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A systematic review of the effect of delayed appropriate antibiotic treatment on the outcomes of patients with severe bacterial infections

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COI summary statement:

EZ reports no conflicts of interest. MB reports grants and personal fees from Angelini, Cidara, Menarini, MSD, Pfizer and Shionogi, and personal fees from Astellas, Basilea, Biomerieux, Nabriva and Paratek. 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. JR reports recent grants or consulting/speakers bureau from AstraZeneca, Roche, Anchoagen, Novartis and Pfizer. HG, GS and LT 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.

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Abbreviation list

CI = confidence interval

HR = hazard ratio

I^2 = heterogeneity

ICU = intensive care unit

OR = odds ratio

Z = overall effect size

Abstract

Background

Patients with severe bacterial infections often experience delay in receiving appropriate treatment. Consolidated evidence of the impact of delayed appropriate treatment is needed to guide treatment and improve outcomes.

Research Question

What is the impact of delayed appropriate antibacterial therapy on clinical outcomes in patients with severe bacterial infections.

Study Design and Methods

Literature searches of MEDLINE and Embase, conducted on 24 July 2018, identified studies published after 2007 reporting the impact of delayed appropriate therapy on clinical outcomes for hospitalised adult patients with bacterial infections. Where appropriate, results were pooled and analysed with delayed therapy modeled three ways: delay versus no delay in receiving appropriate therapy; duration of delay; and inappropriate versus appropriate initial therapy. This paper reports meta-analyses on the effect of delay and duration of delay.

Results

The eligibility criteria were met by 145 studies, of which 37 contributed data to analyses of effect of delay. Mortality was significantly lower in patients receiving appropriate therapy without delay compared with those experiencing delay (odds ratio [OR] 0.57 [95% CI, 0.45–0.72]). Mortality was also lower in the no delay group compared to the delay group in subgroups of studies reporting mortality at 20–30 days, during intensive care unit stay or in patients with bacteraemia (OR 0.57 [95% CI, 0.43–0.76]; OR 0.47 [95% CI, 0.27–0.80]; and OR 0.54 [95% CI, 0.40–0.75]). No difference was found in time to appropriate therapy

between those who died and those who survived (*P* = .09), but heterogeneity between studies was high.

Interpretation

Avoiding delayed appropriate therapy is essential to reduce mortality in patients with severe bacterial infections.

Study registration number

PROSPERO: CRD42018104669

Keywords

Appropriate antibiotic therapy

Treatment delay

Severe infections

Mortality

Introduction

Severe bacterial infections requiring in-hospital treatment are associated with considerable mortality, morbidity and healthcare costs.[1-3] Choice of antibiotic therapy is usually guided by culture-based antimicrobial susceptibility testing; more rapid diagnostic techniques can reduce delays in identifying antimicrobial susceptibility, but are not currently routine.[4] Physicians usually initiate antibiotic therapy before the causative pathogen and its drug-resistance profile are known. Increasing antibiotic resistance makes empiric antibiotic selection more difficult as fewer appropriate treatments are available for resistant pathogens and there is heightened pressure to limit unnecessarily broad-spectrum antibiotic use in patients without resistant infections, to preserve antibiotic susceptibility.[5] This creates the challenge of providing early appropriate therapy while limiting unnecessary antibiotic use with limited diagnostic information. As a result, many patients with severe bacterial infections experience delays in receiving appropriate antibiotics.

The negative consequences of delayed appropriate therapy are widely reported and accepted, and the importance of initiating prompt, appropriate, empiric antibiotic therapy is stressed in guidelines for several types of infection.[6,7] In a retrospective analysis of 17,990 patients with severe sepsis and septic shock, time to first antimicrobial treatment was found to be important for survival.[8] Delayed time to effective treatment of Gram-negative infections has also been shown to impact negatively on hospital length of stay and costs.[9] A consolidated systematic review of the effect of delayed appropriate antibiotic therapy is not currently available; evidence is needed to help physicians identify the likelihood of negative outcomes and guide treatment decisions to optimise prompt appropriate antibiotic therapy for patients most at risk.

The objective of this systematic review was to assess the impact of delayed appropriate antibacterial therapy on outcomes of patients hospitalised with severe bacterial infections. Outcomes of interest included mortality, treatment success/failure, duration and progress of

infection, length of hospital/intensive care unit (ICU) stay and healthcare costs. This article focuses on the impact of delay and time to appropriate antibiotic therapy.

Methods

This systematic review was undertaken according to the principles in the Cochrane handbook and guidance from the Centre for Reviews and Dissemination.[10,11] The protocol was published in the PROSPERO database (CRD42018104669; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=104669).

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.

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.

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).[11-13]

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.

Cut-off times reported for the definition of delay varied between studies and ranged from >1 hour to >5 days (Supplementary Table 2). 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.[10] 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.

Results

Literature searches identified 10,800 unique records for screening; 10,320 were excluded after assessment of the title and abstract. The full texts of 478 documents were assessed and 145 studies, reported in 147 records, were eligible for inclusion. Of these, 37 studies reported comparison of delay versus no delay in receiving appropriate therapy[14-35] and/or time to appropriate therapy[17,21,26,29,31,34,36-50] and are included in this analysis (Fig 1; Supplementary Table 2).

