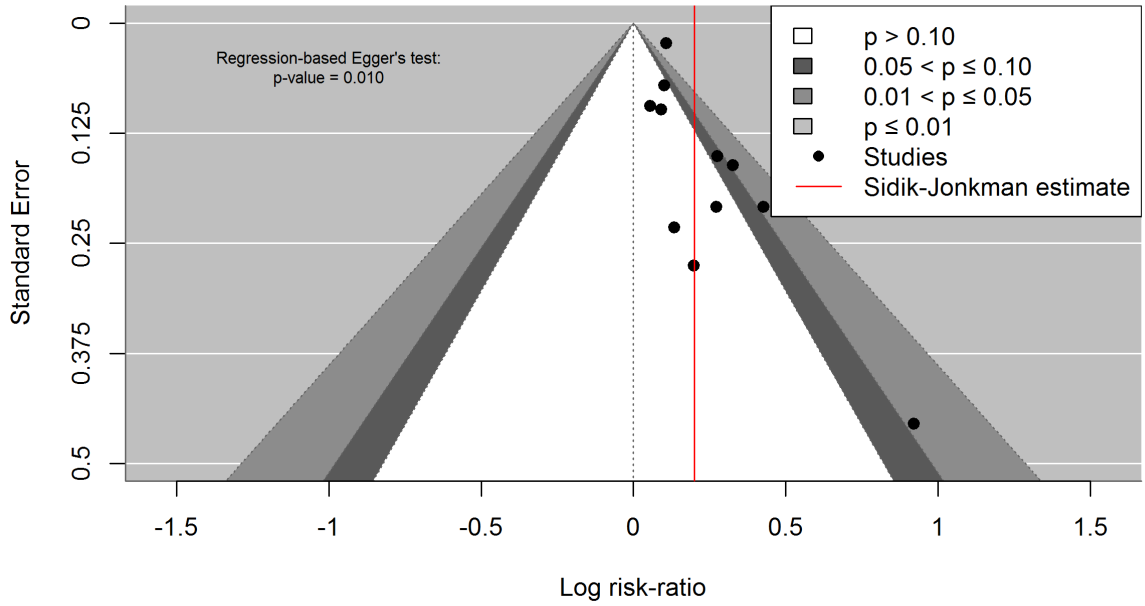

**B. <u>Secondary outcome: ICU mortality</u>**



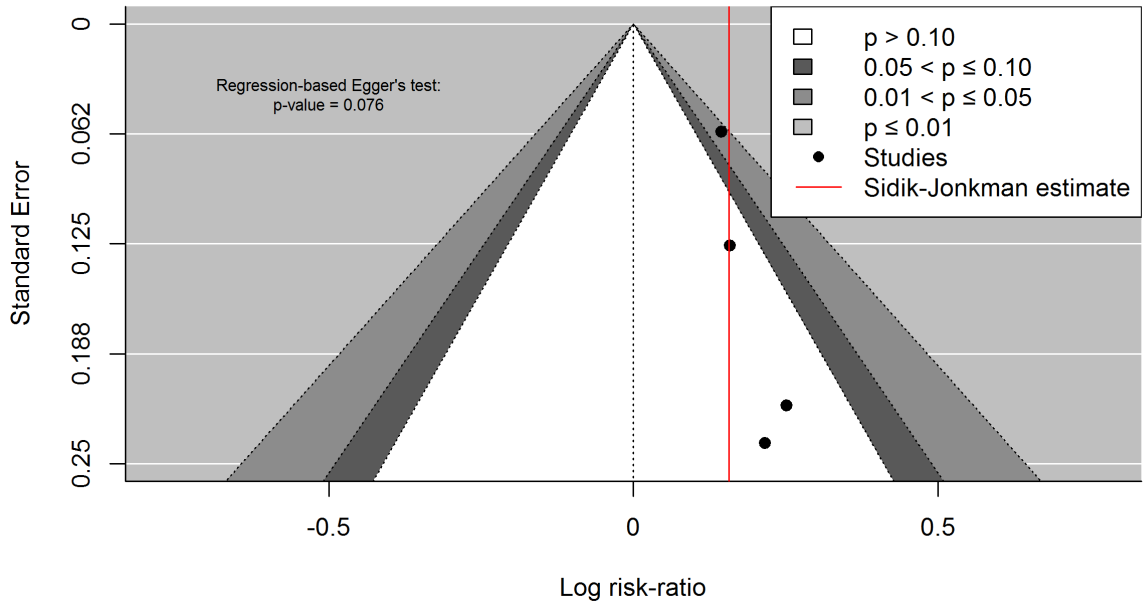
**C. Secondary outcome: ICU length of stay**



