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Rapid versus standard antimicrobial susceptibility testing to guide treatment of bloodstream infection (Review)

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[Intervention Review]

Rapid versus standard antimicrobial susceptibility testing to guide treatment of bloodstream infection

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ABSTRACT

Background

Rapid antimicrobial susceptibility tests are expected to reduce the time to clinically important results of a blood culture. This might enable clinicians to better target therapy to a person's needs, and thereby, improve health outcomes (mortality, length of hospital stay), and reduce unnecessary prescribing of broad-spectrum antibiotics; thereby reducing antimicrobial resistance rates.

Objectives

To assess the effects of rapid susceptibility testing versus standard susceptibility testing for bloodstream infections (BSIs).

Search methods

To identify studies with selected outcomes, we searched the Cochrane Infectious Diseases Group Specialised Register, CENTRAL, MEDLINE, LILACS, and two trials registries, between 1987 and October 2020. We used 'bloodstream infection' and 'antimicrobial susceptibility tests' as search terms. We had no language or publication status limitations.

Selection criteria

Randomized controlled trials (RCTs) comparing rapid antimicrobial susceptibility testing (with a time-to-result of ≤ 8 hours) versus conventional antimicrobial susceptibility testing in people with a BSI caused by any bacteria, as identified by a positive blood culture.

Data collection and analysis

Two review authors independently screened references, full-text reports of potentially relevant studies, extracted data from the studies, and assessed risk of bias. Any disagreement was discussed and resolved with a third review author. For mortality, a dichotomous outcome, we extracted the number of events in each arm, and presented a risk ratio (RR) with 95% confidence interval (CI) to compare rapid susceptibility testing to conventional methods. We used Review Manager 5.4 to meta-analyse the data. For other outcomes, which are time-to-event outcomes (time-to-discharge from hospital, time-to-first appropriate antibiotic change), we conducted qualitative narrative synthesis, due to heterogeneity of outcome measures.

Main results

We included six trials, with 1638 participants. For rapid antimicrobial susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.10, 95% CI 0.82 to 1.46; 6 RCTs, 1638 participants; low-certainty evidence). In subgroup analysis, for rapid genotypic or molecular antimicrobial susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.02, 95% CI 0.69 to 1.49; 4 RCTs, 1074 participants; low-certainty evidence). For phenotypic rapid susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.37, 95% CI 0.80 to 2.35; 2 RCTs, 564 participants; low-certainty evidence).

In qualitative analysis, rapid susceptibility testing may make little or no difference in time-to-discharge (4 RCTs, 1165 participants; low-certainty evidence). In qualitative analysis, rapid genotypic susceptibility testing compared to conventional testing may make little or no difference in time-to-appropriate antibiotic (3 RCTs, 929 participants; low-certainty evidence). In subgroup analysis, rapid phenotypic susceptibility testing compared to conventional testing may improve time-to-appropriate antibiotic (RR -17.29, CI -45.05 to 10.47; 2 RCTs, 564 participants; low-certainty evidence).

Authors' conclusions

The theoretical benefits of rapid susceptibility testing have not been demonstrated to directly improve mortality, time-to-discharge, or time-to-appropriate antibiotic in these randomized studies. Future large prospective studies should be designed to focus on the most clinically meaningful outcomes, and aim to optimize blood culture pathways.

PLAIN LANGUAGE SUMMARY

Tests for identifying the most suitable antibiotics for a bacterial blood infection: are rapid tests better than standard tests?

What is the aim of this Cochrane Review?

People with blood infections need urgent treatment with antibiotics. Identifying the bacteria causing the infection helps ensure the right antibiotic is given. Rapid susceptibility tests are a technology to do this quickly, and aim to improve care. We sought to evaluate whether their use reduce deaths or shortens the illness.

Key messages

Rapid susceptibility tests to identify an appropriate antibiotic quickly for people with blood sepsis may make little to no difference to:

· how many people die within 30 days of diagnosis of blood sepsis;

· how long people stay in hospital;

· whether given a suitable antibiotic.

Larger studies will help determine if using rapid susceptibility tests improves these outcomes.

What was studied in this review?

Susceptibility tests are done in a laboratory, and measure whether bacteria can grow when exposed to a variety of antibiotics, to assure that the antibiotics given are active against the organism causing the infection. The standard approach is to culture the blood samples, but this takes up to 36 hours to obtain a result. Rapid tests to identify bacteria causing blood infections, and their susceptibilities to antibiotics, provide results in eight hours or less. These rapid susceptibility tests include:

· tests that look at the direct effect of antibiotics on bacteria (called phenotypic tests); and

· tests that look for particular genes in the bacteria to see if they are susceptible, or resistant, to an antibiotic (called genotypic tests).

What are the main results of this review?

We found six studies that involved 1638 adults with blood infections. All studies took place in specialized medical centres in high-income countries in Europe, the USA, and East Asia.

Compared with standard tests, rapid susceptibility tests may make little to no difference to

· how many people died within 30 days (evidence from six studies in 1638 people);

· how long people stayed in hospital (4 studies in 1165 people); or

· how long it took for people to be given the right antibiotic to treat the infection (5 studies in 1493 people).

Phenotypic rapid susceptibility tests may reduce the time it takes to receive the right antibiotic; but this is uncertain (evidence from 2 studies in 564 people).

Genotypic rapid susceptibility tests may make little or no difference to the time it takes to receive the right antibiotic (evidence from 4 studies in 1074 people).

Our confidence in the results is limited because:

· the numbers of deaths reported in the studies were too low to show an important difference;

· the tests used and the results from the studies varied widely;

· the studies did not include enough participants to enable firm conclusions.

Further research is likely to change these results.

How up to date is this review?

We included evidence published up to 21 October 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Rapid susceptibility methods versus standard methods versus placebo for bloodstream infection

Rapid susceptibility methods versus convention methods versus placebo

Patient or population: people with bloodstream infections
Setting: hospitals (in Europe, USA, and East Asia)
Intervention: rapid susceptibility methods
Comparison: standard of care (conventional susceptibility methods)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	Risk with rapid susceptibility methods				
Mortality	101 per 1000	111 per 1000 (82 to 147)	RR 1.10 (0.82 to 1.46)	1638 (6 studies)	⊕⊕⊖⊖ Low[a,b]	Rapid AST may make little or no difference to mortality.
Mortality (subgroup genotypic)	119 per 1000	121 per 1000 (82 to 177)	RR 1.02 (0.69 to 1.49)	1074 (4 studies)	⊕⊕⊖⊖ Low[a,b]	Rapid genotypic AST may make little or no difference to mortality.
Mortality (subgroup phenotypic)	73 per 1000	101 per 1000 (59 to 173)	RR 1.37 (0.80 to 2.35)	564 (2 studies)	⊕⊕⊖⊖ Low[a,b]	Rapid phenotypic AST may make little or no difference to mortality.
Mortality (with stewardship)	85 per 1000	98 per 1000 (70 to 137)	RR 1.17 (0.81 to 1.70)	1404 (4 studies)	⊕⊕⊖⊖ Low[a,b]	Rapid AST with stewardship may make little or no difference to mortality.
Mortality (without stewardship)	184 per 1000	175 per 1000 (100 to 292)	RR 0.89 (0.35 to 2.27)	234 (2 studies)	⊕⊕⊖⊖ Low[a,b]	Rapid AST without stewardship may make little or no difference to mortality.
Time-to-discharge from hospital *(days)*	None of the studies demonstrated a difference in time-to-discharge between methods.			1165 (4 studies)	⊕⊕⊖⊖ Low[c]	We were unable to meta-analyse the data. Rapid AST may make no little or no difference to time-to-discharge from hospital.

Time-to-appropriate antibiotic	Two studies using phenotypic susceptibility testing, reported a reduction in time-to-appropriate antibiotic with rapid susceptibility testing. Three studies using molecular susceptibility testing reported no difference. Two studies using antimicrobial stewardship, reported a reduction in time-to-appropriate antibiotic with rapid susceptibility testing. Two studies using antimicrobial stewardship and one not using it reported no difference. Two studies using rapid identification, reported a reduction in time-to-appropriate antibiotic with rapid susceptibility testing. Two studies using rapid identification and one using conventional identification plus rapid susceptibility testing reported no difference.	1493 (5 studies)	⊕⊕⊖⊖ Low[c]	Rapid AST may make little or no difference to time-to-appropriate antibiotic.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **AST**: antimicrobial susceptibility testing.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded by one level for indirectness; this review pools different interventions, and includes studies looking at single gene resistance traits, and those with and without stewardship interventions.
[b]Downgraded by one level for imprecision. As the control group event rate was < 1%, a larger sample size than the total number of participants across trials would be required to show a clinically important difference.
[c]Downgraded by two levels for imprecision; data were presented as means or medians rather than time-to-event data, and the standard deviations or interquartile ranges indicated a broad range.

BACKGROUND

Description of the condition

Bloodstream infections (BSIs) can be defined as the presence of viable bacteria or fungi in the blood that is associated with infection (Laupland 2014). Blood culture is the reference standard for detection of these micro-organisms in blood (Baron 2013). BSIs can be categorized as primary infections, defined as those not secondary to an infection at another body site, and secondary infections, where organisms are seeded from a site-specific infection at another body site, for example a pneumonia. In primary BSIs, organisms can enter the bloodstream through broken skin or mucous membranes, gastrointestinal tract, or by the direct introduction of contaminated material to the bloodstream (Reimer 1997).

Positive blood cultures do not always signify BSI, and can represent contamination or the transient presence of bacteria in the blood that do not cause clinical illness.

Incidence estimates for BSI vary from 166 to 204 episodes per 100,000 person-years in North America and Europe (Goto 2013). BSI is common in sub-Saharan Africa, with a reported incidence of 574 episodes per 100,000 person-years (Deku 2019), with a higher risk in the immunocompromised (Reddy 2010).

BSIs are often associated with sepsis, defined as life-threatening organ dysfunction due to a dysregulated host response to infection (Rhodes 2017). Sepsis can occur in the absence of detectable bloodstream infection. Given the complex nature of the condition and its diagnosis, it is impossible to give precise estimates for the global burden of disease from sepsis. However, the World Health Organization (WHO) estimates that there are up to 31 million global cases of sepsis and 24 million global cases of septic shock, with the clinical conditions resulting in sepsis accounting for up to six million deaths (WHO 2017).