Description of studies

Although 37 studies reported some data relating to the impact of delayed appropriate antibiotic therapy, this was not generally their focus; none had a robust design to assess causality between antibiotic delay and outcomes. In particular, the lack of randomisation and comparability of confounding factors should be noted.

Three prospective cohort studies,[19,23,30] 32 retrospective cohort studies[14-18,20-22,24-29,31,32,34,35,37-50] and two case-control studies[33,36] were included. Two studies were carried out internationally[15,43] and 35 in single countries across Europe,[21,23,30,33,37,42] Asia[15,19,20,22,24,25,27,29,31,32,35,36,40,45] and the Americas[14,16-18,26,28,34,38,39,41,44,46-50] (most commonly the USA [10 studies],[16,26,28,34,38,39,46-48,50] Canada [5 studies][14,17,18,44,49] and Turkey [3 studies]).[20,32,36] Sample sizes ranged from 31 to 40,137 patients; 26 studies analysed data from 100 or more patients.[15-18,20,23-31,34,35,37-40,42-44,47,48,50]

Of the 35 cohort studies, 23 (66%) did not report sufficient description of the groups or distribution of prognostic factors.[15-17,19-22,24-27,30-32,35,37,38,41,42,45-47,49] In all 34 studies, confounding factors were either not comparable across groups or this was unclear, and in seven studies, adjustment for confounding factors was considered inadequate or unclear.[15,19,21,30,38,41,49] Of the two case-control studies, one included only 36 patients and it was unclear whether the sample was representative.[36]

Patient characteristics

Six studies were conducted in ICUs.[14,19,32,35,42,45] The average length of hospital stay prior to infection ranged from 0 to 24 days and 25 to 74% of participants had a history of ICU stay prior to infection, with average length of stay ranging from 5 to 25 days.

Participant age ranged from 15 to 102 years[25] and average age ranged from 47 to 71 years.

Most studies (85%) included infections due to various organisms and 14 reported infections caused by a single pathogen,[15,16,18-24,32,33,41,47,49] most commonly *Staphylococcus aureus* (five studies)[19,22-24,49] and *Streptococcus pneumoniae* (three studies).[16,18,21] Six studies included only infections caused by pathogens resistant to at least one class of antibiotic, or producing extended-spectrum beta-lactamases or carbapenemases.[19,32,33,36,41,43]

Six studies included patients with a variety of infection sites or sources,[19,25,32,41,44,50] 18 only included patients with bacteraemia[17,20-24,27-29,33-36,39,43,47-49] and eight studies included patients specifically with pneumonia.[14,16,18,30,38,40,45,46] Sepsis and meningitis were specifically included in three[26,31,42] and two studies,[15,37] respectively (Supplementary Fig 1).

Most studies reported data on the severity of illness of patients, which varied considerably across studies. The most common methods used to assess severity of illness were the Charlson Comorbidity score (17 studies, scores ranging from 1.9–7), and the Acute Physiology and Chronic Health Evaluation score (10 studies, scores ranging from 13.3–24.7; Supplementary Table 3).

Impact of delayed appropriate therapy

Nineteen studies compared mortality in patients without delay in receiving appropriate therapy with that of patients who experienced delay.[14,17,19-21,23,24,26-35,42,47] In total, 2,546 patients experienced delayed appropriate antibiotic therapy and 6,778 did not. In the pooled analysis, mortality was significantly lower in the no delay group compared to the delayed

group (OR 0.57 [95% CI, 0.45–0.72]; Fig 2, Supplementary Fig 2). Mortality was also lower in the no delay group compared to the delay group in the subgroups of studies reporting mortality at 20–30 days after diagnosis or treatment initiation and during ICU stay (OR 0.57 [95% CI, 0.43–0.76] and OR 0.47 [95% CI, 0.27–0.80], respectively). In the subgroup of studies reporting mortality during hospitalisation, the difference in mortality between patients with no delay in appropriate therapy and those with delay was not significant (OR 0.66 [95% CI, 0.43–1.03]). In subgroup analyses by infection site, mortality was numerically lower in the no delay group compared to the delay group, and this difference was significant for patients with bacteraemia (OR 0.54 [95% CI, 0.40–0.75]). In the subgroup analyses by Gram-negative or Gram-positive pathogen, mortality was significantly lower in the no delay group for patients with infections caused by Gram-negative pathogens; no significant difference was seen in patients with infections caused by Gram-positive pathogens (Fig 2, Supplementary Figure 3). Six studies reported APACHE II scores of >15, indicating severely ill patients populations.[19,26,29,32,33,47] In these studies, mortality was significantly lower with no delay in antibiotic therapy versus with delay (OR 0.50 [95% CI, 0.31–0.82], Fig 2, Supplementary figure 4).

Meta-analyses on the effect of delayed appropriate antimicrobial therapy on treatment failure, infection duration, infection progress and length of hospital or ICU stay were not possible due to limited numbers of studies (see the supplementary information).