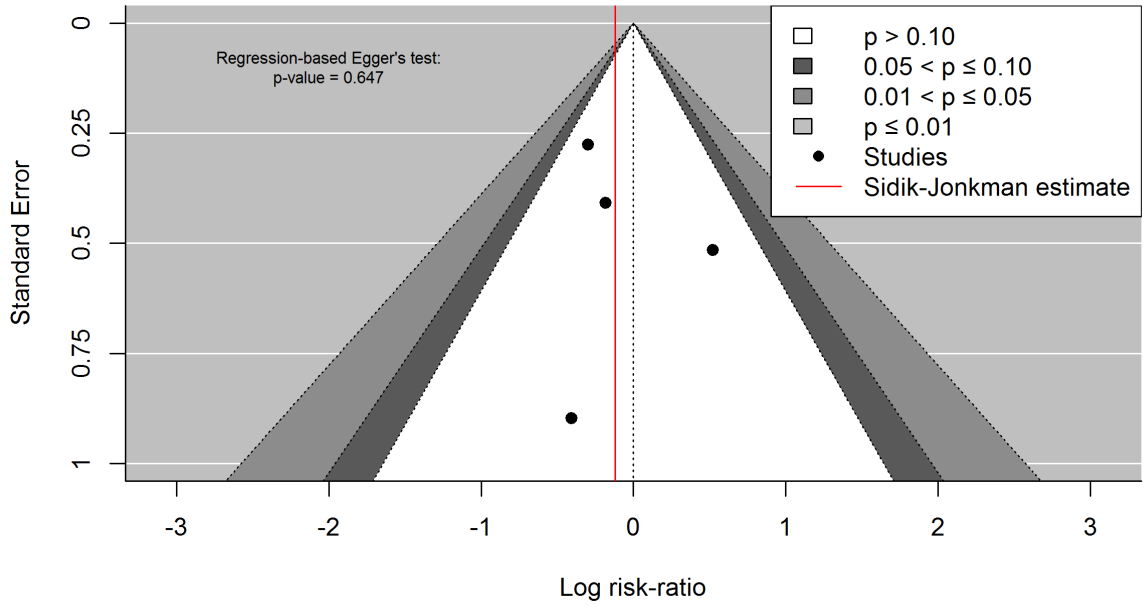

**D. Secondary outcome: clinical cure**



**E. Secondary outcome: microbiological cure**

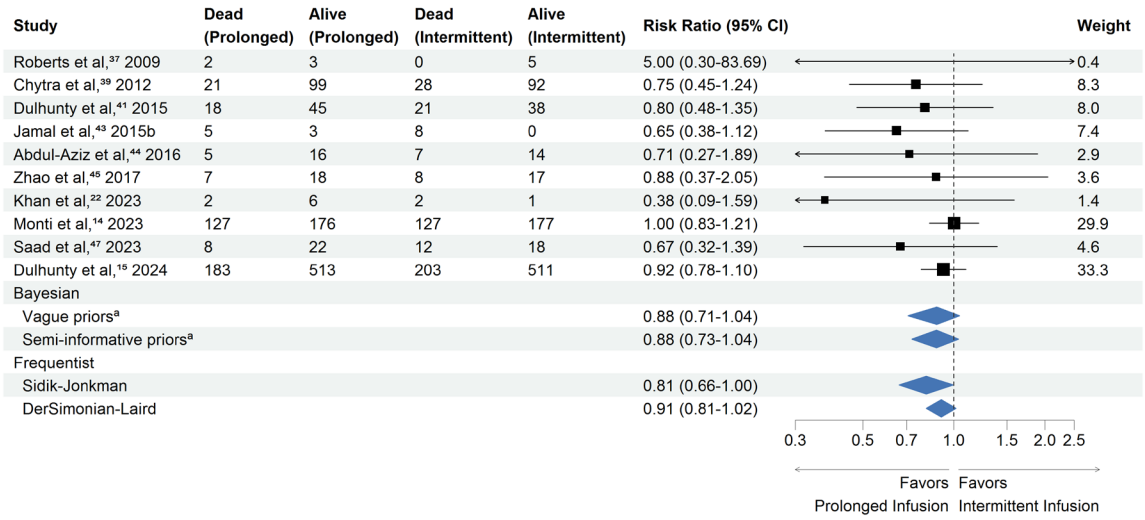



**F. Secondary outcome: adverse events**

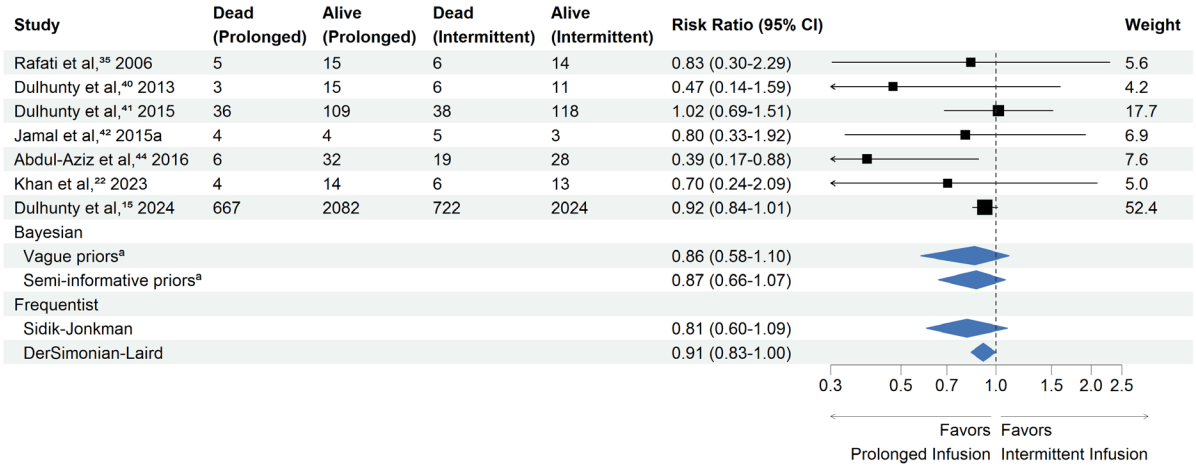


**eFigure 4: All-cause 90-day mortality by study beta-lactam antibiotic i.e. piperacillin/tazobactam versus meropenem**

## A. Meropenem



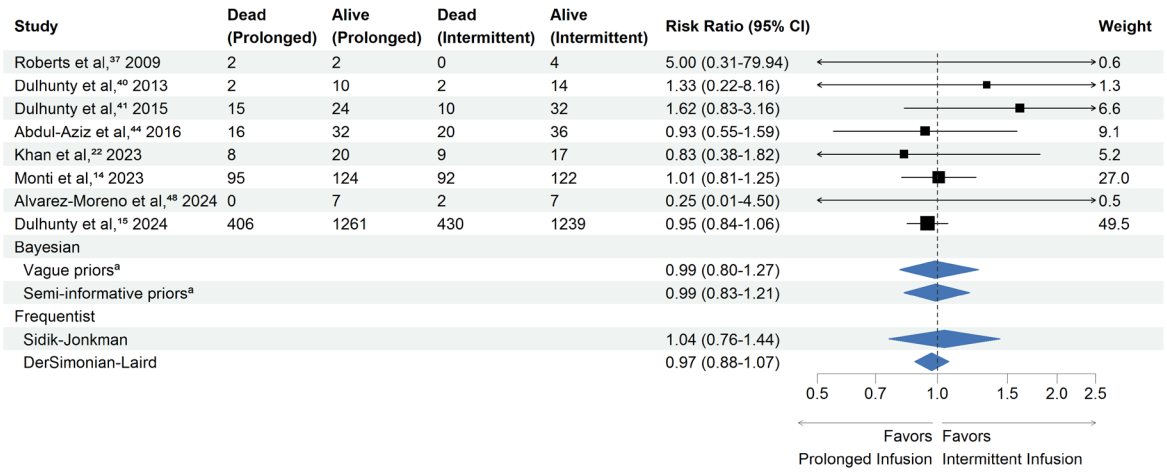