Observational studies have found that inappropriate empirical antimicrobials and delays in the initiation of appropriate antibiotic therapy are risk factors for mortality in sepsis, with a progressive increase in mortality with increasing delays (Ferrer 2014; Kumar 2006; Kumar 2009; Paul 2010). By necessity, the evidence for the antibiotic treatment of sepsis is observational, as randomized controlled trials (RCTs) would be unethical. Notwithstanding this, sepsis guidelines emphasize early broad-spectrum antimicrobial treatment, aimed at ensuring adequate therapy to reduce mortality.

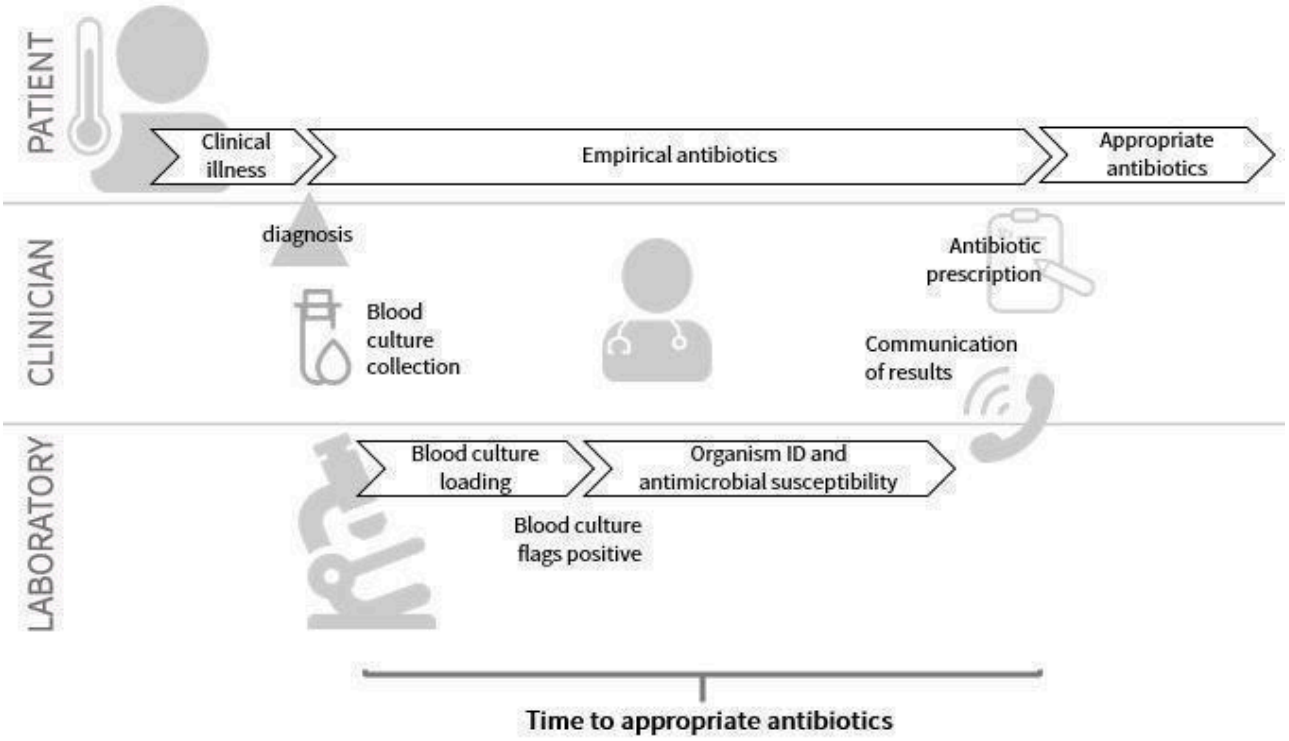
The use of early broad-spectrum antimicrobials has led to concerns that people are exposed to overuse of antimicrobials, which may result in antimicrobial resistance (Silva 2013). Guidelines recommend that antimicrobial therapy be targeted to a specific pathogen, if this is identified microbiologically (Rhodes 2017). The use of targeted therapy is regarded as an important component of antimicrobial stewardship, defined as a set of actions that promote the responsible use of antimicrobials (Dyar 2017).

Description of the intervention

The parallel global drives to improve both the treatment of severe infections associated with BSI and to avoid antimicrobial resistance have catalysed new strategies to reduce the turnaround time between the collection of blood culture samples and the reporting of antimicrobial susceptibility results. Purported benefits of reduced turnaround times include reduced morbidity and mortality, improved care, reduced healthcare costs, and reduced antimicrobial resistance (PHE 2014).

Figure 1 depicts an overview of the conventional laboratory diagnosis and clinical management of BSI. A clinician collects a blood culture from a person with possible BSI, sends it to the microbiology laboratory, and may commence empirical antibiotics. Upon receipt, the laboratory staff load the blood cultures into an incubator. Different blood culture systems then use a variety of methods to detect micro-organisms, and the culture bottles will flag positive if detected. Time-to-positivity is the time between the collection of the culture and the time at which the culture flags positive, and is typically 12 to 24 hours.

Figure 1. Time to appropriate antibiotics: time to first appropriate antibiotic (from collection time of positive blood culture to start of an antibiotic which has in vitro activity versus the identified organism)



After the blood culture flags positive, laboratory staff remove the blood culture from the machine, and conduct a Gram stain and microscopy. Laboratory staff then conduct subcultures to isolate one or more organisms, and use either conventional culture methods or rapid testing to report organism identification and antimicrobial susceptibility. Using conventional methods, this period is typically a further 36 hours (Maurer 2017). Based on the report, the clinician either continues the antibiotics prescribed earlier, or changes them. Time-to-appropriate antibiotic is the time between the collection of the culture, and the time at which targeted antibiotics are prescribed, according to the susceptibility result.

The advent of mass spectrometry over the past decade has greatly reduced the time between the blood culture flagging positive and the identification of the microorganism, known as time-to-identification (Doern 2018). However, reducing the time between a blood culture flagging positive and the availability of the antimicrobial susceptibility results, is a more elusive target.

Antimicrobial susceptibility testing can be grouped into the following two main categories (Maurer 2017).

- Genotypic or molecular antimicrobial susceptibility testing: identifies the presence or absence of a resistance gene or its product. It can indicate to which antimicrobials the organism is unlikely to be susceptible. Genotypic testing may be conducted either directly on a blood sample or on an isolate.
- Rapid phenotypic antimicrobial susceptibility testing: describes the detection of growth in the presence of an antibiotic.

In recent years, numerous non-randomized controlled trials showed the utility of rapid susceptibility testing to improve the time between the identification of positive blood culture tests and the start of effective antimicrobial therapy. This now ranges between seven and nine hours for rapid susceptibility testing (Pardo 2015; Pilmis 2019; Verroken 2016), compared to 25 to 36 hours for conventional testing. However, this review will only consider randomized controlled trials; we will not examine observational and non-randomized studies.

For the purpose of this review, antimicrobial susceptibility testing may be conducted on positive blood culture samples, agar culture isolates following incubation, or on whole blood specimens, drawn directly from the person. Rapid tests include those that produce susceptibility results in ≤ 8 hours from the time the blood culture flags positive. This definition relates to the laboratory work day, during which batch testing is conducted one or more times per eight-hour working shift (Buehler 2015).

How the intervention might work

Rapid antimicrobial susceptibility tests are expected to reduce the time to clinically important results of a blood culture. This might allow clinicians to better target therapy to a person's needs, and thereby both improve the person's outcomes (mortality, morbidity, length of hospital stay), and decrease unnecessary prescribing of broad-spectrum antibiotics, thereby, reducing the rates of antimicrobial resistance.

Why it is important to do this review

Rapid susceptibility testing offers a theoretical benefit to a person's outcomes, with reduced time to targeted antibiotic therapy, and the potential to reduce morbidity and mortality. It also offers theoretical benefit to improve antimicrobial stewardship, and by implication, reduce antimicrobial resistance, which is a key concern globally. Notwithstanding the theoretical benefits, there is uncertainty in the evidence. This Cochrane Review may help reduce uncertainty regarding potential benefits of this emerging technology to a person's outcomes, and stewardship outcomes. It may guide clinicians and laboratories in the effective implementation of rapid susceptibility testing, and appropriate resource allocation to the technology. The review may also help direct future randomized controlled trials.

OBJECTIVES

To assess the effects of rapid susceptibility testing versus standard susceptibility testing for bloodstream infections (BSIs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People of any age with a BSI caused by any bacteria, as identified by a positive blood culture and clinical signs of infection.

Types of interventions

Experimental intervention

Rapid antimicrobial susceptibility testing, defined as an in vitro laboratory test to determine if an antimicrobial agent will be active in inhibiting the growth of an organism, conducted directly on a positive blood culture bottle, with a time-to-result ≤ 8 hours from the blood culture flagging positive. These may include molecular antimicrobial susceptibility tests or phenotypic antimicrobial susceptibility tests, using the definitions given above, and may include other methods not incorporated by these definitions, if they are identified by our search. Appendix 1 lists interventions that may meet these criteria.

Comparator

Conventional, routine, standard antimicrobial susceptibility techniques (automated systems, broth microdilution, manual susceptibilities, disc diffusion or e-tests).

Types of outcome measures

Primary outcomes

- Mortality (all-cause 30-day mortality, after date of positive blood culture)
- Time-to-discharge from hospital after positive blood culture, in days

Secondary outcomes

Time-to-appropriate antibiotic change to targeted or definitive therapy, measured as time from a positive blood culture result to a person's receipt of an antibiotic with in vitro activity against the identified organism. This may include:

- Switching from an empirical broad- to a narrow-spectrum antibiotic, or discontinuation of one or more antibiotics.
- Switching from an empirical narrow- to a broad-spectrum antibiotic, or initiation of one or more antibiotics.

Search methods for identification of studies

We attempted to identify all relevant studies, regardless of language or publication status (published, unpublished, in press, ongoing).

Electronic searches

We searched the following databases, using the search terms and strategy described in Appendix 2:

- Cochrane Infectious Diseases Group Specialized Register (searched 21 October 2020);
- Central Register of Controlled Trials (CENTRAL; 2020, Issue 10), published in the Cochrane Library (searched 21 October 2020);
- MEDLINE PubMed (1966 to 21 October 2020);
- Embase OVID (1947 to 21 October 2020); and
- LILACS BIREME (Latin American and Caribbean Health Science Information database; 1982 to 21 October 2020).