Effect of delay duration

Seven studies reported mortality as a function of time to appropriate therapy.[29,34,36,38-40,42] Mean time to appropriate therapy ranged from 3.8 to 166 hours in patients who had died and from 1.8 to 67.2 hours in those who survived. In the pooled analysis, there was no significant difference in time to appropriate therapy between those who died and those who survived (mean difference 2.71 h [95% CI, −0.45–5.86]). However, heterogeneity between studies was high (Fig 3, Supplementary Fig 5). No significant difference was identified in time to

appropriate therapy between those who died and those who survived in subanalyses by infection type, but few studies were included (one study each in patients with pneumonia[38] and septic shock[42] and four in patients with bacteraemia).[29,36,39,40]

Eight studies reported mortality by multiple periods of time to appropriate therapy; four found a significant effect (Fig 4).[17,29,34,37,38,45-47] Three studies reported an overall hazard ratio (HR) or OR for death according to delay duration and two found a significant effect: Gutierrez-Gutierrez reported a HR for death per day of delay of 1.02 (95% CI, 1.01–1.04; $P < .0001$)[43]; Schweizer reported a HR for death per day of delay of 0.79 (95% CI, 0.60–1.03; not significant)[48]; and Hamandi reported an OR for death per hour of delay of 1.012 (95% CI, 1.006–1.018; $P < .001$).[44]

Meta-analyses on the effect of time to appropriate therapy on clinical response, length of hospital or ICU stay, and hospitalisation costs were not possible due to limited numbers of studies (see supplementary information).

Discussion

This systematic review showed a high prevalence of delayed appropriate antibiotic therapy in hospitalised patients with severe bacterial infections (27% of patients in the analysis of mortality). Mortality was significantly lower in patients who did not experience delayed appropriate antibiotic therapy compared with patients who did (OR 0.57 [95% CI, 0.45–0.72]). These findings are consistent with those of a large retrospective cohort study of 56,357 patients with Gram-negative infections that was published after our searches.[9] This study found an approximately 20% higher risk of in-hospital mortality or discharge to hospice in patients who experienced delayed appropriate antibiotics compared with those who did not, regardless of the antibiotic susceptibility of the causative pathogen.

In subgroup analyses, the impact of delay was significant for patients with bacteraemia who represent a key population also from a microbiological perspective, where the source and cause of infection is often clear; patients with pneumonia and septic shock showed numerically higher mortality rates with delayed appropriate therapy compared with those not experiencing delay.;. However, outcomes by infection site were reported in few studies. Another study in patients with ventilator-associated pneumonia, which was excluded from our analysis due to a lack of detailed outcomes, also reported no impact of delayed appropriate therapy on mortality.[51] Difficulties in definitively diagnosing pneumonia make it likely that many patients will have been misdiagnosed with this infection,[52] diminishing the ability to measure an association between delayed antibiotic therapy and outcome. In contrast, this issue would be much less pronounced for cases with bacteraemia. Due to limited data, it was not possible to perform subgroup analyses by individual pathogens; however, a subgroup analysis of Gram-negative versus Gram-positive pathogens indicated that the impact of delay was significant for patients with infections caused by Gram-negative pathogens but not significant for those caused by Gram-positive pathogens. Furthermore, a subgroup analysis of six studies reporting mortality in severely ill patients (APACHE II score

>15) showed that delay in antibiotic therapy significantly impacted patient mortality. Collectively, these findings may suggest that prompt antibiotic therapy is most important for severely ill patients with Gram-negative infections. However, it should be noted that the study numbers included in these sub analyses are very small, and studies were not developed to assess particular patient populations or pathogens. Future research is required in order to gain clear understanding of the impact of delayed antibiotic therapy on mortality by pathogen, severity or illness and site of infection. This would provide novel information to guide physicians on the priority infections for rapid administration of appropriate antibiotic therapy in the emergency departments and intensive care units.

The high heterogeneity in time to appropriate therapy between studies may be partly explained by the varying infecting organisms and associated drug-resistance profiles. Infections in the Balkan (2014) study were all carbapenem resistant,[36] in Cheng (2016), 79% of causative pathogens were resistant to at least one fluoroquinolone and 53% were multidrug resistant,[40] and in Zasowski (2017), 56% and 63% of infections were resistant to ampicillin and vancomycin, respectively.[34] In studies where resistance was less prevalent, time to appropriate therapy would be expected to be short and in studies where the majority of patients had drug-resistant infections, time to appropriate therapy would likely be much longer. However, details of resistance were not reported in the majority of studies and site-specific prescribing practices are unknown.

There is significant focus on the development of rapid diagnostic techniques to determine antimicrobial susceptibility.[53-56] As meta-analyses of outcomes following different durations of delay to appropriate treatment were not performed, it is not possible to specify a time point by which techniques should aim to deliver antibiotic-susceptibility results; however, reduced delay times were generally associated with improved outcomes.