## B. Piperacillin/tazobactam



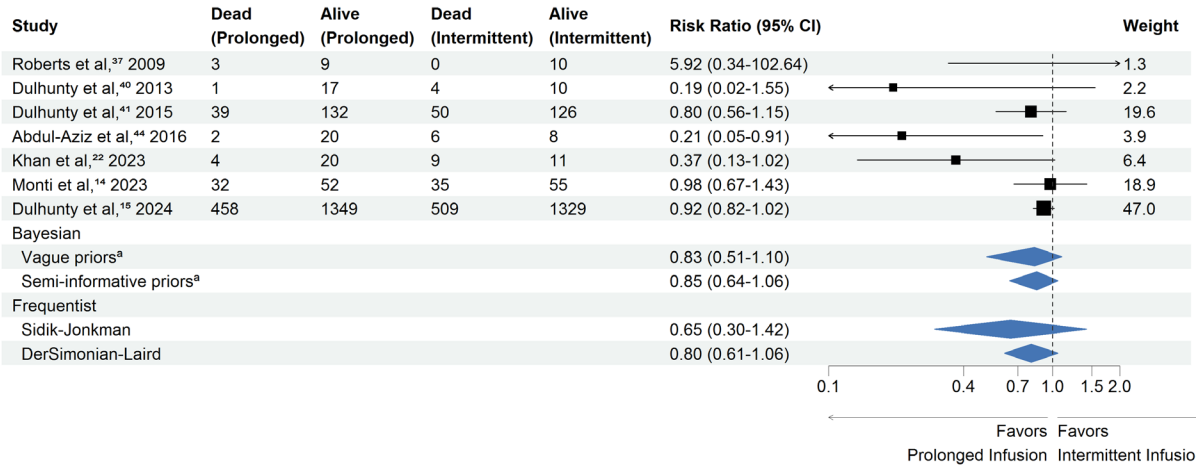

**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

## eFigure 5: All-cause 90-day mortality by culture-positive infection versus culture-negative infection

### A. Culture-positive infection




### B. Culture-negative infection

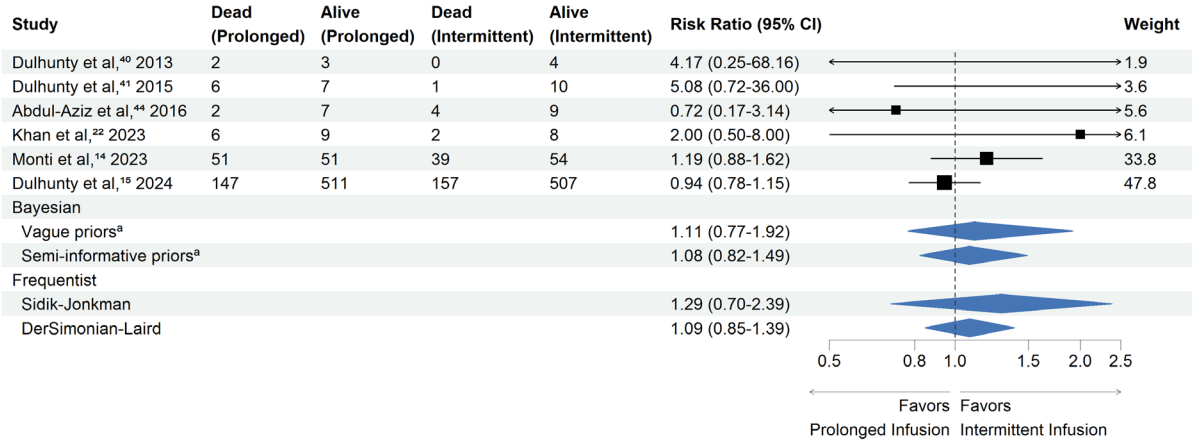



**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 6: All-cause 90-day mortality by Gram-negative infection versus Gram-positive infection**