We also searched the World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp; searched 21 October 2020), and ClinicalTrials.gov (clinicaltrials.gov; searched 21 October 2020), for trials in progress, using "bloodstream infection*" and "antimicrobial susceptibility tests" as search terms.

Searching other resources

Reference lists

We checked the reference lists of all studies identified by the above methods, and of previously published reviews, and used the 'similar articles' function in PubMed to identify related studies and references.

Researchers and organizations

In addition to the electronic searches described above, we contacted authors of studies in progress.

Data collection and analysis

Selection of studies

Two review authors (VA and PH) independently screened references by title and abstract, according to the inclusion criteria. We only included studies that reported on at least one of our primary outcomes. We included studies that assessed a single resistance trait. We resolved any disagreement through discussion; we planned to discuss disagreements with a third author, but this was not necessary at the review stage. We obtained and assessed the full-text of potentially eligible articles. We listed studies we excluded after full-text screening and their reasons for exclusion in the 'Characteristics of excluded studies' table. We presented a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two review authors (VA and PH) independently extracted data using data extraction form. We planned to resolve any disagreement by discussion or through a third review author (TP), but there was no disagreement. For dichotomous outcomes (mortality), we extracted the number of events in each arm of the included RCTs. For all other outcomes, which were time-to-event outcomes, we planned to extract the log hazard ratio and its standard error from Cox proportional hazards models. Unfortunately, none of the included studies reported time-to-event outcomes with hazard ratios, instead reporting mean or median averages. We contacted study authors for data, but were unable to obtain these.

Assessment of risk of bias in included studies

Two review authors (VA and PH) independently assessed risk of bias using the Cochrane risk of bias tool, and resolved disagreement via discussion (Higgins 2011). We recorded the rationale used to determine the risk of bias in each of the six domains, for each included study. The six domains included: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

Measures of treatment effect

For mortality, a dichotomous outcome, we calculated risk ratio (RR), comparing rapid susceptibility testing to conventional methods, with respective 95% confidence intervals (CIs).

For all other outcomes, which are time-to-event outcomes (time-to-discharge from hospital and time-to-first appropriate antibiotic), we planned to use hazard ratios (HRs) with respective 95% CIs. However, as we were unable to extract HRs due to heterogeneity in outcome measures, we conducted a qualitative narrative synthesis.

Unit of analysis issues

When a trial with more than two arms contributed multiple comparisons to a particular meta-analysis, we combined treatment groups to avoid double-counting.

Dealing with missing data

We assessed missing data to ascertain whether it may be related to the outcomes. We contacted trial authors for clarification, and to request further information if missing data restricted the use of the study in quantitative synthesis. We only analysed available studies when data were missing at random.

Assessment of heterogeneity

We inspected the forest plots for overlapping CIs as an indicator of heterogeneity. We assessed the Chi^2 and I^2 tests of heterogeneity. For the purposes of this review, an I^2 statistic value > 75% indicated considerable heterogeneity. However, we did not consider this as a simple 'threshold', but instead, interpreted this in the context of the size and direction of events, the Chi^2 P value, and possible causes. Where heterogeneity remained considerable, we did not conduct meta-analysis.

Assessment of reporting biases

We did not generate funnel plots to assess reporting bias as fewer than 10 studies contributed to an outcome in meta-analyses.

Data synthesis

We meta-analysed data using Review Manager 5 (Review Manager 2020). We anticipated that we would find heterogenous populations and interventions, so we planned to use a random-effects model for meta-analysis for dichotomous data.

In addition to quantitative synthesis using meta-analysis, we conducted planned qualitative (narrative) synthesis, based on formal guidance. We were unable to meta-analyse time-to-event data due to heterogeneity in outcome measures. Therefore, for time-to-discharge and time-to-antibiotic, we used textual descriptions of studies, groupings and clusters, and tabulation (Popay 2006).

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses:

- Genotypic compared to phenotypic techniques
- Rapid susceptibility alone or in conjunction with antimicrobial stewardship
- Rapid susceptibility simultaneously with organism identification or without organism identification

Sensitivity analysis

We planned to do worst-case scenario, but we did not, because it would not have influenced our conclusions. We planned to conduct sensitivity according to high risk of bias, but we did not encounter any trials with high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We summarised our findings in a Summary of findings table. We presented the following primary and secondary outcomes: all-cause 30-day mortality after date of positive blood culture, time-to-discharge from hospital after positive blood culture, time-to-participant receipt of an antibiotic with in vitro activity versus the identified organism, time-to-de-escalation: switching from a broad- to a narrow-spectrum antibiotic or discontinuation of one or more antibiotics, time-to-escalation: switching from a narrow- to a broad-spectrum antibiotic or initiation of one or more antibiotics, as outlined in the Types of outcome measures section. We described the study settings, number of participants, and number of studies addressing each outcome.

We assessed the certainty of evidence using the GRADE approach (Guyatt 2011; GRADE 2014), and GRADEpro GDT software (GRADEpro GDT). We rated each important outcome as described by Balshem 2011.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

RCTs start as high certainty of evidence, but can be downgraded if there are valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias (Balshem 2011).

RESULTS

Description of studies

Results of the search

The search (3 December 2018, plus an updated search on 21 October 2020) identified 3192 studies, dated from 1987. After removing duplicates and screening titles and abstracts, we identified 45 potentially relevant studies, for which we obtained and reviewed the full text. We excluded 34 studies. Figure 2 illustrates the search results in a PRISMA flow diagram.

Figure 2. Flowchart of study selection

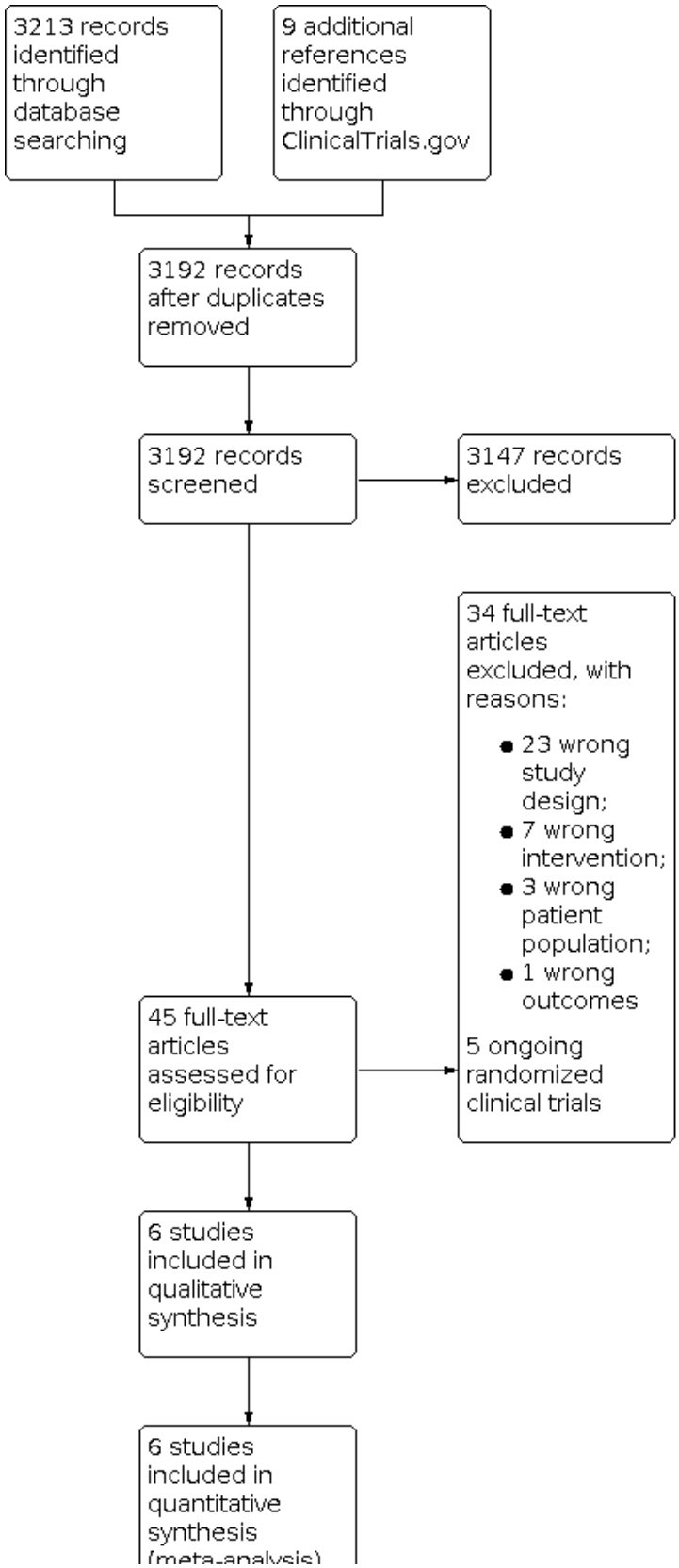
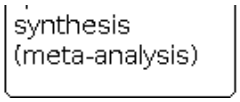


Figure 2. (Continued)



Authors' contacted

We contacted three authors of eligible studies to obtain additional data on reported outcomes and methods (Allaouchiche 1999; Beuving 2015; Emonet 2015). In addition, we approached two authors to request preliminary results of unpublished studies (Banerjee 2020; Kim 2021). One author contacted us back, providing us with the requested data (Banerjee 2020).

Included studies

Six randomized controlled trials (RCTs) met the inclusion criteria. All studies were conducted in tertiary care medical centres in high income settings. All studies included adults. Three studies included people with both gram-positive and gram-negative BSIs (Banerjee 2015; Beuving 2015; Kim 2021). Two studies included people with only gram-positive BSIs (Allaouchiche 1999; Emonet 2015)), and one included people with only gram-negative BSIs (Banerjee 2020). Kim 2021 included only people with known haematological malignancy, rather than a general hospital population.

