Systematic review of the impact of appropriate versus inappropriate initial antibiotic therapy on outcomes of patients with severe bacterial infections

Highlights

- Systematic review with meta-analyses assessing the impact of appropriate versus inappropriate antimicrobial therapy
- Early administration of appropriate antimicrobial therapy significantly reduces rates of mortality
- Early administration of appropriate antimicrobial therapy significantly reduces length of hospital stay
- Early initiation of appropriate antimicrobial therapy increases clinical cure rates and reduces hospital costs
- Increasing the availability of rapid diagnostics is essential in order to improve outcomes for patients

A systematic review on the impact of appropriate versus inappropriate initial antibiotic therapy on the outcomes of patients with severe bacterial infections

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Abbreviation list

CI, confidence interval; ED, emergency department; HR, hazard ratio; I^2, heterogeneity; ICU, intensive care unit; LOS, length of hospital stay; MD, mean difference; OR, odds ratio; RR, risk ratio; SD, standard deviation; UTI, urinary tract infection; Z, overall effect

Abstract

Background: We investigated the impact of appropriate versus inappropriate initial antimicrobial therapy on the clinical outcomes of patients with severe bacterial infections as part of a systematic review with meta-analyses assessing the impact of delay in appropriate antimicrobial therapy.

Methods: Literature searches of MEDLINE and Embase, conducted on 24 July 2018, identified studies published after 2007 reporting the impact of delay in appropriate antibiotic therapy for hospitalised adult patients with bacterial infections. Results were statistically pooled for outcomes including mortality, length of hospital stay (LOS) and treatment failure. Subgroup analyses were explored by site of infection where data permitted.

Results: Inclusion criteria were met by 145 studies, of which 122 reported data on the impact of appropriate versus inappropriate initial therapy. In pooled analysis, rates of mortality were significantly in favour of appropriate therapy (odds ratio [OR] 0.44 [95% CI 0.39–0.50]). Across ten studies, LOS was significantly shorter with appropriate therapy compared with inappropriate therapy (mean difference [MD] −2.95 days [95% CI −5.46 to −0.43]). In patients who received appropriate therapy, incidence of treatment failure was significantly lower compared with patients who received inappropriate therapy (six studies: OR 0.33 [95% CI 0.16–0.66]) as was mean hospital cost (four studies: MD −7.38 thousand US Dollars or Euros [95% CI −14.14 to −0.62]).

Conclusions: Initiation of appropriate versus inappropriate antibiotics can reduce mortality, reduce treatment failure and decrease LOS, highlighting the importance of broad‐spectrum empiric therapy and rapid diagnostics for early identification of the causative pathogen.

Study registration: PROSPERO: CRD42018104669

Keywords (3–6 free type)

Appropriate antibiotic therapy

Empiric therapy

Length of hospital stay

Mortality rate

Treatment failure

1. Introduction

Severe bacterial infections are associated with considerable mortality, morbidity and healthcare costs (1-4). Assessment of the appropriateness of antibiotic therapy can be performed by evaluating cultures of causative pathogens and their antimicrobial susceptibility, whose testing typically takes at least 48–72 hours (5); the adoption of rapid diagnostic techniques to detect antimicrobial susceptibility can reduce therapeutic delay, but is not currently routine practice. Consequently, physicians initiate antibiotic treatment before test results have confirmed the causative pathogen and its drug resistance pattern. Initiation of inappropriate antibiotic treatment is associated with higher mortality and longer length of hospital stay (LOS) (4). These results have been observed in patients with pneumonia, with appropriate initial therapy resulting in higher survival rates, shorter hospital rates and lower healthcare costs (6, 7).

We performed a systematic review to assess the impact of delayed appropriate antibacterial therapy on clinical outcomes (i.e. mortality, LOS, cost and treatment failure) of patients with community- and hospital-acquired severe bacterial infections. Here we focus on the impact of appropriate versus inappropriate initial therapy.

2. Methods

This systematic review was undertaken according to the principles in the Cochrane handbook and guidance published by the Centre for Reviews and Dissemination (8, 9). The protocol was published in the PROSPERO database (CRD42018104669; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=104669).