This study has several limitations. Due the volume of literature, a pragmatic search approach was taken to balance precision and sensitivity and we therefore supplemented database

searches with a methodical citation search. The impact of delayed appropriate therapy was not generally the focus of the studies: none randomised participants to different antibiotic timings and none had a robust design to assess causality between antibiotic delay and outcomes. As such, determining the exact timing of appropriate therapy in the included studies is difficult, particularly for retrospective studies. In particular, the lack of comparability of confounding factors is a serious concern. It is also noted that point estimates of effect used in our meta-analyses were unadjusted. Patient populations varied across the studies in terms of disease characteristics including the type and severity of illness, and there was heterogeneity in how delayed therapy and outcomes were measured and how missing data were handled. The available information on diagnostics and susceptibility profiling also varied across studies; however, where information was available, most studies referred to culture methodologies only. For inclusion, reports had to provide a definition of “appropriate” therapy and an identifiable delay, but these definitions were not consistent across studies. Definitions of appropriate antibiotics usually included therapy to which the causative organism was eventually found to be susceptible *in vitro*; dosages and pharmacokinetic/pharmacodynamic properties were not usually considered but may be relevant. For example, high dosages or extended infusions of beta-lactams, as used in current practice for *Pseudomonas* pneumonia, are associated with improved outcomes even in "resistant" organisms.[57] In addition, breakpoints for definition of susceptibility *in vitro* differ between guidelines and have been changed over time.[58,59] Furthermore, the definitions used did not incorporate the concerns of overuse of broad spectrum antibiotics reported in some published studies.[60,61] It was not possible to discern from the papers included in this study whether broad spectrum overuse resulted in inappropriate treatment, and this is a limitation. Lastly, antimicrobial resistance is a constantly evolving issue, making the data presented in this analysis potentially already outdated at the time of submission. Many countries are reporting rising levels of resistance, and outbreaks of multidrug resistant organisms are increasing in prevalence.[62] With this continued spread and rise in resistance, it may be

anticipated that the issue of delay to appropriate antibiotic therapy will continue, and may even become more problematic where rising resistance limits available treatment options.

Interpretation

Patients with severe bacterial infections are often seriously ill and can deteriorate quickly, and physicians may need to initiate treatment before the causative pathogen and its drug-resistance profile are confirmed. The results of this analysis underscore the importance of providing appropriate therapy early in the course of infection to improve meaningful outcomes such as mortality. This provides support for the recommended approach of early broad-spectrum empiric therapy, followed by de-escalation to targeted treatment, rather than use of antibiotic escalation strategies. Results also highlight the need for increased availability of rapid techniques to determine antibiotic susceptibility to identify patients with or without drug-resistant infections. This would facilitate rapid de-escalation of broad-spectrum therapy and rapid escalation in cases where empiric therapy is not optimal for the causative pathogen.

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Author contributions

RM takes responsibility for the content of the manuscript, including the data and analysis.

EZ and MB contributed to protocol development, data analysis and writing of this report. FB contributed to manuscript review and editing. HG and JR contributed to protocol development, data analysis and writing of this report. GS contributed to protocol development, and writing of this report. LT 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.

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Disclosures

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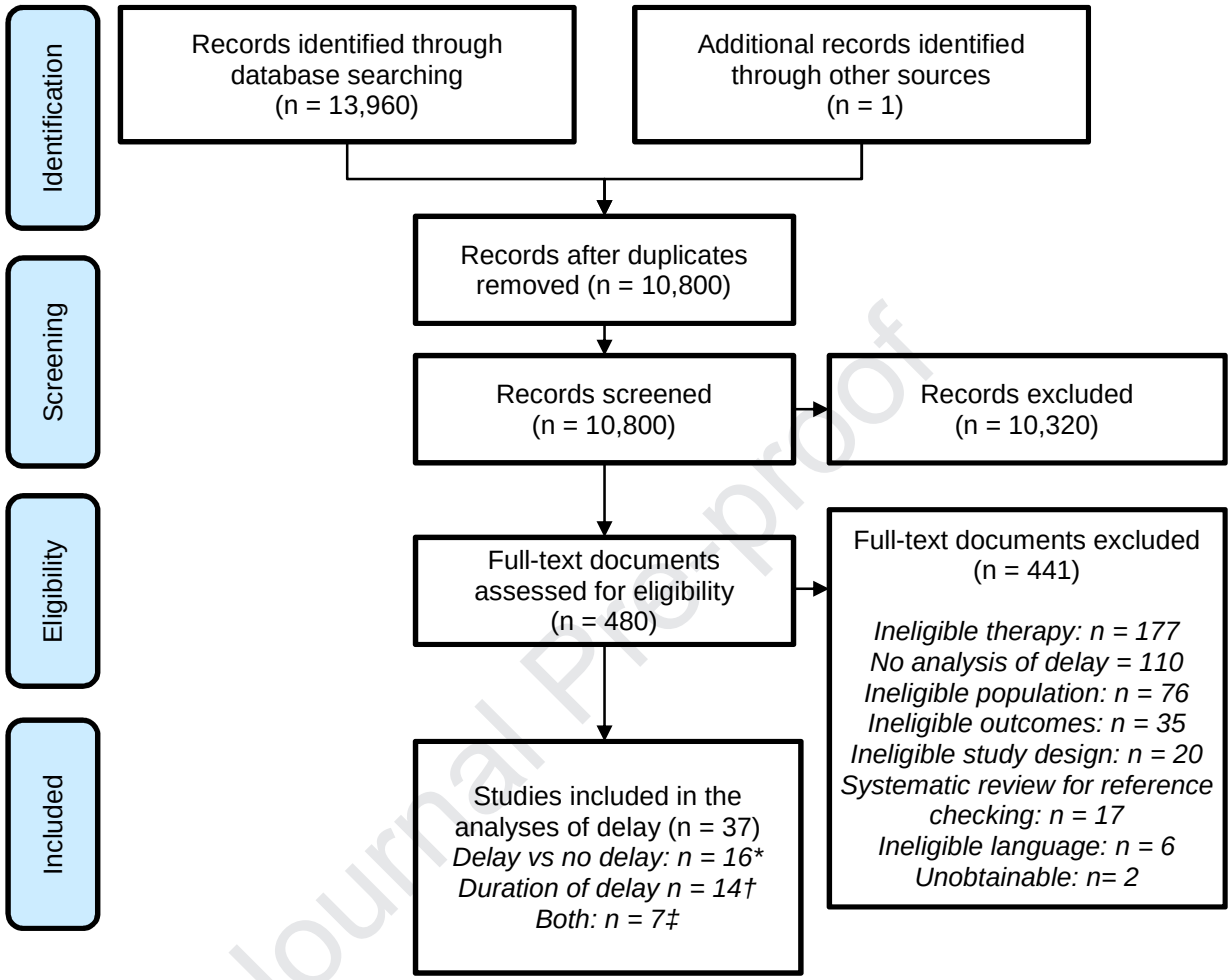
Figures