Four studies used molecular testing platforms that detected only a limited number of resistance genes (Allaouchiche 1999; Banerjee 2015; Beuving 2015; Emonet 2015). Two studies used a rapid system to determine methicillin resistance in *Staphylococcus aureus* blood stream infection; Allaouchiche 1999 detected mecA/ gyrA genes, and Emonet 2015 detected mecA/ femA genes. Banerjee 2015 detected three antimicrobial resistance genes: mecA for *Staphylococcus spp.*; vanA/B for *Enterococcus spp.*; and bla_{KPC} for *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or a member of the family *Enterobacteriaceae*. Beuving 2015 used real-time polymerase chain reaction (PCR) to detect the presence of different resistance genes.

Only two studies used a phenotypic assay that provided the susceptibility interpretation based on a wide panel of antimicrobial agents that were tested (Banerjee 2020; Kim 2021). Banerjee 2020 used real-time morphokinetic cellular analysis by dark-field microscopy, whilst Kim 2021 used a method based on microscopic imaging analysis with microfluidic chip technology to provide susceptibility results.

In five studies, rapid susceptibility testing was conducted simultaneously with the identification of the bacteria (Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015; Kim 2021).

Characteristics of included studies showed reported proportion of resistant organisms: 49% (Kim 2021), 31% (Allaouchiche 1999), 19% (Banerjee 2020), 13% (Emonet 2015), 4% (Beuving 2015); see Table 1. Participants on inadequate empirical antibiotic accounted for 49% (Banerjee 2015), 28% (Emonet 2015), 26% (Beuving 2015), 25% (Allaouchiche 1999), and 16% (Kim 2021); see Table 2.

There were different approaches to antimicrobial stewardship interventions between studies. Two studies implemented a formal antibiotic stewardship program, combined with identification and antimicrobial susceptibility testing results of rapid and conventional group, including a Monday to Friday prospective audit and feedback, and a computer-based monitoring system of antimicrobials (Banerjee 2015; Banerjee 2020). Four studies provided the results and advice of the optimal antibiotic (Banerjee 2015; Banerjee 2020; Beuving 2015; Kim 2021), whereas two studies only communicated the results to the responsible medical team, without any antimicrobial advice from an infection specialist (Allaouchiche 1999; Emonet 2015). See Characteristics of included studies.

With respect to our primary outcomes:

- Mortality (all-cause 30-day mortality, after date of positive blood culture): all six studies provided data (Allaouchiche 1999; Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015; Kim 2021).
- Time-to-discharge from hospital after positive blood culture in days: four studies provided data (Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015).

With respect to our secondary outcome:

- Time-to-appropriate antibiotic change to targeted or definitive therapy: five studies provided data (Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015; Kim 2021).

See Characteristics of included studies for further details.

Excluded studies

We excluded 23 studies because they were not RCTs. We excluded seven studies because they used interventions that were not relevant. We excluded three studies that looked at the wrong population, and one study that reported outcomes that were not relevant for this review (see Characteristics of excluded studies).

Ongoing studies

We identified five ongoing studies, but could not find further information about when these were expected to publish (see Characteristics of ongoing studies).

Risk of bias in included studies

See Figure 3 and Figure 4 for a summary of the risk of bias assessments. Further details are available in the Characteristics of included studies table.

Figure 3. Risk of bias summary: a summary table of review authors' judgements for each risk of bias item for each study.

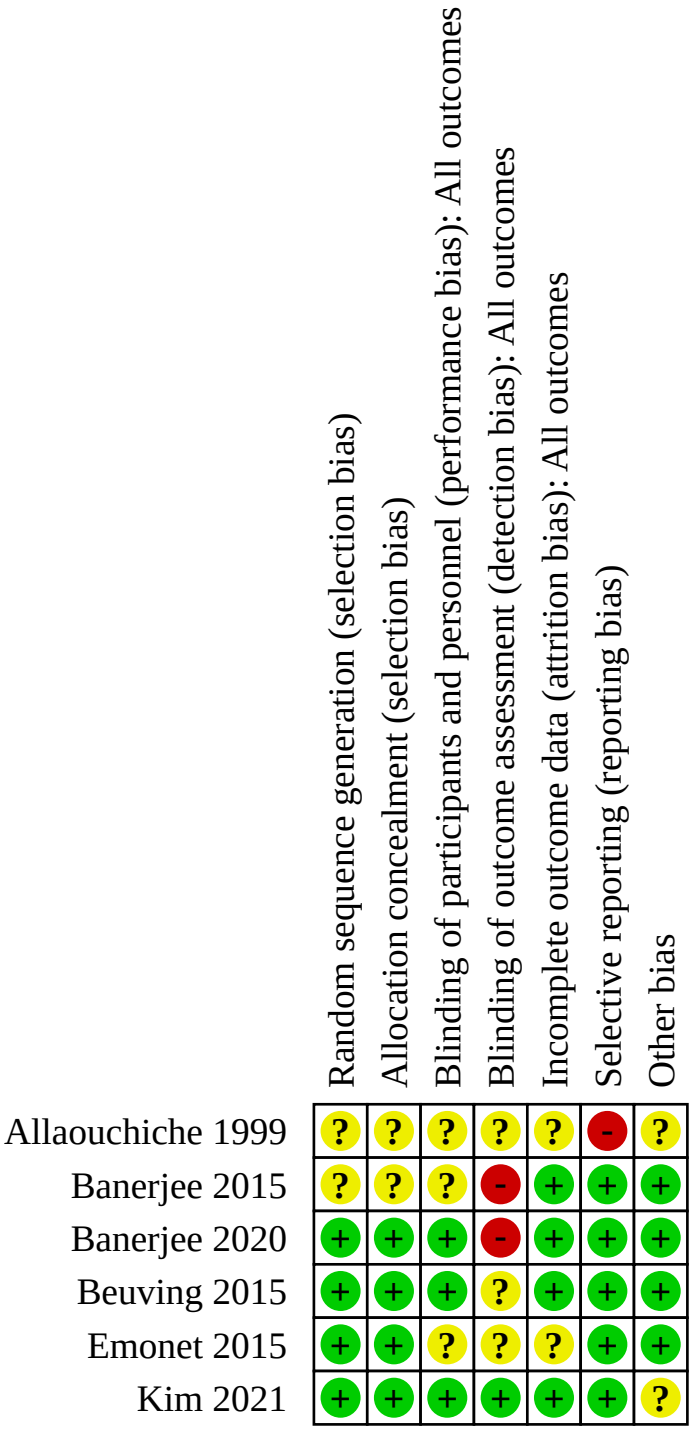
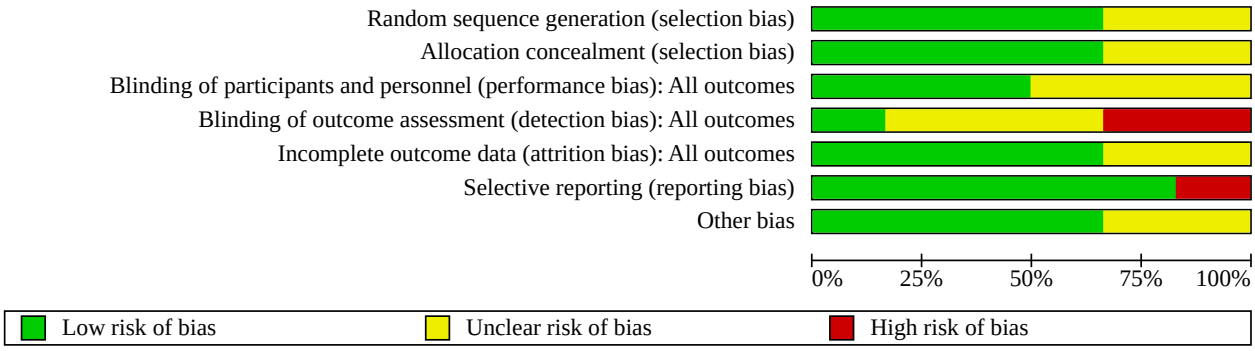


Figure 4. Risk of bias graph: a plot of the distribution of review authors' judgements across studies for each risk of bias item.



Allocation

We judged four studies to have low risk of selection bias, as they adequately described generation of allocation sequences (Banerjee 2020; Beuving 2015; Emonet 2015; Kim 2021). We judged two studies at unclear risk of selection bias, as study authors did not provide sufficient information (Allaouchiche 1999; Banerjee 2015).

Blinding

We judged one study at high risk of detection bias, and unclear risk of performance bias (Banerjee 2015). We judged three studies at low risk of performance bias, but unclear risk of detection bias (Banerjee 2020; Beuving 2015; Kim 2021). Description of blinding was unclear in two studies (Allaouchiche 1999; Emonet 2015).

Incomplete outcome data

We judged four trials at low risk of attrition bias (Banerjee 2015; Banerjee 2020; Beuving 2015; Kim 2021). We considered two trials at unclear risk of attrition bias (Allaouchiche 1999; Emonet 2015).

For the analysis of mortality, no data were missing. Heterogeneity for time-to-discharge and time-to-antibiotic stopped us from conducting a meta-analysis for these outcomes. However, the trial authors reported no missing data for time-to-discharge and time-to-antibiotic.

Selective reporting

We judged five trials at low risk of reporting bias (Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015; Kim 2021). We judged one trial at high risk of reporting bias (Allaouchiche 1999).

Other potential sources of bias

We judged four trials at low risk of other potential sources of bias (Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015), and two trials at unclear risk of other bias (Allaouchiche 1999; Kim 2021).

Effects of interventions

See: **Summary of findings 1** Rapid susceptibility methods versus standard methods versus placebo for bloodstream infection

Mortality

In pooled analysis, for rapid antimicrobial susceptibility testing compared to conventional methods, there was little or no difference in mortality between groups (RR 1.10, 95% CI 0.82 to 1.46; 6 RCTs, 1638 participants); see Analysis 1.1.

Subgroup analysis

For rapid genotypic or molecular antimicrobial susceptibility testing compared to conventional methods, there was little or no difference between groups (RR 1.02, 95% CI 0.69 to 1.49; 4 RCTs, 1074 participants); see Analysis 1.1. Two studies reported phenotypic rapid susceptibility testing compared to conventional methods, and reported little or no differences in mortality (RR 1.37, 95% CI 0.80 to 2.35, 2 RCTs, 564 participants); see Analysis 1.1.

For rapid susceptibility testing combined with antimicrobial stewardship compared to standard of care, there was little or no difference between groups (RR 1.17, 95% CI 0.81 to 1.70; 4 RCTs, 1404 participants); see Analysis 1.2.