2.1. Eligibility criteria

Studies were eligible for inclusion if they reported the impact of delayed appropriate antibiotic therapy for hospitalised adult patients with severe bacterial infections, including but not limited to: urinary tract infections, nosocomial pneumonia, bacteraemia, intra-abdominal infections, central nervous system infections, skin and soft tissue infections, and endocarditis. Studies were required to report the appropriateness of antibiotic therapy, an identifiable delay to initiation of appropriate therapy and at least one of the following outcomes: mortality, treatment success, infection progression, clinical cure, microbiological eradication, duration of antibiotic treatment, length of hospital or ICU stay, or healthcare cost. Randomised controlled trials, non-randomised comparative studies and observational studies were eligible.

Studies involving patients less than 18 years or with prostatitis, cystic fibrosis, *Clostridium difficile* or sexually transmitted infections were excluded. Systematic reviews and meta-analyses were included in the search for study identification purposes but were excluded from analysis. To reflect contemporary practice, reports published before 2007 were excluded, as were those not in English.

2.2. Identification of relevant literature

MEDLINE and Embase were searched on 24 July 2018 using a strategy structured as follows: (non-specific infections OR specific infections) AND treatment delay AND (hospitalisation OR named disease severity scores) (see supplementary information).

Database searches were supplemented by a methodical citation search (see supplementary information). Reference lists of relevant systematic reviews were also checked for eligible studies.

Two reviewers (SK, JP or KW) independently screened titles and abstracts for inclusion and assessed potentially relevant full texts against the eligibility criteria. A third reviewer resolved conflicts. Where results for one study were reported in more than one paper, related papers were grouped to ensure participants were only included once.

2.3. Data extraction and bias assessment

One person (SK or JP) extracted data from eligible studies using a piloted data extraction form and a second reviewer verified every data point. A third reviewer resolved conflicts. Data elements for which data were sought are detailed in Supplementary Table 1. The risk of bias was assessed using the relevant tool (Newcastle Ottawa Scale, CRD Cohort study checklist or Cochrane Risk of Bias Tool).[10-12] Additionally, a funnel plot was generated to assess publication bias where a large enough sample of studies (> 10) were available and included in the meta-analysis.

2.4. Statistical analysis

Results were grouped according to the comparison reported: delay versus no delay in receiving appropriate antibiotic therapy; time to appropriate therapy; and appropriate vs inappropriate therapy (see supplementary materials for examples). Definitions of appropriate antibiotics varied between studies, but usually included therapy to which the microorganism

was susceptible, and could also specify appropriate dosing or concordance with guidelines. Where a study reported different definitions of adequate therapy, the most conservative was used. Details of the definitions of treatment failure, treatment success, and clinical cure described in the included studies can be found in supplementary Table 2.

Cut-off times reported for the definition of delay varied between studies and ranged from >1 hour to >5 days (Supplementary Table 3). Where a study reported several cut-off times, the time point closest to 24 hours was selected. Where a study reported several time points for an outcome, specific time points (eg. “at 24 h”) were selected in preference to periods varying between participants (eg, “in hospital”), and the earliest specific time point was selected.

Raw data for the number of events and sample size for each outcome were extracted from each paper, and the presented odds ratios for each study were calculated during meta-analyses using a random effects model. Where appropriate, results were statistically pooled for outcomes of interest. Due to heterogeneity between studies, random effects models were used for meta-analyses to estimate the mean of the distribution of true effects, weighting studies according to their size and variance. The odds ratio (OR), overall effect (Z) and heterogeneity (I^2) were calculated. Pairwise meta-analyses to pool evidence from comparisons of two interventions were performed using standard frequentist approaches.(13) RevMan (version 5.3) was used to conduct the analyses.

Subgroup analyses were explored by infection site where data permitted. Further subgroup analyses based on pathogens and infection severity were planned but were unfeasible with the data identified.

3. Results

The literature searches yielded 10,800 unique records for screening. Of these, 10,320 studies were excluded after an assessment of the title and abstract. The full texts of the remaining 478 articles were assessed against inclusion and exclusion criteria and 145 studies, reported in 147 records, were eligible for inclusion in the systematic review. Of these 145 studies, 114 reported a comparison between receiving appropriate versus inappropriate initial therapy (Fig. 1, Supplementary Table 3).