Figure 1: Flow chart of literature search and article selection.



* n = 5 studies were also included in analysis of appropriate versus inappropriate therapy.
† n = 7 studies were also included in analysis of appropriate versus inappropriate therapy.
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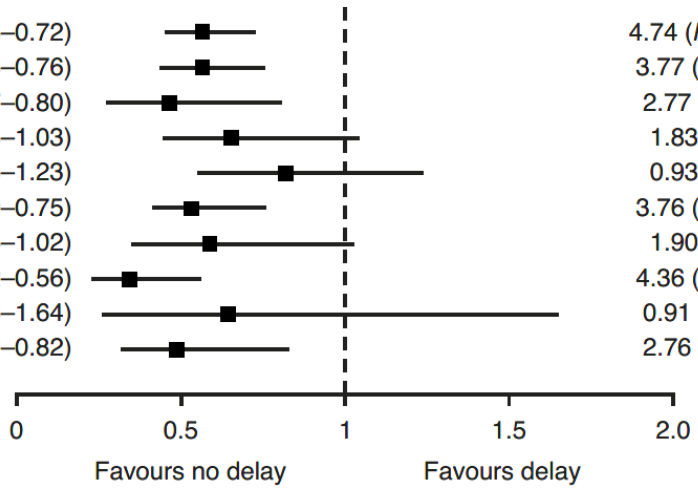
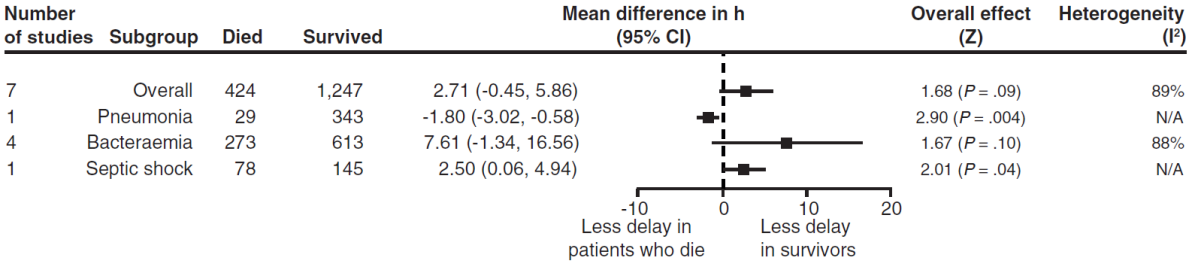
Figure 2. Summary of effect of delay versus no delay in receiving appropriate antibiotics on mortality.

Number of studies	Subgroup	No delay Events	No delay Total	Delay Events	Delay Total	Odds ratio (95% CI)	Overall effect (Z)	Heterogeneity (I^2)
19	Overall	953	6,778	643	2,546	0.57 (0.45–0.72)	4.74 ($P < .00001$)	50%
13	20–30 days	838	6,381	403	2,056	0.57 (0.43–0.76)	3.77 ($P = .0002$)	62%
3	During ICU stay	66	218	42	96	0.47 (0.27–0.80)	2.77 ($P = .006$)	0%
3	During hospital stay	49	179	198	394	0.66 (0.43–1.03)	1.83 ($P = .07$)	0%
3	Pneumonia	205	1,990	46	591	0.83 (0.55–1.23)	0.93 ($P = .35$)	5%
11	Bacteraemia	570	4,092	344	1,460	0.54 (0.40–0.75)	3.76 ($P = .0002$)	60%
2	Septic shock	136	579	28	70	0.59 (0.34–1.02)	1.90 ($P = .06$)	0%
5	Gram -ve pathogens	93	579	69	145	0.35 (0.22–0.56)	4.36 ($P < .0001$)	0%
4	Gram +ve pathogens	88	466	51	177	0.65 (0.26–1.64)	0.91 ($P = .036$)	62%
6	APACHE II score >15	120	298	328	608	0.50 (0.31–0.82)	2.76 ($P = .006$)	42%