## A. Gram-negative infection

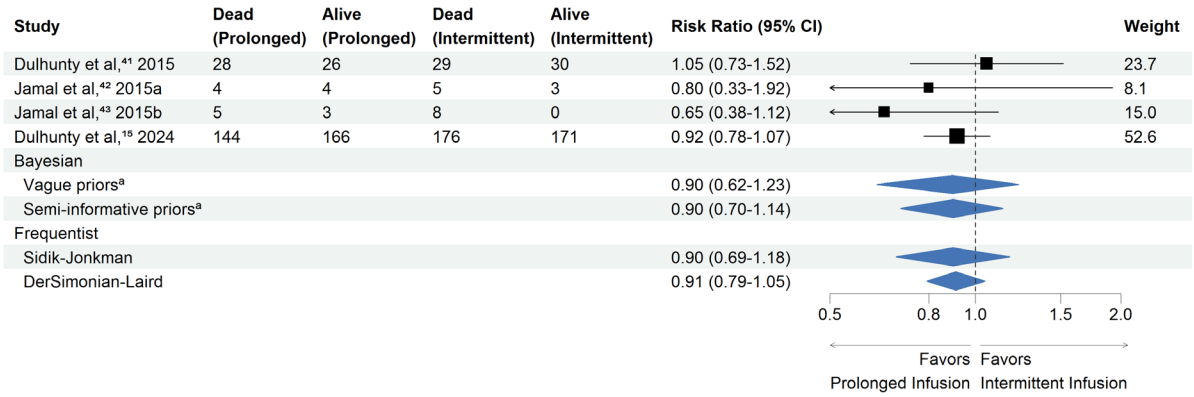

## B. Gram-positive infection



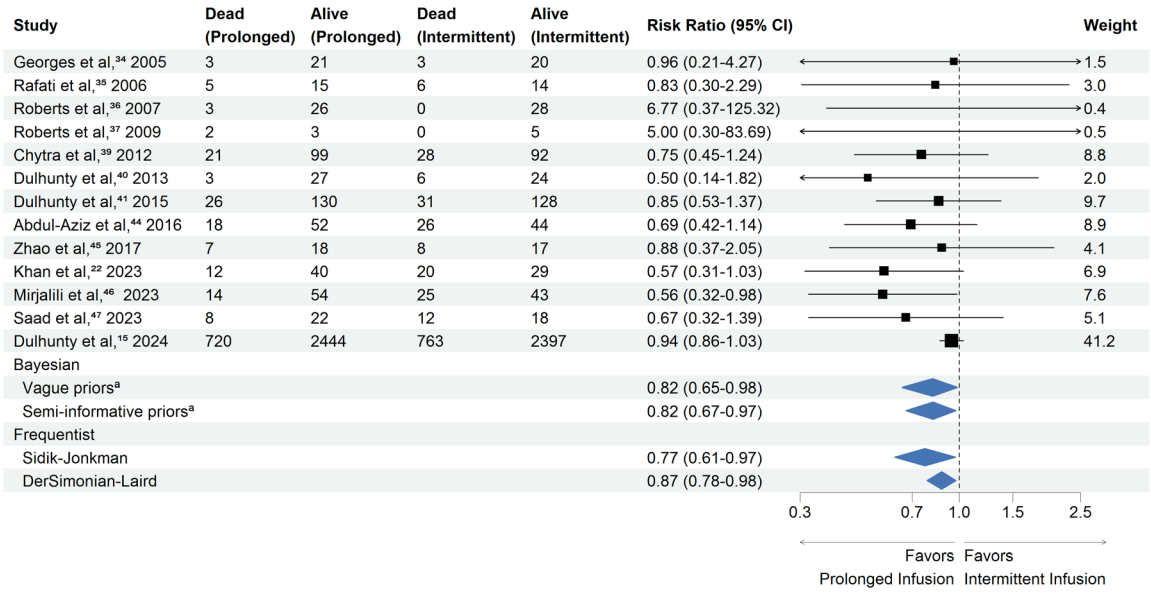

**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 7: All-cause 90-day mortality by receipt of kidney replacement therapy versus no kidney replacement therapy**

## A. Kidney replacement therapy




## B. Non-kidney replacement therapy

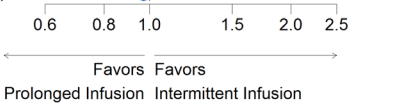



**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

## eFigure 8: All-cause 90-day mortality by lung infection versus other infections

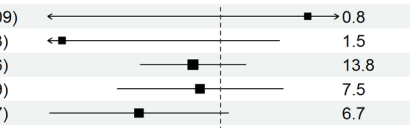
### A. Lung infection

| Study | Dead (Prolonged) | Alive (Prolonged) | Dead (Intermittent) | Alive (Intermittent) | Risk Ratio (95% CI) | Weight |
|---|---|---|---|---|---|---|
| Roberts et al,[36] 2007 | 3 | 25 | 0 | 28 | 7.00 (0.38-129.55) | 0.6 |
| Roberts et al,[37] 2009 | 1 | 1 | 0 | 3 | 4.00 (0.24-67.71) | 0.7 |
| Dulhunty et al,[40] 2013 | 2 | 12 | 1 | 15 | 2.29 (0.23-22.59) | 1.0 |
| Dulhunty et al,[41] 2015 | 33 | 81 | 32 | 87 | 1.08 (0.71-1.63) | 13.7 |
| Abdul-Aziz et al,[44] 2016 | 11 | 35 | 14 | 22 | 0.61 (0.32-1.19) | 7.7 |
| Khan et al,[22] 2023 | 6 | 18 | 9 | 16 | 0.69 (0.29-1.65) | 5.2 |
| Monti et al,[14] 2023 | 48 | 48 | 43 | 56 | 1.15 (0.85-1.56) | 19.3 |
| Dulhunty et al,[15] 2024 | 593 | 1585 | 647 | 1602 | 0.95 (0.86-1.04) | 51.4 |
| Bayesian | | | | | | |
| Vague priors[a] | | | | | 0.98 (0.76-1.28) | |
| Semi-informative priors[a] | | | | | 0.98 (0.81-1.20) | |
| Frequentist | | | | | | |
| Sidik-Jonkman | | | | | 1.02 (0.67-1.56) | |
| DerSimonian-Laird | | | | | 0.97 (0.86-1.09) | |