When rapid identification and antimicrobial susceptibility results provided simultaneously on the same assay was compared with conventional method, there was little or no difference between groups (RR 1.25, 95% CI 0.77 to 2.03; 4 RCTs, 876 participants); see Analysis 1.3.

Time-to-discharge

Four trials reported time to discharge as median times with interquartile ranges (IQR (Banerjee 2015; Emonet 2015); N = 706), median time with range (Beuving 2015; N = 223), and mean with standard deviation (SD (Banerjee 2020); N = 448).

The included studies detected little or no differences in time-to-discharge between rapid antimicrobial susceptibility testing and conventional methods (Banerjee 2015; Banerjee 2020; Beuving 2015; Emonet 2015; N = 1377). Each study reported wide ranges or standard deviation; see Table 3

We were unable to conduct a meta-analysis for time-to-discharge using available data. We approached authors for additional data to conduct time-to-event analysis, but were unable to obtain this.

Time-to-appropriate antibiotic change to targeted or definitive therapy

Five studies reported time-to-appropriate antibiotic. Two reported median time (Banerjee 2015; Emonet 2015; N = 706); three reported mean time (Banerjee 2020; Beuving 2015; Kim 2021; N = 787).

Subgroup analysis

Rapid genotypic antimicrobial susceptibility testing compared to conventional methods, showed little or no differences in time-to-appropriate antibiotic (Banerjee 2015; Beuving 2015; Emonet 2015; N = 929); see Table 4.

In subgroup analysis, rapid phenotypic susceptibility testing compared to conventional testing showed reduced time-to-appropriate antibiotic (RR -17.29, CI -45.05 to 10.47; 2 RCTs, 564 participants); see Analysis 1.4.

Time-to-escalation and time-to-de-escalation of antibiotics

Participants whose culture underwent the antimicrobial stewardship intervention in addition to rapid susceptibility testing experienced appropriate de-escalation of antibiotics sooner (21 hours (IQR 7 to 37) versus 34 hours (IQR 21 to 55); P < 0.001), and appropriate escalation of antibiotics sooner (5 hours (IQR 2 to 22) versus 24 hours (IQR 3 to 67); P = 0.04) compared with conventional testing (Banerjee 2015; N = 617). Banerjee 2020 (N = 448) also found that it took less time to escalate antibiotics in the rapid susceptibility testing group combined with antimicrobial stewardship compared with the standard testing (18.4 hours (IQR 5.8 to 72) versus 61.7 hours (IQR 30.4 to 72); P = 0.01), but time to de-escalation showed little or no difference between groups.

We were only able to conduct a meta-analysis for time-to-appropriate antibiotic for the subgroup of rapid phenotypic testing. We approached trial authors for additional data to conduct time-to-event analysis, but were unable to obtain this.

DISCUSSION

Summary of main results

Summary of findings 1 summarizes the main results.

Rapid susceptibility testing compared to conventional testing may make little or no difference in 30-day mortality (6 RCTs, 1638 participants; low-certainty evidence).

In subgroup analysis, for rapid genotypic susceptibility testing compared to conventional methods, there was little or no difference between groups (4 RCTs, 1074 participants; low-certainty evidence). Two studies (564 participants) reported phenotypic rapid susceptibility testing compared to conventional methods, but the 95% confidence interval crossed the line of no effect, and this was low-certainty evidence. In subgroup analysis, for rapid susceptibility testing combined with antimicrobial stewardship compared to conventional testing, there was little or no difference between the groups (4 RCTs, 1404 participants; low-certainty evidence). Rapid identification and susceptibility testing may make no difference in mortality (4 RCTs, 876 participants; low-certainty evidence).

Rapid susceptibility testing may make little or no difference in time-to-discharge (4 RCTs, 1165 participants; low-certainty evidence).

Rapid genotypic susceptibility testing compared to conventional testing may make little or no difference in time-to-appropriate antibiotic (4 RCTs, 1165 participants; low-certainty evidence). In subgroup analysis, for rapid phenotypic susceptibility testing compared to conventional methods, may improve time-to-appropriate antibiotic, but the evidence is uncertain (2RCTs, 564 participants; low-certainty evidence).

Rapid susceptibility testing combined with antimicrobial stewardship may make little or no difference in time-to-appropriate antibiotic (4 RCTs, 1404 participants; low-certainty evidence). Rapid identification along with rapid susceptibility testing may make little or no difference in time-to-appropriate antibiotic (4 RCTs, 876 participants; low-certainty evidence).

Different factors may have influenced the differences observed in time-to-appropriate antibiotic between phenotypic and genotypic techniques, such as providing a panel of phenotypic susceptibilities for various antibiotics rather than having only one resistant gene marker to indicate possible resistance to a specific antibiotic. This may have helped in the selection of an appropriate antibiotic in a shorter time. The implementation of antimicrobial stewardship and the provision of rapid identification results, along with rapid susceptibility testing may also contribute to the differences observed in time-to-appropriate antibiotic.

Overall completeness and applicability of evidence

All six included studies were based in large academic teaching hospitals in Europe, the USA, and East Asia. Therefore, applicability of findings may be limited in other settings, which may have different interfaces between laboratory and clinical work. Factors specific to the laboratory workflow and technical resources available within clinical trials may influence the applicability of our findings to routine clinical practice.

People with gram-positive and gram-negative bloodstream infections (BSI) were only represented in two trials (Banerjee 2015; Kim 2021). The rest of the studies only included people with gram-positive BSI (Allaouchiche 1999; Beuving 2015; Emonet 2015), or only gram-negative BSI (Banerjee 2020). In particular, Emonet 2015 had a less representative participant spectrum, as this study focused on *Staphylococcus aureus,* using molecular susceptibility testing, which targeted the microorganism *S aureus,* and the detection of the mecA gene.

Banerjee 2020 and Kim 2021 showed a significant reduction in time-to-optimal antibiotic with the implementation of rapid phenotypic susceptibility testing and antimicrobial stewardship program. However, they detected no differences in clinical outcomes.

Interestingly, Banerjee 2015 did not observe significant improvement in time-to-appropriate antibiotic, despite the implementation of an antimicrobial stewardship program. This may be due to the characteristics of the genotypic rapid susceptibility testing method used, which looked at a restricted number of resistance genes (mecA, vanA/B, blaKPC) instead of the rapid phenotypic testing used in Banerjee 2020, which included a broad panel of antimicrobial susceptibility results. Secondly, Banerjee 2015 included gram-positive and gram-negative bacteria and fungi, whereas Banerjee 2020, only included gram-negative bacteria.

Antimicrobial resistance rates in the studied populations did not seem to have a direct influence on time-to-appropriate antibiotic. Kim 2021 found a shorter time-to-appropriate antibiotic when using rapid phenotypic testing, in a haematological population with high bacterial resistance rates. In contrast, Banerjee 2015 found no improvement in time-to-antibiotic with rapid genotypic susceptibility, in a population with similarly high resistance rates .

Finally, rapid identification may have played a role in reducing time-to-appropriate antibiotic when combined with both rapid susceptibility testing and antimicrobial stewardship (Banerjee 2020; Kim 2021). In contrast, rapid identification and susceptibility without antimicrobial stewardship did not show an improvement in time-to-antibiotics or in clinical outcomes (Beuving 2015; Emonet 2015).

There are several factors that may explain why expected clinical benefits have not been observed in this review. First, the antibiotic resistance rate of the included studies was quite variable with a reported low prevalence of antibiotic-resistant bacteria ranging from 4% to 19% in three studies (Beuving 2015; Emonet 2015; Banerjee 2020), moderate of 31% (Allaouchiche 1999) and high of 49% (Banerjee 2015; Kim 2021). Rapid AST may have a greater impact if the prevalence of antimicrobial resistance increases (Kim 2021).

Second, only around 25% (Allaouchiche 1999; Beuving 2015; Emonet 2015; Kim 2021), and 49% (Banerjee 2015) of the participants were on inadequate antibiotic therapy at the time of antimicrobial susceptibility results. This probably means that larger sample size would be needed to demonstrate differences in mortality and length of stay.

Third, for many organisms, rapid antimicrobial susceptibility testing may not have a great impact. However, people with infections caused by key pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant Enterococcus (VRE) or carbapenem-resistant Enterobacteriaceae (CRE) may benefit from rapid AST (Banerjee 2020; Kim 2021; Timbrook 2017).

Quality of the evidence

Certainty of the evidence

We found the evidence regarding the mortality outcome to be of low certainty; we considered that the data were indirect due to differing clinical interventions, including studies that looked at single gene resistance traits, and those with and without stewardship interventions. We also judged that the mortality data was imprecise, as the control group event rate was < 1%. A larger sample size than the total number of participants across trials would be required to show a clinically important difference. As the evidence pertaining to time-to-discharge and time-to-antibiotic was variably reported using means and medians, with evidence of wide standard deviations or interquartile ranges, we considered that the data were imprecise, and downgraded the certainty to low.

Potential biases in the review process

The key limitation in the review process was that we were not able to obtain time-to-event data to allow meaningful meta-analysis for time-to-discharge and time-to-appropriate antibiotic. Such a meta-analysis may have demonstrated a beneficial effect.

The heterogeneity in processes used in individual studies may represent a further potential bias. Banerjee 2015, Banerjee 2020, and Emonet 2015 reported time-to-appropriate antibiotic as time from Gram stain to effective in vitro antibiotic. Beuving 2015 and Kim 2021 defined time-to-appropriate antibiotic as time from blood draw to administration of the appropriate antibiotic. This heterogeneity in the time point measurement might have had an impact in time-to-antibiotic results, as time from blood drawing can be less controllable but more representative of true time-to-appropriate antibiotic than time from Gram stain. Notification methods and action taken on results varied between studies.

The results were phoned directly to the responsible clinician, who could take immediate action to change antimicrobial treatment (Banerjee 2015; Emonet 2015), or reported to the medical microbiologist or infectious diseases specialist, who then advised the attending clinician of the appropriate antibiotic therapy by telephone (Banerjee 2020; Beuving 2015; Kim 2021).

Heterogeneity in the epidemiological settings and microbiological methods of the trials, such as resistance traits assessed and bacteria targeted by the intervention, was observed between studies.