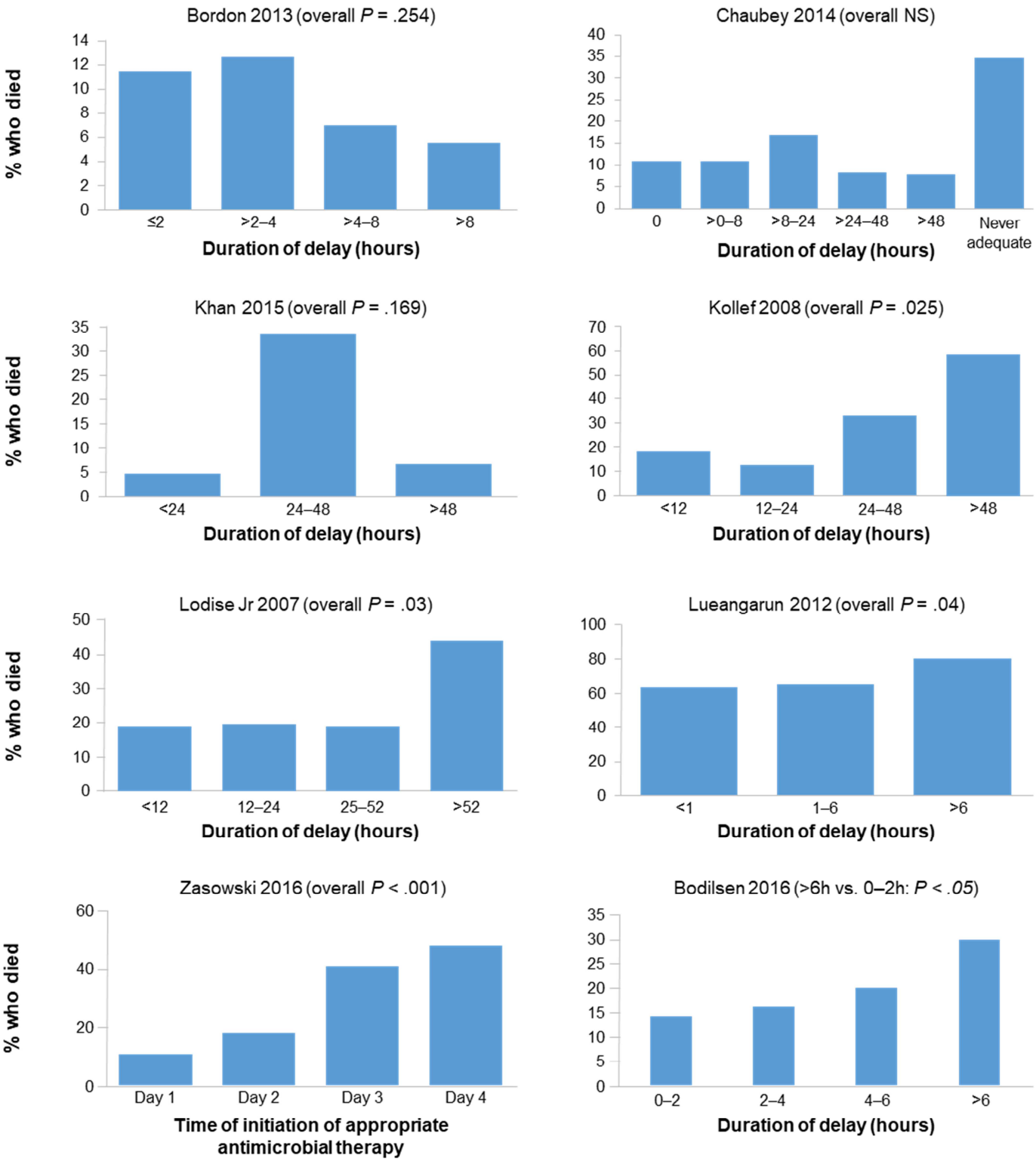
CI = confidence interval.
ICU = intensive care unit.

Figure 3. Effect of duration of delay to appropriate therapy on mortality.



CI = confidence interval.
NA = not applicable.

Figure 4. Effect of duration of delay to appropriate therapy on mortality.