### B. Other infections

| Study | Dead (Prolonged) | Alive (Prolonged) | Dead (Intermittent) | Alive (Intermittent) | Risk Ratio (95% CI) | Weight |
|---|---|---|---|---|---|---|
| Roberts et al,[37] 2009 | 1 | 2 | 0 | 2 | 2.25 (0.13-38.09) | 0.8 |
| Dulhunty et al,[40] 2013 | 1 | 13 | 5 | 11 | 0.23 (0.03-1.73) | 1.5 |
| Dulhunty et al,[41] 2015 | 21 | 75 | 28 | 71 | 0.77 (0.47-1.26) | 13.8 |
| Abdul-Aziz et al,[44] 2016 | 7 | 17 | 12 | 22 | 0.83 (0.38-1.79) | 7.5 |
| Khan et al,[22] 2023 | 6 | 22 | 11 | 13 | 0.47 (0.20-1.07) | 6.7 |
| Monti et al,[14] 2023 | 40 | 69 | 32 | 58 | 1.03 (0.71-1.50) | 19.2 |
| Dulhunty et al,[15] 2024 | 271 | 1021 | 292 | 965 | 0.90 (0.78-1.04) | 50.0 |
| Bayesian | | | | | | |
| Vague priors[a] | | | | | 0.86 (0.62-1.11) | |
| Semi-informative priors[a] | | | | | 0.87 (0.69-1.07) | |
| Frequentist | | | | | | |
| Sidik-Jonkman | | | | | 0.80 (0.56-1.14) | |
| DerSimonian-Laird | | | | | 0.89 (0.78-1.01) | |

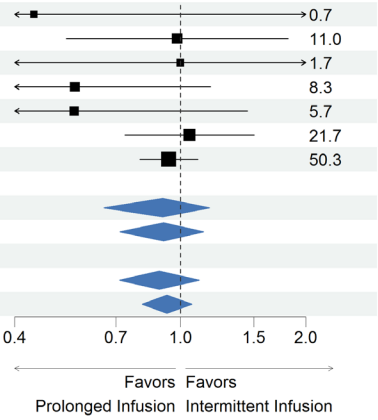



**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

## eFigure 9: All-cause 90-day mortality by sepsis versus septic shock

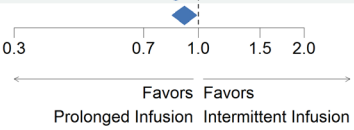
### A. Sepsis

| Study | Dead (Prolonged) | Alive (Prolonged) | Dead (Intermittent) | Alive (Intermittent) | Risk Ratio (95% CI) | Weight |
|---|---|---|---|---|---|---|
| Dulhunty et al,[40] 2013 | 0 | 8 | 1 | 10 | 0.44 (0.02-9.69) | 0.7 |
| Dulhunty et al,[41] 2015 | 15 | 42 | 15 | 41 | 0.98 (0.53-1.81) | 11.0 |
| Jamal et al,[42] 2015a | 1 | 1 | 1 | 1 | 1.00 (0.14-7.10) | 1.7 |
| Abdul-Aziz et al,[44] 2016 | 8 | 35 | 15 | 30 | 0.56 (0.26-1.18) | 8.3 |
| Khan et al,[22] 2023 | 5 | 23 | 9 | 19 | 0.56 (0.21-1.45) | 5.7 |
| Monti et al,[14] 2023 | 40 | 76 | 40 | 82 | 1.05 (0.74-1.50) | 21.7 |
| Dulhunty et al,[15] 2024 | 222 | 786 | 244 | 795 | 0.94 (0.80-1.10) | 50.3 |
| Bayesian | | | | | | |
| Vague priors[a] | | | | | 0.91 (0.65-1.17) | |
| Semi-informative priors[a] | | | | | 0.91 (0.72-1.14) | |
| Frequentist | | | | | | |
| Sidik-Jonkman | | | | | 0.89 (0.71-1.11) | |
| DerSimonian-Laird | | | | | 0.93 (0.81-1.07) | |




### B. Septic shock

| Study | Dead (Prolonged) | Alive (Prolonged) | Dead (Intermittent) | Alive (Intermittent) | Risk Ratio (95% CI) | Weight |
|---|---|---|---|---|---|---|
| Dulhunty et al,[40] 2013 | 3 | 19 | 5 | 14 | 0.52 (0.14-1.89) | 1.5 |
| Dulhunty et al,[41] 2015 | 39 | 114 | 45 | 117 | 0.92 (0.64-1.33) | 11.0 |
| Jamal et al,[42] 2015a | 3 | 3 | 4 | 2 | 0.75 (0.28-2.00) | 2.5 |
| Jamal et al,[43] 2015b | 5 | 3 | 7 | 0 | 0.65 (0.38-1.13) | 6.3 |
| Abdul-Aziz et al,[44] 2016 | 10 | 17 | 11 | 14 | 0.84 (0.43-1.63) | 4.8 |
| Khan et al,[22] 2023 | 7 | 17 | 11 | 9 | 0.53 (0.25-1.11) | 4.0 |
| Monti et al,[14] 2023 | 87 | 100 | 87 | 95 | 0.97 (0.78-1.21) | 20.8 |
| Dulhunty et al,[15] 2024 | 642 | 1824 | 695 | 1773 | 0.92 (0.84-1.01) | 48.9 |
| Bayesian | | | | | | |
| Vague priors[a] | | | | | 0.89 (0.71-1.04) | |
| Semi-informative priors[a] | | | | | 0.88 (0.74-1.03) | |
| Frequentist | | | | | | |
| Sidik-Jonkman | | | | | 0.86 (0.74-1.01) | |
| DerSimonian-Laird | | | | | 0.91 (0.84-0.99) | |