There was heterogeneity in antimicrobial stewardship interventions between different studies. Two studies implemented a formal antibiotic stewardship programme, and combined it with either rapid or conventional identification and antimicrobial susceptibility testing (Banerjee 2015; Banerjee 2020). Different studies found variable rates of antibiotic-resistant organisms and adequacy of empiric treatment; see Table 1; Table 2.

Agreements and disagreements with other studies or reviews

Observational studies assessing the clinical impact of rapid antimicrobial susceptibility testing for BSIs have shown a reduction in time-to-appropriate antibiotic, but did not report improvement in mortality or length of stay (Ehren 2020; Huang 2013; Nicolsen 2013; Pilmis 2019). Suzuki 2015 found a reduction in 30-day mortality with rapid susceptibility testing compared to standard care. However, this was a non-randomized observational prospective study, and results should be interpreted with caution.

A systematic review concluded that rapid diagnostic testing, including organism identification, resistance mechanism detection, or both, was associated with a decreased time-to-effective antibiotic, length of stay, and mortality, in the presence of an antimicrobial stewardship program (Timbrook 2017). However, these findings should be interpreted in view of certain limitations: most studies were pre- and post-intervention observational studies, only one randomized clinical trial showed a reduction in mortality when using rapid organism identification testing without susceptibility testing, and with no antimicrobial stewardship intervention (Ly 2008). This contrasts with a recent multicentre, randomized controlled trial that showed no reduction in patient mortality, despite using rapid identification testing alone (MacGowan 2020).

This is the first systematic review that exclusively considers rapid versus standard antimicrobial susceptibility testing for blood stream infections. Previous systematic reviews focused on the use of rapid diagnostics, including identification techniques, not only antimicrobial susceptibility testing (Timbrook 2017; Vardakas 2015). In addition, the majority of the systematic reviews on rapid diagnostics included heterogeneous studies designs (retrospective, prospective non-randomized trials, and prospective randomized trials), and concluded that the evidence is insufficient to support the use of rapid testing in daily practice.

AUTHORS' CONCLUSIONS

Implications for practice

The theoretical benefits of rapid susceptibility testing have not been shown in these randomized studies to directly improve mortality, time-to-discharge, or time-to-appropriate antibiotic, but the certainty of evidence is low.

Implications for research

It is likely that studies to date, and this meta-analysis, do not have large enough numbers to detect a difference in the most important outcomes. Adequately powered prospective studies should focus on reporting the most clinically meaningful outcomes. Studies should use time-to-event analysis rather than comparing average times, as the latter may mask important differences. Evaluation of clinical outcomes should also consider analyses based on the number of participants who are on effective or ineffective antibiotic therapy before susceptibility testing results are available. One possible outcome could be a combined time-to-appropriate antibiotic and stewardship outcome, which includes, for each participants, the time between which the blood culture sample was taken and the time at which the optimal antibiotic was administered, where optimal could be defined as the narrowest effective antibiotic based on antimicrobial susceptibility results.

Studies should be designed to optimise workflows to process blood cultures, to bridge any delays from the initial draw of blood culture samples to the final susceptibility results of blood cultures, and ensure the results are rapidly acted on to change the person's care. To date, rapid susceptibility testing is only available for blood culture specimens following one or two days of incubation, rather than directly on a person's blood sample. That delay may interfere with the real clinical impact of rapid testing for bloodstream infections. Therefore, more efforts are required to reduce the overall blood culture incubation time.

Rapid susceptibility results should always be followed with a direct communication of results. Studies should investigate how best results could be communicated, to ensure appropriate changes in antimicrobial therapy are made.

We did not conduct a cost-effectiveness analysis, as it was not one of our objectives for this Cochrane Review. Nevertheless, future studies are needed to evaluate the cost-effectiveness of the intervention.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allaouchiche 1999

Study characteristics	
Methods	Randomized controlled trial
Participants	Adult inpatients with positive blood cultures for *Staphylococcus aureus*

Allaouchiche 1999 *(Continued)*

	Included organisms: gram-positive bacteria (*S.aureus*) **Number of included participants:** 145 (73 rapid; 72 standard care)
Interventions	• **Only rapid antimicrobial susceptibility testing (AST) and standard identification (ID):** rapid AST using Multiplex-polymerase chain reaction (PCR) assay; detection of mecA, gyrA resistance genes; standard ID using cumpling factor, coagulase, heat-stable DNAse • **Standard AST and ID:** standard AST using traditional overnight technique, serial dilutions in Mueller-Hinton agar. Stardard ID cumpling factor, coagulase, heat-stable DNAse
Outcomes	• **Primary:** survival in intensive care unit; favourable infection outcome (defined as resolution of clinical signs, negative subsequent blood cultures) • **Secondary:** length of hospital stay; duration of treatment; antibiotic cost
Setting	Intensive care unit hospital, France
Other relevant laboratory techniques	
Notes	• **Prevalence of antibiotic resistance:** 31% (45/145) methicillin-resistant *Staphylococcus aureus* (MRSA) • **% of participants on inadequate antibiotic:** 25% (18/72) of participants in the rapid group • **Antimicrobial stewardship program:** no • **Communication of results and advice of the optimal antibiotic:** not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	Composite outcomes reported; mortality outcomes not reported by study group; secondary outcomes not reported
Other bias	Unclear risk	No information

Banerjee 2015

Study characteristics	
Methods	Randomized controlled trial; parallel group
Participants	Adults and children who had positive blood cultures between August 2013 and March 2014 **Included organisms:** gram-positive, gram-negative, and fungi (*S.aureus*, CoNs, *Enterococcus* spp, *Streptococcus* spp, Enterobacteriaceae, *Pseudomonas* aeruginosa, *Acinetobacter* spp, *Candida* spp) **Number of included participants:** 617 (198 rapid; 212 rapid and stewardship; 207 standard of care)
Interventions	• **Only rapid AST and standard ID**: rapid AST: rapid PBP2a testing plus FilmArray Blood Culture Identification (BCID) Panel is a polymerase chain reaction (PCR) panel that identifies 19 types of bacteria, 5 types of fungi, and select antimicrobial-resistance genes mecA, vanA/B, blaKPC; standard ID: MALDI-TOF • **Standard AST and ID**: standard AST: rapid PBP2a testing plus conventional bacterial culture (standard Mayo practices), specific technique not specified; standard ID: MALDI-TOF
Outcomes	• **Primary:** duration of antimicrobial therapy in the 4 days after enrolment • **Secondary:** 30-day mortality; length of stay; time-to-first active antibiotic; time-to-first appropriate de-escalation; time-to-first appropriate escalation
Setting	Mayo Clinic, Roshester, Minnesota
Other relevant laboratory techniques	MALDI-TOF (Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry)
Notes	• **Prevalence of antibiotic resistance:** not provided • **% of participants on inadequate antibiotic:** 49% (303/ 617) of all participants • **Antimicrobial stewardship program:** yes. Antimicrobial stewardship interventions were in place for all study groups, including Monday to Friday prospective audit and feedback and computer-based monitoring system of antimicrobials. • **Communication of results and advice of the optimal antibiotic:** yes • **3 study arms:** 1) standard of care. 2) rapid AST alone. 3) rapid AST and antimicrobial stewardship. For 1) and 2) results reported by telephone and by electronic medical reports in real time, with template comments to guide antimicrobial prescribing. For 3) telephone advice at the time of results available and over the 3 days following enrolment if a modification of antibiotic was appropriate.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Limited information; states randomization was stratified by age, ICU admission, and admission to solid organ or bone marrow transplant service
Allocation concealment (selection bias)	Unclear risk	Limited information; randomization appears to have taken place at laboratory level
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	High risk	'Laboratory technologists and investigators were not blinded to study arm assignment'.

Banerjee 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for exclusion after randomization clearly listed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Disclaimer that diagnostics company had no input on study design, collection, analysis, interpretation, or manuscript preparation

Banerjee 2020

Study characteristics	
Methods	Prospective randomized controlled trial
Participants	People who had a positive blood culture with Gram stain showing gram-negative bacteria, identified during laboratory business hours; October 2017 to October 2018 **Included organisms:** gram-negative bacteria (*E.coli*, Klebsiella species, Proteus species, Enterobacter species, *Pseudomonas aeruginosa*, *Serratia marcescens*, Citrobacter species, *Acinetobacter baumanii*) **Number of included participants**: 448 (226 standard of care; 222 intervention group)
Interventions	• **Rapid AST and rapid ID**: Accelerate PhenoTest™ BC Kit, performed on the Accelerate Pheno™ System (AXDX) – microscopy-based method by dark-field microscopy that enables single-cell analysis for ID and AST. Panel of antibiotics provided for AST included: TZP, piperacillin/tazobactam; CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; ATM, aztreonam; ETP, ertapenem; MEM, meropenem; AMK, amikacin; TOB, tobramycin; GEN, gentamicin; CIP, ciprofloxacin; CST, colistin; MIN, minocycline • **Standard AST and standard ID**: standard AST: broth micro-dilution or agar dilution; standard ID: MALDI-TOF
Outcomes	• **Primary:** time-to-first antibiotic modification within 72 hours after randomization • **Secondary:** in-hospital mortality within 30 days of randomization; length of stay in the hospital after randomization up to 30 days
Setting	2 academic medical centres in USA
Other relevant laboratory techniques	
Notes	• **Prevalence of antibiotic resistance:** 19% (84/448) resistant gram-negative bacteria • **% of participants on inadequate antibiotic:** not provided • **Antimicrobial stewardship program:** yes; all participants in both arms underwent prospective audit and feedback by institutional antimicrobial stewardship program • **Communication of results and advice of the optimal antibiotic:** yes; telephone advice by the antimicrobial stewardship physician or pharmacist to the attending doctor, if modifications to therapy were indicated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were assigned to each arm in a 1:1 ratio, using permuted blocks, stratified by site

Banerjee 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomization was conducted by laboratory technologists at the time the Gram stain detecting GNB was identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The primary service was unaware of group assignment at the time of randomization. Antimicrobial stewardship providers were not blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Once blood culture results became available, or AS interventions, or both, were made, treating providers may have been aware of group assignment due to faster reporting of ID and AST results using RAPID.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for exclusion after randomization clearly listed
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Disclaimer that diagnostics company had no input on study design, collection, analysis, interpretation, or manuscript preparation