In total, 114 studies reported some data relating to the impact of appropriate versus inappropriate antibiotic therapy; overall however, the studies did not have a robust design to assess causality between antibiotic appropriateness and delay/outcomes. Studies included one randomised controlled trial, seven case-control studies, 14 prospective cohort studies, and 92 retrospective cohort studies (study references and details of study design, location, setting and patient population are reported in Supplementary Table 3). Of these studies, three were international, and 111 were carried out in single countries across Europe, Asia and the Americas. Sample size ranged from 13 to 40,137 patients. Seven studies (6.0%) included fewer than 50 patients, 18 (15.5%) included 50–100 patients and 89 (78.1%) included over 100 patients (see overall sample size in Supplementary Table 3).

In the single identified randomised controlled trial (14), rather than being randomised to different antibiotic regimens or timings, patients were randomly assigned to have different diagnostic procedures. The treatment allocation and blinding process were unclear.

Of the 94 cohort studies, 57 did not report detailed descriptions of the groups or the distribution of prognostic factors. In 88 studies, confounding factors were not comparable, or were unclear across groups. In 14 studies, adjustment for confounding factors was inadequate or unclear (for references and details of individual study quality/bias see Supplementary Table 3).

Of the seven case-control studies (15-21), one was small (36 patients) and it was unclear if the sample size was representative (15), three had missing data (17, 18, 20) and one did not control for confounding factors (19).

3.1. Patient characteristics

In total, 95 studies assessed the general hospital population, whereas 19 were conducted specifically in intensive care units (ICUs; Supplementary Table 3). Age of participants in studies ranged from 17 to 102 years.

The majority of studies included infections due to a variety of microorganisms and 40 studies (42.6%) reported infections caused by a specific pathogen (*Acinetobacter* spp.: 16 studies [14.8%]; *Pseudomonas aeruginosa*: 14 studies [11.5%]; *Staphylococcus aureus*: 5 studies [4.1%]; *Klebsiella pneumoniae*: 5 studies [4.1%]). Twelve studies (9.8%) included patients with a variety of sites or sources of infection, 69 (56.6%) only included patients with bacteraemia, bloodstream infections and sepsis, and six (4.9%) included patients specifically with bacteraemic pneumonia (Supplementary Fig. 1).

The average LOS prior to infection was not widely reported, but when reported, it ranged from 0 to 46.6 days. A history of ICU stay prior to infection ranged from 5% to 100% of participants, with the average length of ICU stay ranging from 6 to 30.1 days.

3.2. Mortality

In total, 94 studies reported raw mortality data that could be included in a pooled analysis comparing deaths in patients receiving appropriate versus initial inappropriate antibiotics. Overall, rates of mortality were significantly lower with appropriate versus inappropriate therapy (OR 0.44 [95% CI 0.38–0.50]). Mortality rates compared at specific time points, significantly favoured appropriate versus inappropriate therapy at 14–15 days after diagnosis

or treatment initiation (OR 0.45 [95% CI 0.29–0.70]) and at 21–30 days (OR 0.40 [95% CI 0.33–0.50]); no significant difference was identified at 2–7 days after diagnosis or treatment initiation (OR 0.65 [95% CI 0.27–1.57]; Fig. 2, Supplementary Fig. 2). In studies that reported patient mortality during ICU or hospital stay, mortality rates were significantly lower with appropriate versus inappropriate therapy for both time points (OR 0.27 [95% CI 0.15–0.50], and 0.47 [95% CI 0.36–0.61], respectively; Fig. 2, Supplementary Fig. 2). Pooled subgroup analyses found mortality rates significantly in favour of appropriate therapy in patients with bacteraemia, sepsis and septic shock (63 studies; OR 0.44 [95% CI 0.37–0.52]), and patients with pneumonia (19 studies; OR 0.35 [95% CI 0.24–0.51]), although there was high heterogeneity between studies ($P<0.01$, $I^2 = 78\%$; Fig. 2). No significant difference in rates of mortality between appropriate versus inappropriate therapy was identified for patients with acute pyelonephritis and UTIs (three studies; OR 0.46 [95% CI 0.17–1.23]; Supplementary Fig. 3).