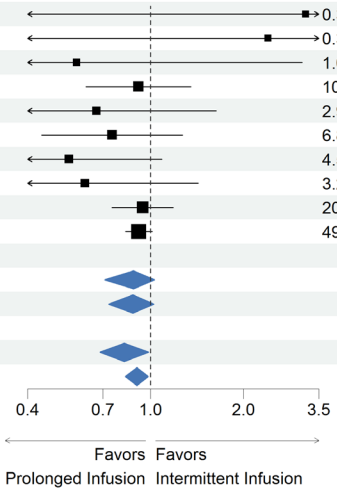



**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

## eFigure 10: All-cause 90-day mortality by sex i.e. male versus female participants

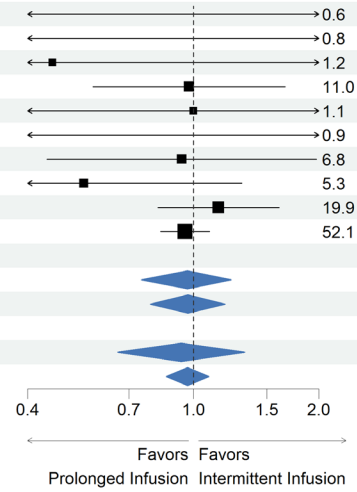
### A. Male participants

| Study | Dead (Prolonged) | Alive (Prolonged) | Dead (Intermittent) | Alive (Intermittent) | Risk Ratio (95% CI) | Weight |
|---|---|---|---|---|---|---|
| Roberts et al,[36] 2007 | 1 | 15 | 0 | 17 | 3.18 (0.14-72.75) | 0.3 |
| Roberts et al,[37] 2009 | 1 | 3 | 0 | 3 | 2.40 (0.13-44.41) | 0.3 |
| Dulhunty et al,[40] 2013 | 2 | 20 | 3 | 16 | 0.58 (0.11-3.09) | 1.0 |
| Dulhunty et al,[41] 2015 | 34 | 94 | 39 | 95 | 0.91 (0.62-1.35) | 10.4 |
| Jamal et al,[42] 2015a | 4 | 4 | 3 | 1 | 0.67 (0.27-1.63) | 2.9 |
| Jamal et al,[43] 2015b | 5 | 2 | 5 | 0 | 0.75 (0.44-1.27) | 6.8 |
| Abdul-Aziz et al,[44] 2016 | 9 | 37 | 18 | 32 | 0.54 (0.27-1.09) | 4.5 |
| Khan et al,[22] 2023 | 7 | 26 | 9 | 17 | 0.61 (0.26-1.42) | 3.2 |
| Monti et al,[14] 2023 | 80 | 115 | 91 | 118 | 0.94 (0.75-1.18) | 20.6 |
| Dulhunty et al,[15] 2024 | 563 | 1727 | 612 | 1667 | 0.92 (0.83-1.01) | 49.7 |
| Bayesian | | | | | | |
| Vague priors[a] | | | | | 0.88 (0.71-1.03) | |
| Semi-informative priors[a] | | | | | 0.87 (0.73-1.02) | |
| Frequentist | | | | | | |
| Sidik-Jonkman | | | | | 0.82 (0.68-0.98) | |
| DerSimonian-Laird | | | | | 0.90 (0.83-0.98) | |