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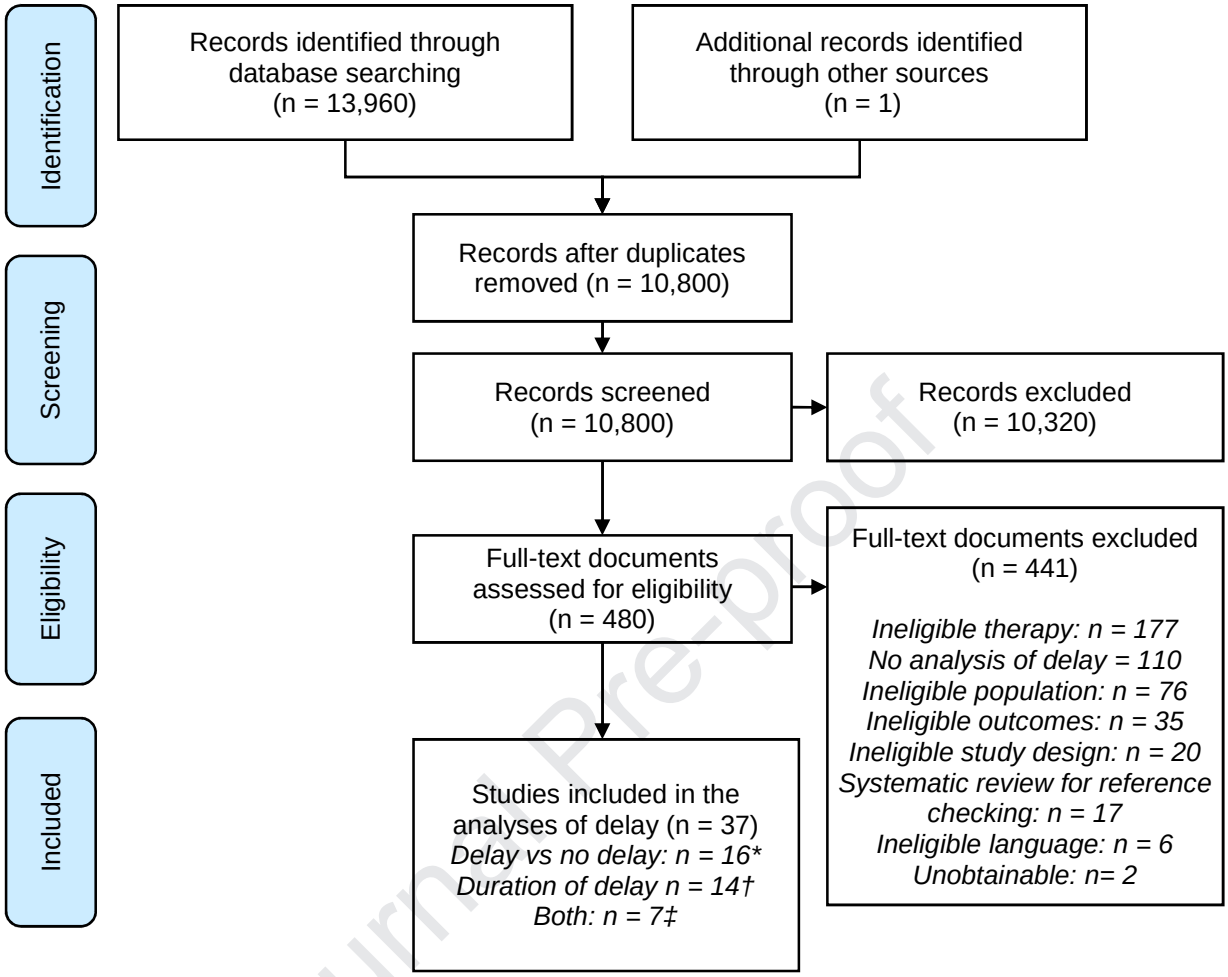