Twenty-two studies reported adjusted hazard ratios (HRs) for death, of which 15 were significantly in favour of appropriate therapy (HR and 95% CI <1; Supplementary Table 4). Fifty-seven studies reported adjusted ORs for death, of which 35 were significantly in favour of appropriate therapy (OR and 95% CI <1) and the other 22 were non-significant (95% CI spans 1; Supplementary Table 45). Two studies reported adjusted risk ratios (RRs) for death, both significantly in favour of appropriate therapy (RR and 95% CI <1; Supplementary Table 6).

3.3. Duration of hospital stay

Eight studies reported mean LOS (22-29). In the majority of studies, and with pooled treatment effect, the LOS was significantly shorter with appropriate versus inappropriate antibiotics (mean difference [MD] −2.54 days [95% CI −5.30 to −0.23]) (Fig. 3, Supplementary Fig. 4). Of three studies reporting LOS in the ICU (22-24), none showed a

significant difference in the LOS between the two groups (MD 0.39 days [95% CI −2. 19–2.98]).

In the pooled treatment effect by site of infection, the duration of hospital stay was significantly shorter with appropriate antibiotics in studies including patients with bacteraemia or sepsis (four studies; MD −5.04 days [95% CI −8.31 to −1.77]). The difference was not significant in studies of patients with pneumonia (three studies (23, 25, 28); MD −1.43 day [95% CI −3.99–1.13]) or skin infections (one study (29); MD −0.50 days [95% CI −2.31–1.31]) (Fig. 3, Supplementary Fig. 5).

Seven studies reported various ORs and HRs of LOS associated with inappropriate therapy, Five of which were significantly in favour of appropriate antibiotics (4, 24, 25, 30, 31); the results of the other two studies were not significant (Supplementary Table 7) (32, 33).

3.4. Treatment failure

Across six studies reporting treatment failure outcomes (26, 34-38), the incidence of treatment failure was significantly lower in patients receiving appropriate versus inappropriate initial therapy (OR 0.33 [95% CI 0.16–0.66]; Fig 4, Supplementary Fig. 6). This was supported by data at specific time points of 3–7 days after diagnosis or treatment initiation (four studies (26, 34-36); OR 0.25 [95% CI 0.08–0.80]), 30 days post treatment initiation, (one study (37); OR 0.67 [95% CI 0.49–0.92]), and during hospital stay (one study (38), OR 0.24 [95% CI 0.10–0.60]) (Fig. 4, Supplementary Fig. 6). Incidence of treatment failure was significantly lower with appropriate versus inappropriate therapy in patients with UTIs or acute pyelonephritis (two studies (36, 37); OR 0.51 [95% CI 0.27–0.96]), and with bacteraemia or sepsis (four studies (26, 34, 35, 38); OR 0.22 [95% CI 0.06–0.83]; Supplementary Fig. 7). One study reported treatment success outcomes (24); Incidence of response was significantly greater in patients who received appropriate therapy compared with those who did not (OR 8.79 [95% CI 3.63–21.27]; Supplementary Fig. 8).

3.5. Clinical cure and hospital costs

Two studies reported clinical cure at 2–8 days after diagnosis or treatment initiation (24, 39). One of these three studies (39) reported that the incidence of clinical cure was significantly higher in patients who received appropriate therapy (OR 9.75 [95% CI 2.83–33.64]; Supplementary Fig. 9).

Three studies reported mean hospital costs (23, 26, 27), two of which (26, 27) showed lower mean hospital costs for patients who received appropriate therapy (Fig. 5, Supplementary Fig. 10). Another study reported an adjusted effect size of around 1.5-fold increased cost with inappropriate antibiotics (30). One additional study reported the OR for patients experiencing one or more elements of a composite economic outcome composed of subsequent hospital admissions, emergency department visits or unscheduled visits to a healthcare provider specifically related to study infection (40). Results showed increased costs associated with inappropriate therapy (OR 1.79 [95% CI 1.01 to −3.16]; $P < 0.05$). Two studies reported the mean duration of antibiotic treatment, which was significantly shorter for patients receiving appropriate therapy (MD −3.22 days [95% CI −4.65 to −1.78]) (16, 24).