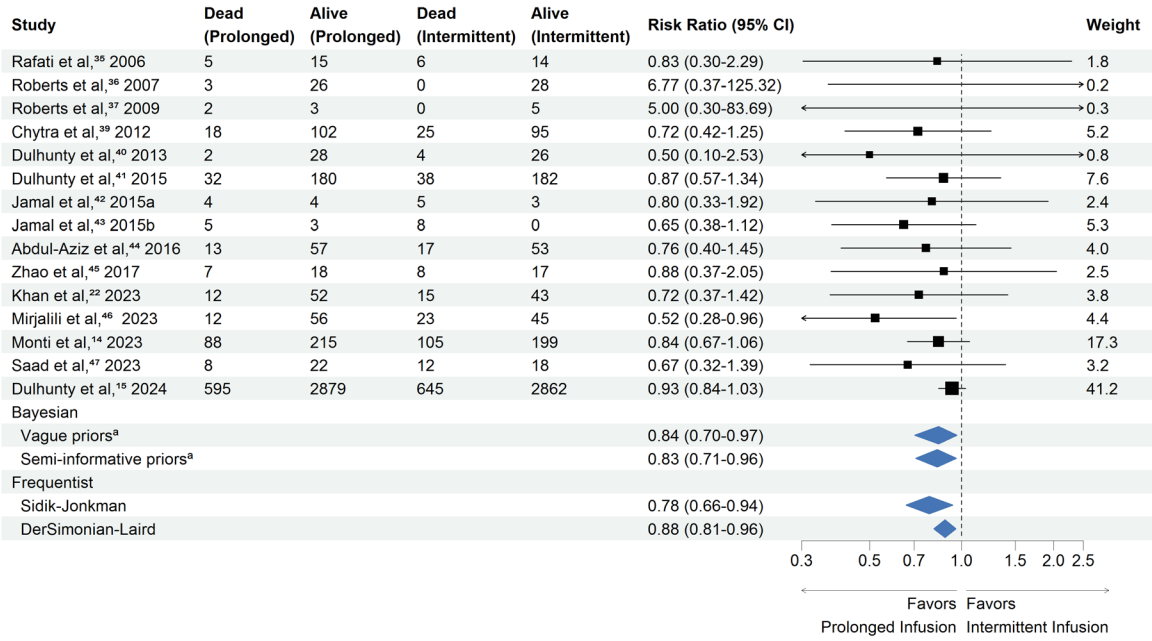

### B. Female participants

| Study | Dead (Prolonged) | Alive (Prolonged) | Dead (Intermittent) | Alive (Intermittent) | Risk Ratio (95% CI) | Weight |
|---|---|---|---|---|---|---|
| Roberts et al,[36] 2007 | 2 | 11 | 0 | 11 | 4.29 (0.23-80.81) | 0.6 |
| Roberts et al,[37] 2009 | 1 | 0 | 0 | 2 | 4.50 (0.32-63.94) | 0.8 |
| Dulhunty et al,[40] 2013 | 1 | 7 | 3 | 8 | 0.46 (0.06-3.64) | 1.2 |
| Dulhunty et al,[41] 2015 | 20 | 62 | 21 | 63 | 0.98 (0.57-1.66) | 11.0 |
| Jamal et al,[42] 2015a | 0 | 0 | 2 | 2 | 1.00 (0.12-8.56) | 1.1 |
| Jamal et al,[43] 2015b | 0 | 1 | 3 | 0 | 0.29 (0.03-3.24) | 0.9 |
| Abdul-Aziz et al,[44] 2016 | 9 | 15 | 8 | 12 | 0.94 (0.45-1.97) | 6.8 |
| Khan et al,[22] 2023 | 5 | 15 | 11 | 13 | 0.55 (0.23-1.31) | 5.3 |
| Monti et al,[14] 2023 | 47 | 61 | 36 | 59 | 1.15 (0.82-1.61) | 19.9 |
| Dulhunty et al,[15] 2024 | 301 | 883 | 327 | 901 | 0.95 (0.83-1.09) | 52.1 |
| Bayesian | | | | | | |
| Vague priors[a] | | | | | 0.97 (0.75-1.23) | |
| Semi-informative priors[a] | | | | | 0.97 (0.79-1.19) | |
| Frequentist | | | | | | |
| Sidik-Jonkman | | | | | 0.93 (0.66-1.33) | |
| DerSimonian-Laird | | | | | 0.97 (0.86-1.09) | |



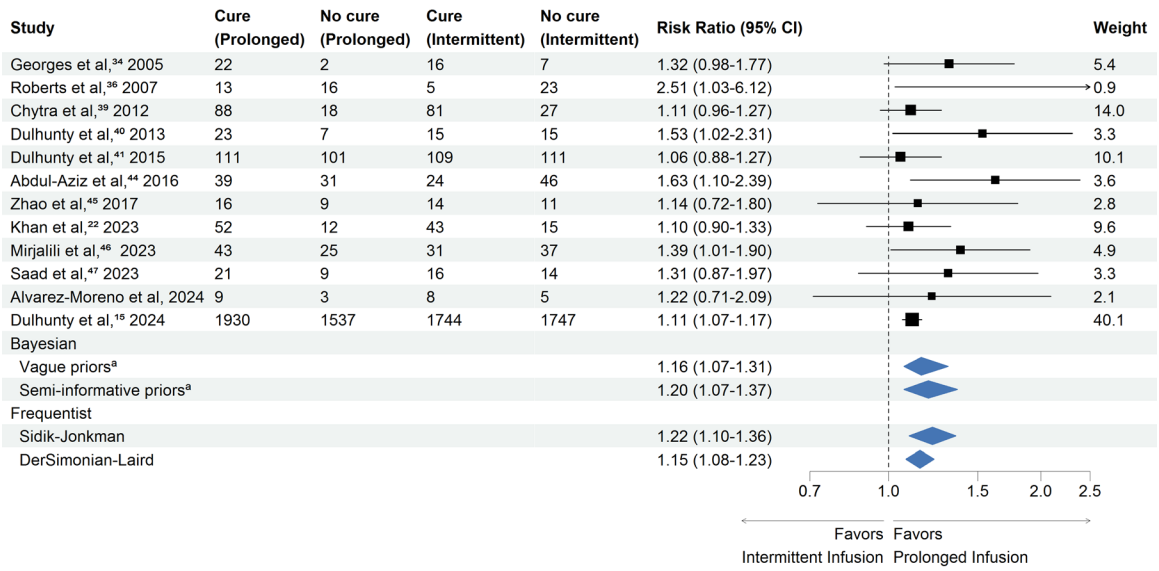

**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 11: Forest plot for ICU mortality for the comparison between prolonged infusions of beta-lactam antibiotics versus standard intermittent infusions**