Beuving 2015

Study characteristics	
Methods	Randomized controlled trial
Participants	People with a positive blood culture with gram-positive or aerobic gram-negative bacteria **Organisms included:** gram-positive (*Staphylococcus* spp, *Streptococcus* spp, *Enterococcus* spp) and gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli*) **Number of included participants:** 223 (114 rapid; 109 standard of care)
Interventions	• **Rapid AST and rapid ID:** RAMAST platform (real-time-PCR) for bacterial identification and detection of growth in the presence or absence of antibiotics • **Standard AST and ID:** standard sub-culturing and BD Phoenix Automated Microbiology System
Outcomes	• **Primary:** time-to-effective antibiotic from positive blood culture • **Secondary:** 30-day mortality; length of hospital stay
Setting	Maastrich University Medical Centre
Other relevant laboratory techniques	
Notes	• **Prevalence of antibiotic resistance:** 4% (4/96) enterobacteriaceae • **% of participants on inadequate antibiotic:** 26% of all participants • **Antimicrobial stewardship program:** no formal antibiotic stewardship programme • **Communication of results and advice of the optimal antibiotic:** telephone advice of the optimal antibiotic therapy by the medical microbiologist to the attending physician within 1 hour of obtaining the results
Risk of bias	

Beuving 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients randomised separately in blocks of four patients [...] according to a computer-generated list, which was not accessible to researchers"
Allocation concealment (selection bias)	Low risk	"Randomisation was performed by drawing a sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were unaware of the group for which they were randomised." Microbiologists could not be blinded due to shorter turnaround time.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 retrospective exclusions
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Disclaimer that diagnostics company had no input on study design, collection, analysis, interpretation, or manuscript preparation

Emonet 2015

Study characteristics	
Methods	Randomized controlled trial
Participants	All hospitalised adults (aged 18 years) with at least two positive bottles with gram-positive cocci in clusters in the tested set of blood cultures during weekdays (7 a.m. to 3 p.m.) were screened for inclusion. **Organisms included:** gram-positive bacteria (*S.aureus*, CoNs) **Number of included participants:** 89 (48 rapid; 41 standard of care)
Interventions	• **Rapid AST and rapid ID:** multiplex real-time PCR for identification and detection of mecA, femA resistance genes • **Standard AST and ID**: standard AST: disk diffusion method; ID: MALDI-TOF
Outcomes	• **Primary**: time-to-effective antibiotic from gram-stain result • **Secondary:** 28-day mortality; length of total hospital stay; length of stay in ICU
Setting	Division of Infectious Diseases, Geneva University Hospital, Geneva
Other relevant laboratory techniques	MecA resistance gene detection was only relevant to half of the participants included in the study, with *S. aureus* BSI 50% (53/100)
Notes	• **Prevalence of antibiotic resistance:** 13% (7/53) MRSA • **% of participants on inadequate antibiotic:** 28% (25/89) of all participants • **Antimicrobial stewardship program:** no formal antibiotic stewardship programme

Emonet 2015 *(Continued)*

- **Communication of results and advice of the optimal antibiotic:** not specified if antimicrobial advice given or only results provided. Results were reported to the attending physician and the attending infectious diseases specialist the same day they were available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised using the method of randomly permuted blocks."
Allocation concealment (selection bias)	Low risk	"Allocation concealment was simply sequential, that is each new patient satisfying inclusion criteria was given the next number in the randomization table by one of the co-investigators and thereby allocated to intervention or control group."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 excluded from intervention, 9 from control
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Three authors received honoraria from diagnostics companies. Consultancies were not linked with the present studies.

Kim 2021

Study characteristics	
Methods	Randomized controlled trial
Participants	People with haematological malignancies and at least one positive blood culture **Organisms included:** gram-positive and gram-negative bacteria **Number of included participants:** 116 (rapid 56; conventional 60)
Interventions	• **Rapid AST and rapid ID:** rapid phenotypic AST in addition to standard methods. Rapid phenotypic AST was conducted using the QMAC-dRAST (QuantaMatrix, Inc, Seoul, Republic of Korea), a method based on microscopic imaging analysis with microfluidic chip technology, coupled with MALDI-TOF. Results available 6 hours after Gram staining. • **Standard AST and standard ID:** the MicroScan (Beckman Coulter, Inc., Atlanta, GA) for gram-positive bacteria and the VITEK2 system (bioMerieux, Inc.) for gram-negative bacteria were automatically used for colonies isolated on the same day
Outcomes	• **Primary outcome:** proportion of patients receiving optimal targeted antibiotics 72 hr after blood collection for culture.

Kim 2021 *(Continued)*

	• **Secondary outcomes:** time-to-optimal targeted antibiotic treatment; Bacteraemia-related mortality within 30 days of randomization.
Setting	Haematology department, Seoul National University Hospital and College of Medicine, Seoul, Republic of Korea
Other relevant laboratory techniques	
Notes	• **Prevalence of antibiotic resistance organisms:** 49% (57/116) • **% of participants on inadequate antibiotic:** 16% (19/116) of all participants • **Antimicrobial stewardship program:** no formal antibiotic stewardship programme • **Communication of results and advice of the optimal antibiotic:** the QMAC-dRAST machine automatically conveyed the AST results to ID physicians by text message. The ID physicians contacted the primary medical team and recommended antibiotics based on these results. • **Funding**: This work was supported by the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (Grants No. HI13C- 1468), Seoul National University Hospital Research Fund (Grants No. 03-2018-0370) and QuantaMatrix Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization method with computerized generation of random numbers and a block size of eight
Allocation concealment (selection bias)	Low risk	Randomization was conducted by independent microbiology laboratory personnel blinded to medical information about individual participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel was applied until the results of rapid phenotypic AST were reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Three independent ID physicians, who were unaware of the group assignments, determined classification of the antibiotic treatments for each participant.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for exclusion after randomization clearly listed.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	Principal investigators serve as consultants for QuantaMatrix.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bloos 2010	Not a randomized controlled trial (RCT); controlled observational study
Bookstaver 2017	Not a RCT; quasi-experimental cohort study

Study	Reason for exclusion
Box 2015	Not a RCT; pre-post, quasi-experimental study
Bruins 2005	Quasi-RCT; participants randomized on basis of sum of the day and month of their date of birth). Wrong intervention, antimicrobial susceptibility over 8 hours in some participants included in the intervention arm
Burnham 2019	Not RCT; prospective cohort study; no clinical outcomes; "theoretical opportunities to reduce the time to antibiotic"
Buss 2018	Not a RCT; 3-arm pre/post intervention study
Cambau 2017	Not a RCT; cluster-randomized cross-over trial; no clinical outcomes
Chan, 2009	Not a RCT; cross-sectional study; no clinical outcomes, only evaluation
Clerc 2014	No relevant outcomes reported. RCT comparing standard antibiotic susceptibility testing to a GeneXpert® MRSA test. Primary outcome was diagnostic accuracy.
Cosgrove 2016	Wrong intervention, not an antimicrobial susceptibility method; only rapid identification technique was conducted (Peptide nucleic acid fluorescence in situ hybridization)
Doern 1994	Quasi-RCT; randomization method inappropriate, participants randomized on basis of first letter of last name. Participant group inappropriate; included participants without bloodstream infections
Draz 2013	Not a RCT; study compared laboratory performance of broad range 16s RNA PCR to conventional methods; no clinical outcomes reported
Ehren 2019	Not RCT; quasi-experimental before-after study
Farfour 2019	Not RCT; observational study; control period versus intervention period; no clinical outcomes; evaluation study
Garcia-Vazquez 2013	Not a RCT. Retrospective analysis on 'randomly selected data'.
Garnier 2019	Population not relevant; not exclusively participants with bloodstream infection; other samples, including respiratory, urinary and blood
Grijalva 2020	Not RCT; wrong study design (retrospective)
Idelevich 2015	Wrong intervention; not an antimicrobial susceptibility method; only rapid identification technique was conducted (Multiplex PCR (mPCR) for bacterial identification directly from blood)
Jeyaratnam 2008	Not a RCT; cluster-randomized cross-over trial; no BSIs; no clinical outcomes
Kerremans 2008	Population not relevant; not exclusively participants with bloodstream infection; other samples, including respiratory, urinary and blood
Koncelik 2016	Not a RCT; pre- and post-implementation comparison
Lucignano 2011	Not a RCT; study compared laboratory performance of rapid technique to conventional methods; no clinical outcomes reported

Study	Reason for exclusion
Ly 2008	Wrong intervention; not an antimicrobial susceptibility method; only rapid identification technique was conducted (peptide nucleic acid fluorescence in situ hybridization)
MacGowan 2020	Wrong intervention (only identification of organisms, not susceptibility testing)
May 2015	Population not relevant; not participants with bloodstream infection; included participants with cutaneous abscess, and an incision and drainage procedure
Naucler 2020	wrong study design (literature review)
Pilmis 2019	Not RCT; case-control study
Rodrigues 2013	Wrong intervention; not an antimicrobial susceptibility method; only rapid identification technique was conducted (SeptiFast)
Rodrigues 2019	Wrong Intervention; only rapid identification, no antimicrobial susceptibility testing
Roshdy 2015	Not a RCT; quasi-experimental design comparing pre- and post-intervention groups
Shang 2005	Not a RCT; study compared laboratory performance of PCR to conventional methods; no clinical outcomes reported
Suzuki 2015	Not a RCT; clinical data were compared with those of a control period
Trenholme 1989	Wrong intervention; antimicrobial susceptibility over 8 hours in some participants included in the intervention arm
Ward 2018	Not a RCT; study compared laboratory performance of rapid system to conventional methods; no clinical outcomes reported

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR2000034973

Study name	Clinical research and trial program of early rapid pathogen identification strategy for sepsis
Methods	Randomized controlled trial
Participants	360 participants with bloodstream infections (Gram positive and Gram negative)
Interventions	Carbapenem-resistant Enterobacteriaceae (CRE) screening based on blood culture and PMseqTM rapid detection of pathogenic microorganisms based on metagenomic sequencing
Outcomes	28-day mortality; length of stay
Starting date	Not yet recruiting
Contact information	1931174@tongji.edu.cn (Shanghai Oriental Hospital; 150 Jimo Road, Pudong New District, Shanghai, China)
Notes	