4. Discussion

It is widely acknowledged that the use of inappropriate empiric antibiotics for the treatment of severe infections is associated with poor patient outcomes and increased hospital costs.(41-46) This systematic review assessed the impact of appropriate versus inappropriate antibiotic therapy on multiple outcomes including mortality rates, treatment failure or success, rate of clinical cure, length of hospital stay and hospital costs. The findings demonstrated significantly lower mortality rates overall and at the majority of time points, in patients who received appropriate antibiotic therapy compared with patients who received inappropriate therapy (overall, OR 0.44 [95% CI 0.38–0.50]). The only time point at which a significant reduction in mortality rates was not reported was at 2–7 days after diagnosis or treatment initiation, possibly due to the low number of studies included in this analysis (n = 6), and the difficulties around assessing mortality benefit at this early time point. Rates of treatment failure were significantly reduced in patients receiving appropriate therapy compared with inappropriate therapy, including in patients with UTI or acute pyelonephritis, bacteraemia or sepsis. Appropriate therapy was associated with higher rates of clinical cure and reduced LOS compared with inappropriate therapy. Collectively, these findings highlight that early initiation of appropriate therapy is essential to reduce rates of mortality, improve patient outcomes, and reduce the impact and economic burden on healthcare systems.

Previous studies have shown that empiric, broad-spectrum treatment can be costly when the chosen agent is not affective against the causative organism. Furthermore, empiric use of broad-spectrum antibiotics is known to contribute toward the development of antibiotic resistance,(47-49) which can further complicate the management of patients. Physicians in the intensive care setting often need to initiate treatment before test results can confirm the type of infection and antibiotic resistance pattern. In these cases, rapid diagnostics for early identification of causative pathogens are required to ensure appropriate initial antimicrobial therapy. However, while rapid molecular testing and point-of-care diagnostics are becoming

more accessible, limitations in the currently available molecular methodologies need to be improved for the future (50-52). This consideration, along with the results reported herein, suggest that in some critically-ill patients, the early initiation of effective broad-spectrum empiric therapy may be preferable, but should be based on amalysis of local risk factors and should be followed by subsequent de-escalation to targeted treatment as soon as possible upon characterisation of the causative pathogen.This study has several limitations for consideration. The included studies were not robustly designed to assess causality between antibiotic appropriateness and treatment outcome. In particular, the lack of randomisation and lack of comparability of confounding factors should be noted, along with the fact that analysed estimates of effect were unadjusted in most cases. Definitions of "appropriate" therapy were not consistent across studies and depended on the type and severity of the infection, as well as the study location of the study (see Supplementary Table 23 for different definitions of appropriate therapy). Furthermore, while data were common for some specific sites or sources of infection, such as bacteraemia, the data for other sites of infection were limited to a few studies, meaning that subgroup analyses were not always possible. Additionally, subgroup analyses that divided patients into subgroups of septic shock with bloodstream infections and pneumonia might not have been appropriate. Septic shock is a systemic response rather than an infectious site, and bloodstream infections include different infectious sites. The proportions of different types of infection were not equal.

In this study, pneumonia was compared as a single subgroup. Due to the difficulty in diagnosing some types of pneumonia (53), it would be useful in future studies to stratify by severity, as well as by bacteraemic and non-bacteraemic pneumonia in order to accurately measure an association between appropriate antibiotic therapy and outcome. In contrast, this issue of misdiagnosis would be less pronounced in patients with bacteraemia, which may explain differences in results between the pneumonia and bacteraemia groups in this study. Future research could benefit from focussing on specific types of infections. It should

be noted that for some infection sites, such as intra-abdominal infections, both source control and antimicrobial coverage impact mortality outcomes (54).

A funnel plot was generated to assess publication bias among studies reporting data for the impact of appropriate versus inappropriate therapy on mortality (supplementary figure 11). The distribution was generally deemed symmetrical, with larger studies with higher power towards the top and smaller studies scattered at the bottom. However, visual interpretation of funnel plots remains a topic of discussion, and interpretation of publication bias in this way should be performed with caution [58].