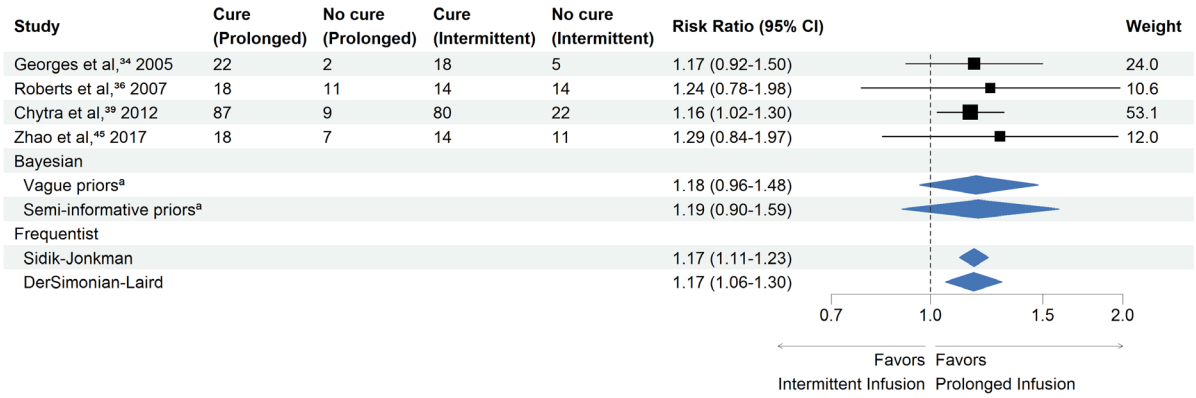

**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 12: Forest plot for clinical cure for the comparison between prolonged infusions of beta-lactam antibiotics versus standard intermittent infusions**



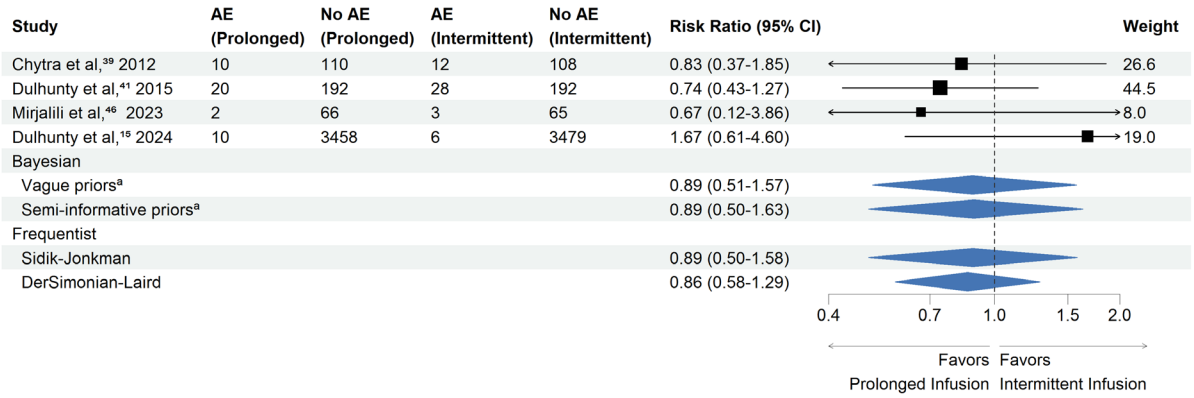

**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 13: Forest plot for microbiological cure for the comparison between prolonged infusions of beta-lactam antibiotics versus standard intermittent infusions**



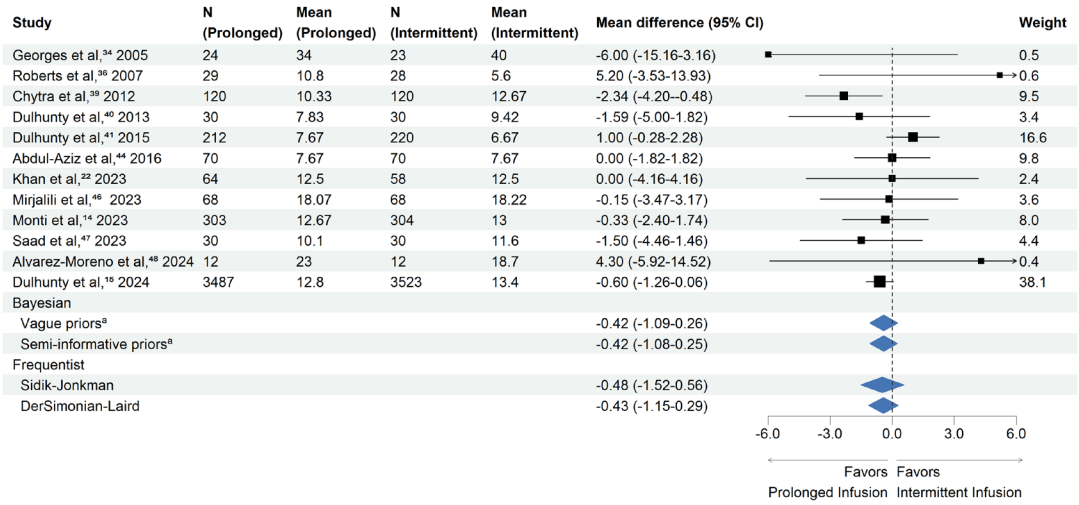

**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 14: Forest plot for adverse events for the comparison between prolonged infusions of beta-lactam antibiotics versus standard intermittent infusions**




**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis

**eFigure 15: Forest plot for ICU length of stay for the comparison between prolonged infusions of beta-lactam antibiotics versus standard intermittent infusions**




**Legend:** The black boxes represent point estimates, and the sizes of the boxes are proportional to the weight of the studies. The weights displayed are based on Bayesian analysis with vague priors. The whiskers represent confidence intervals. For the diamonds, the width represents the trials pooled estimate confidence interval, and the middle point represents the point estimates. [a]Credible intervals are presented for Bayesian analysis