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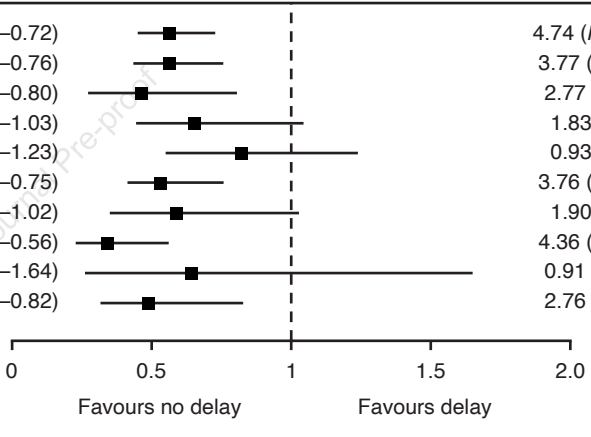
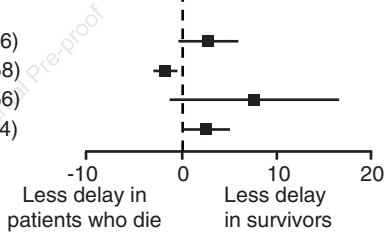
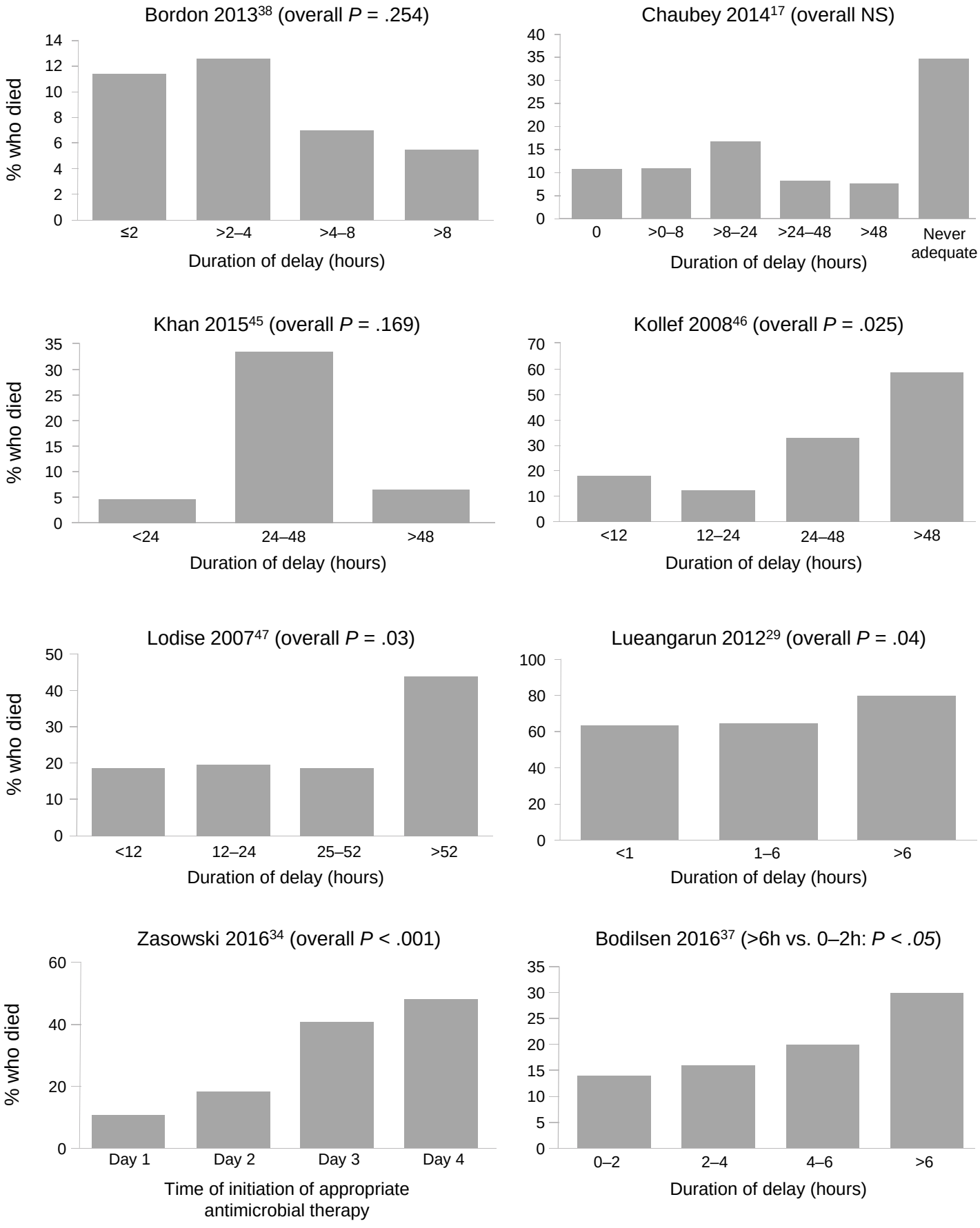


CI = confidence interval.
ICU = intensive care unit.

Number of studies	Subgroup	Died	Survived	Mean difference in h (95% CI)	Overall effect (Z)	Heterogeneity (I^2)
7	Overall	424	1,247	2.71 (-0.45, 5.86)	1.68 (P = .09)	89%
1	Pneumonia	29	343	-1.80 (-3.02, -0.58)	2.90 (P = .004)	N/A
4	Bacteraemia	273	613	7.61 (-1.34, 16.56)	1.67 (P = .10)	88%
1	Septic shock	78	145	2.50 (0.06, 4.94)	2.01 (P = .04)	N/A




Bordon 2013[38] (overall P = .254)
% who died
14
12
10
8
6
4
2
0
≤2
>2–4
>4–8
>8
Duration of delay (hours)
Chaubey 2014[17] (overall NS)
40
35
30
25
20
15
10
5
0
0
>0–8
>8–24
>24–48
>48
Never adequate
Duration of delay (hours)
Khan 2015[45] (overall P = .169)
% who died
35
30
25
20
15
10
5
0
<24
24–48
>48
Duration of delay (hours)
Kollef 2008[46] (overall P = .025)
70
60
50
40
30
20
10
0
<12
12–24
24–48
>48
Duration of delay (hours)
Lodise 2007[47] (overall P = .03)
% who died
50
40
30
20
10
0
<12
12–24
25–52
>52
Duration of delay (hours)
Lueangarun 2012[29] (overall P = .04)
100
80
60
40
20
0
<1
1–6
>6
Duration of delay (hours)
Zasowski 2016[34] (overall P < .001)
% who died
60
40
20
0
Day 1
Day 2
Day 3
Day 4
Time of initiation of appropriate antimicrobial therapy
Bodilsen 2016[37] (>6h vs. 0–2h: P < .05)
35
30
25
20
15
10
5
0
0–2
2–4
4–6
>6
Duration of delay (hours)