5. Conclusion

In summary, patients with severe bacterial infections, especially carbapenem-resistant infections, are often seriously ill and can deteriorate quickly (55, 56). Increasing the availability of rapid diagnostics and thus, the incidence of early appropriate antimicrobial therapy is essential in order to reduce rates of mortality, and improve outcomes for patients with severe bacterial infections. In turn, this approach will reduce LOS and healthcare costs, reducing the impact and burden of these infections on healthcare systems.

Acknowledgements

RM takes responsibility for the content of the manuscript, including the data and analysis. MB and JR contributed to protocol development, data analysis and writing of this report. FB contributed to manuscript review and editing. HG contributed to protocol development, data analysis and writing of this report. GS contributed to protocol development and writing of this report. LT and EZ contributed to protocol development, data analysis and writing of this report. MA contributed to protocol development, literature searches and writing of the report. RM contributed to protocol development, data analysis and writing of this report. JP contributed to data analysis and writing of this report. SL, DM, SN, KT and SA contributed to protocol development, data analysis and writing of this report. All authors approved the final version for submission.

Declarations

Funding: The study was funded by Shionogi BV. The authors would like to acknowledge Grace Wilson, of Ashfield Healthcare Communications, part of UDG Healthcare plc for medical writing support that was funded by Shionogi BV and Sarah King and Katy Wilson, of York Health Economics Consortium, University of York for support with study selection and data extraction that was funded by Shionogi BV.

Competing Interests: MB reports grants and personal fees from Angelini, Cidara, Menarini, MSD, Pfizer and Shionogi, and personal fees from Astellas, Basilea, Biomerieux, Nabriva and Paratek. JR reports recent grants or consulting/speakers bureau from AstraZeneca, Roche, Anchoagen, Novartis and Pfizer. FB has participated in advisory boards and/or received speaker honoraria from AstraZeneca, Bayer, Chiesi, GSK, Grifols, Guidotti, INSMED, Menarini, Mylan, Nabriva, Novartis, Pfizer, Roche and Zambon. HG, GS, LT and EZ report no conflicts of interest. MA and RM are employees of York Health Economics

Consortium who were paid consultancy fees by Shionogi to carry out the review. JP received consultancy fees from York Health Economics Consortium who were funded by Shionogi BV to carry out the review. CL and JL are full-time employees of Shionogi BV. DM was a full-time employee of Shionogi BV during the conduct of the study and is a current full-time employee of Qiagen Ltd. KT is an employee of Shionogi BV. SN is an employee of Shionogi Inc. SA reports grants and personal fees from Aradigm Corporation, Bayer Healthcare, Chiesi, Grifols and INSMED, and personal fees from Actavis UK Ltd, Astra Zeneca, Basilea, Horizon, Novartis, Raptor and Zambon.

Ethical Approval: Not required

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Figures

Fig. 1. Flow chart of literature search and article selection.

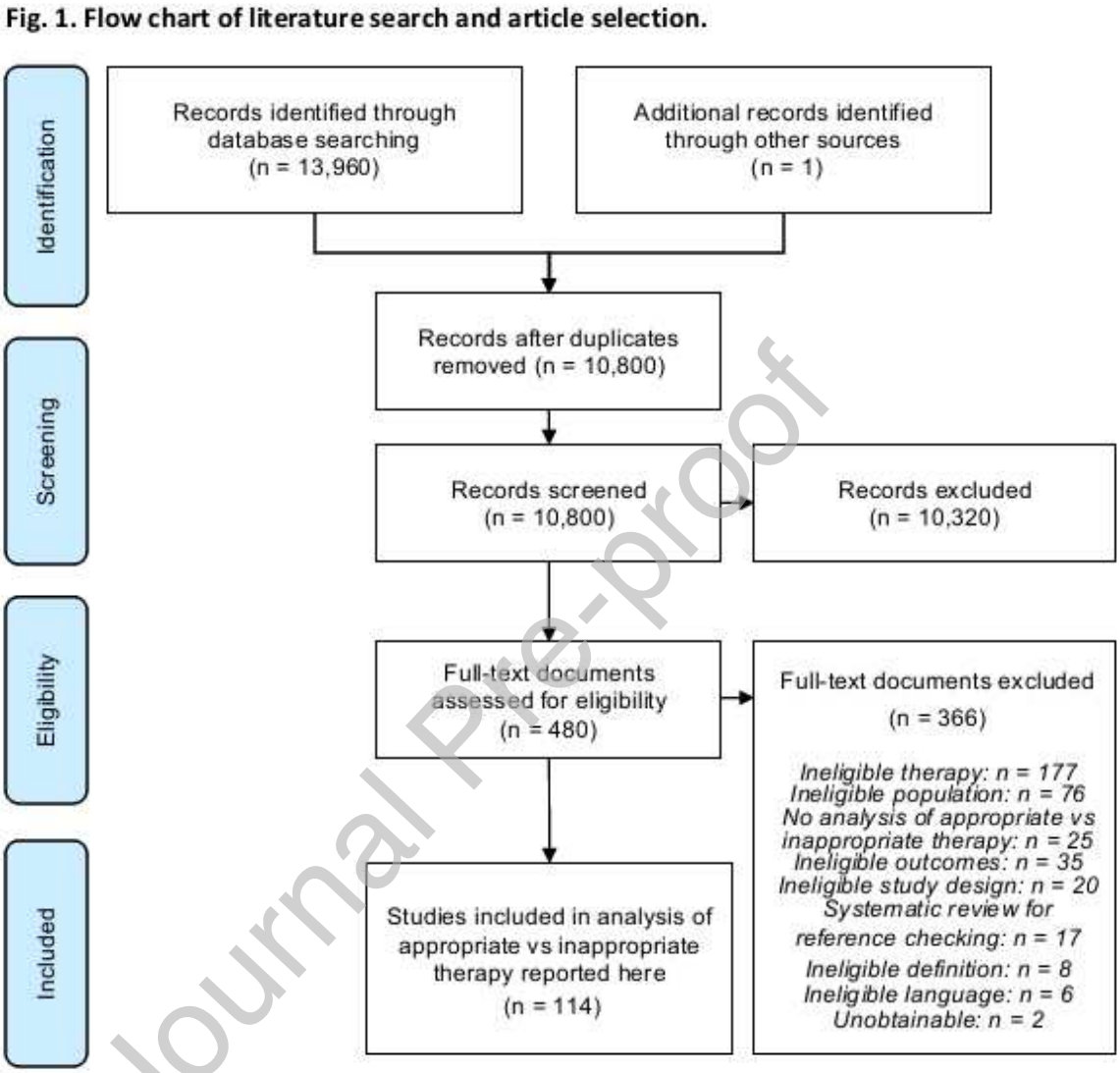
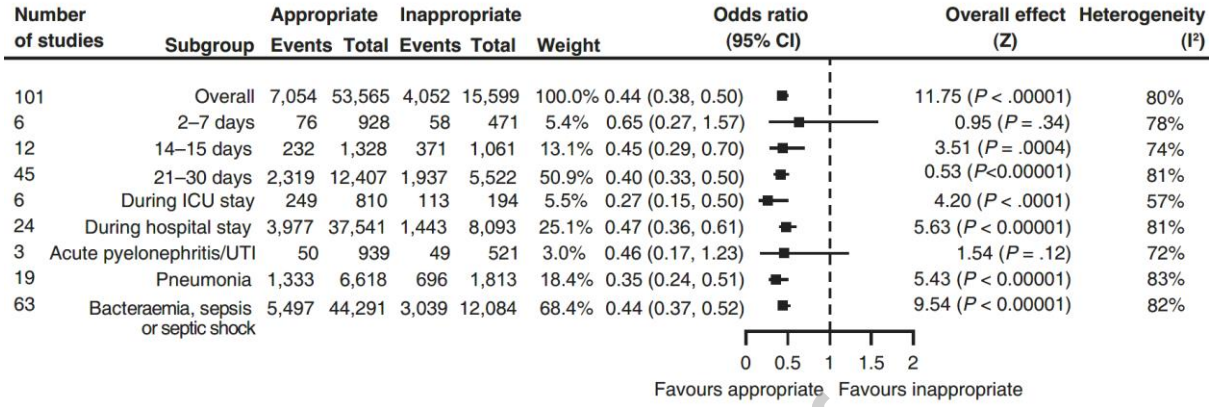
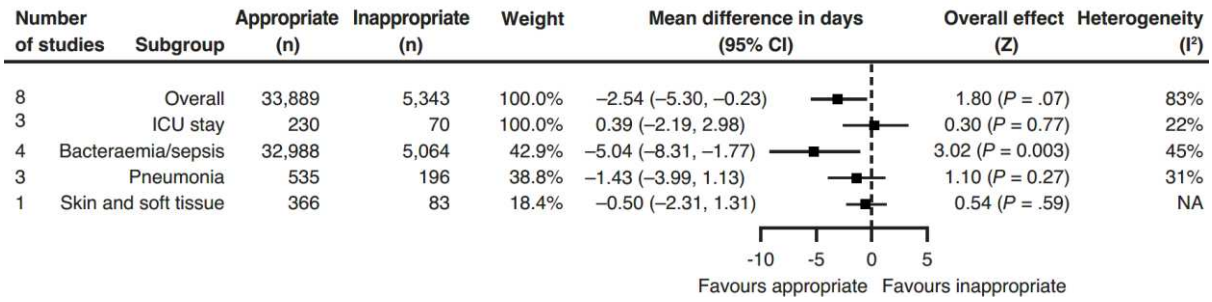


Fig. 2. Summary of effect of appropriate versus inappropriate antibiotic therapy on mortality.



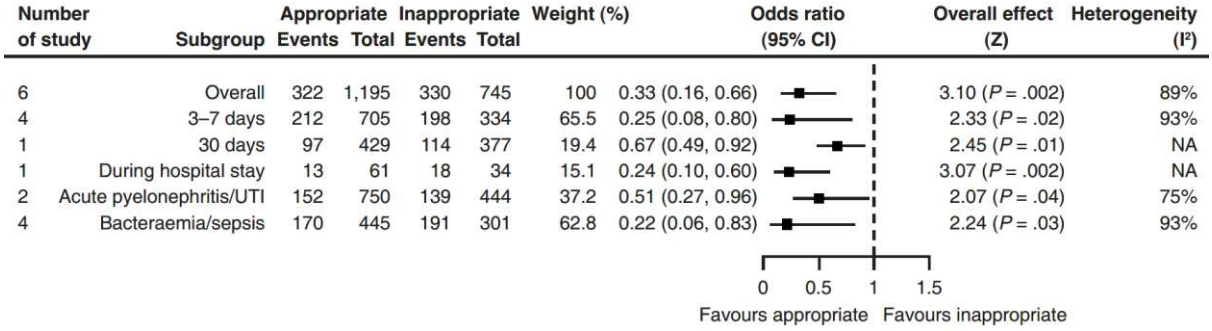
CI, confidence interval; ICU, intensive care unit; UTI, urinary tract infection.

Fig. 3. Summary of effect of appropriate versus inappropriate therapy on length of hospital stay.



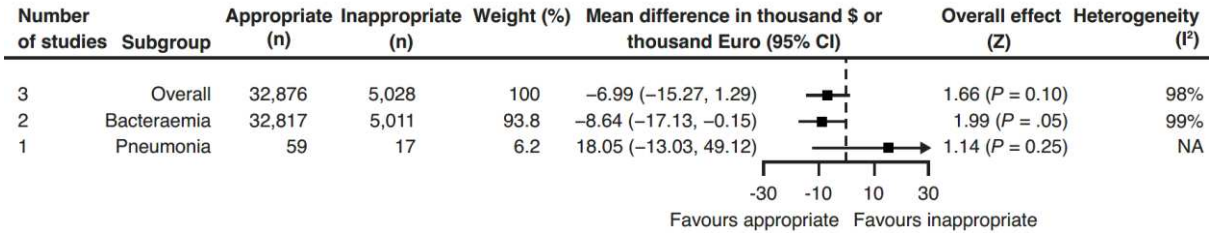
CI, confidence interval; ICU, intensive care unit; NA, not applicable.

Fig. 4. Summary of effect of appropriate versus inappropriate therapy on treatment failure.



CI, confidence interval; NA, not applicable; UTI, urinary tract infection.

Fig. 5. Summary of impact of appropriate versus inappropriate therapy on costs.



CI, confidence interval.