NCT03744728

Study name	Genotypic versus phenotypic susceptibility testing of positive blood cultures
Methods	Interventional (randomized clinical trial)
Participants	466 participants
Interventions	Active comparator: Accelerate Pheno; fast ID and AST of positive blood culture bottles using the Accelerate PhenoTest™ BC kit with the Accelerate Pheno™ System Active comparator: standard of care; standard culture and AST of positive blood culture bottles plus the Verigene® BC-GP/GN
Outcomes	Mean duration of anti-pseudomonal beta-lactam therapy Mean duration of methicillin-resistant *Staphylococcus aureus* (MRSA) therapy
Starting date	November 2018
Contact information	Shawn H Macvane
Notes	

NCT03745014

Study name	Clinical impact of fast Phenotypic antimicrobial susceptibility testing on patients with gram-negative rod bacteraemia
Methods	Randomized clinical trial; parallel assignment; open label
Participants	Adults (≥ 18 years of age) hospitalized with positive blood culture due to gram-negative rod (on Gram stain)
Interventions	Intervention: diagnostic test: Accelerate Pheno Control: standard of care
Outcomes	Desirability of outcome ranking (DOOR) – composite outcome
Starting date	30 September 2019
Contact information	Contact: Amira A Bhalodi; 520-260-5957; abhalodi@axdx.com
Notes	

NCT03876990

Study name	Clinical and medico-economic evaluation of a rapid test (ePlex-BCID®, GenMark) for the diagnosis of bacteraemia and fungaemia (HEMOFAST)
Methods	Randomized controlled trial
Participants	400 participants with bacteraemia or fungaemia, or both

NCT03876990 *(Continued)*

Interventions	Multiplex PCR: microorganism identification and detection of resistance markers
Outcomes	Delay from suspicion of sepsis to optimized antibiotic or antifungal treatment 30-day mortality; length of hospital stay; antibiotic treatment duration
Starting date	20 June 2019
Contact information	Grenoble University Hospital – SDavidTchouda@chugrenoble.fr
Notes	

NCT04153682

Study name	Trial on a strategy combining rapid diagnostic testing and antimicrobial stewardship to improve antibiotic use in patients with hospital-acquired pneumonia (SHARP)
Methods	Randomized controlled trial
Participants	200 participants with hospital-acquired pneumonia
Interventions	Experimental: antimicrobial stewardship + rapid diagnostic testing: Filmarray® Pneumonia Panel (FA-PP) Active comparator: antimicrobial stewardship
Outcomes	Primary: number of days on broad-spectrum antibiotics at day 30 or end-of follow-up for 100 patients-days Secondary: mortality; in-hospital length of stay; overall antibiotic use
Starting date	21 February 2020
Contact information	Solen Kernéis, MD, PhD; +33 1 58.41.19.08; solen.kerneis@aphp.fr Guillaume Masson, MSc: +33 1 58 41 34 78: guillaume.masson@aphp.fr
Notes	

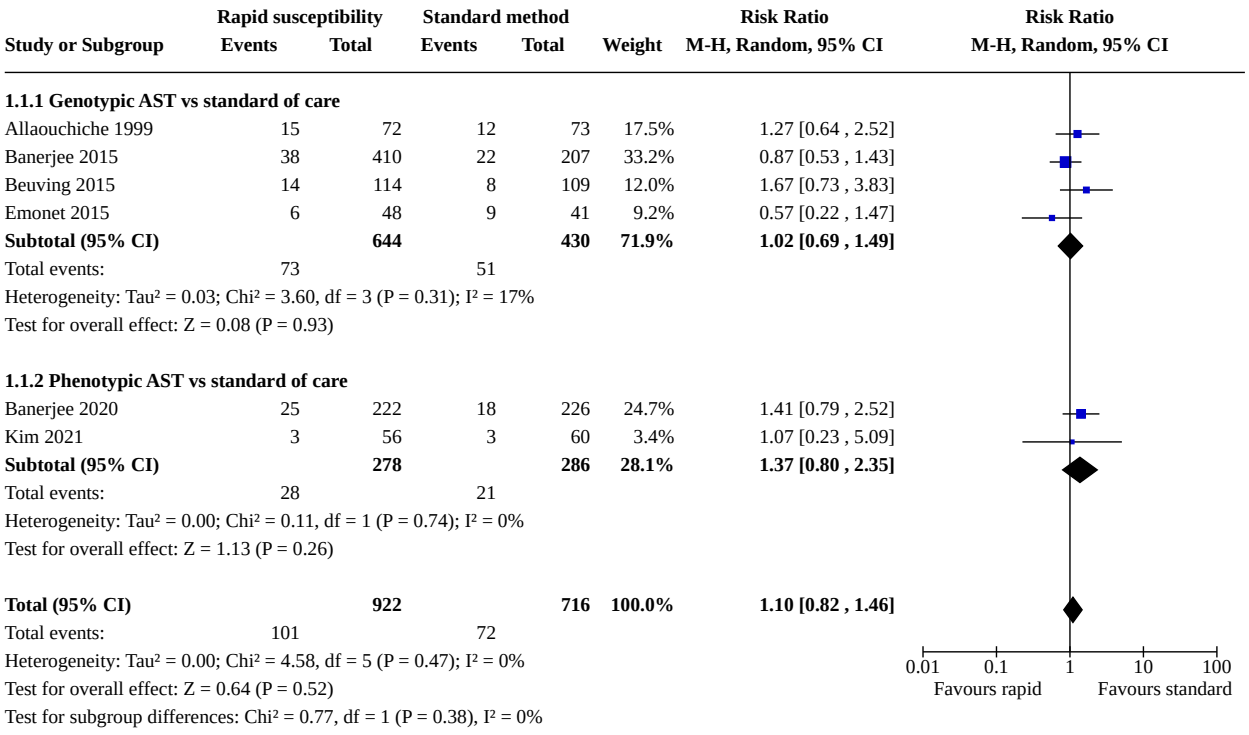
DATA AND ANALYSES

Comparison 1. Rapid versus standard antibiotic susceptibility testing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality (subgroups: genotypic, phenotypic)	6	1638	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.82, 1.46]
1.1.1 Genotypic AST vs standard of care	4	1074	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.69, 1.49]

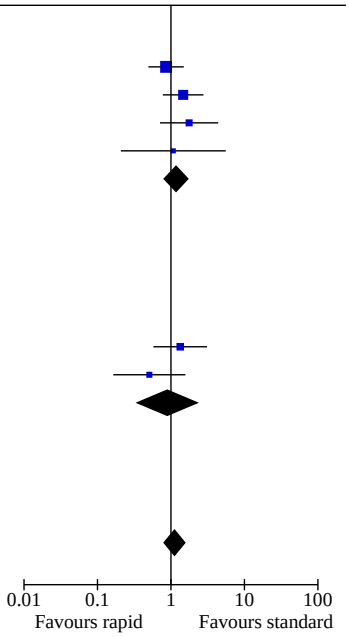
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.2 Phenotypic AST vs standard of care	2	564	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.80, 2.35]
1.2 Mortality (subgroups: antimicrobial stewardship, without antimicrobial stewardship)	6	1638	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.81, 1.54]
1.2.1 Rapid AST and antimicrobial stewardship vs standard	4	1404	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.81, 1.70]
1.2.2 Rapid AST alone vs standard	2	234	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.35, 2.27]
1.3 Mortality (subgroups: rapid ID and AST, AST alone	6	1638	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.81, 1.54]
1.3.1 Rapid AST and ID vs standard	4	876	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.77, 2.03]
1.3.2 Rapid AST alone vs standard	2	762	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.62, 1.56]
1.4 Time-to-appropriate antibiotic (phenotypic testing)	2	564	Mean Difference (IV, Random, 95% CI)	-17.29 [-45.05, 10.47]

Analysis 1.1. Comparison 1: Rapid versus standard antibiotic susceptibility testing, Outcome 1: Mortality (subgroups: genotypic, phenotypic)



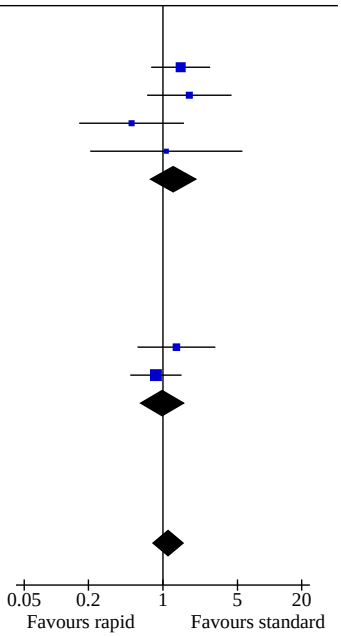
Analysis 1.2. Comparison 1: Rapid versus standard antibiotic susceptibility testing, Outcome 2: Mortality (subgroups: antimicrobial stewardship, without antimicrobial stewardship)

Study or Subgroup	Rapid susceptibility Events	Total	Standard method Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Rapid AST and antimicrobial stewardship vs standard						
Banerjee 2015	38	410	22	207	34.3%	0.86 [0.49 , 1.49]
Banerjee 2020	25	222	18	226	26.0%	1.47 [0.78 , 2.77]
Beuving 2015	14	114	8	109	12.7%	1.77 [0.71 , 4.40]
Kim 2021	3	56	3	60	3.9%	1.08 [0.21 , 5.56]
Subtotal (95% CI)		**802**		**602**	**76.9%**	**1.17 [0.81 , 1.70]**
Total events:	80		51			
Heterogeneity: Tau² = 0.00; Chi² = 2.48, df = 3 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.2.2 Rapid AST alone vs standard						
Allaouchiche 1999	15	72	12	73	14.9%	1.34 [0.58 , 3.10]
Emonet 2015	6	48	9	41	8.2%	0.51 [0.16 , 1.57]
Subtotal (95% CI)		**120**		**114**	**23.1%**	**0.89 [0.35 , 2.27]**
Total events:	21		21			
Heterogeneity: Tau² = 0.21; Chi² = 1.81, df = 1 (P = 0.18); I² = 45%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**922**		**716**	**100.0%**	**1.12 [0.81 , 1.54]**
Total events:	101		72			
Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 5 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%						



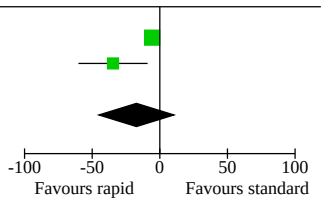
Analysis 1.3. Comparison 1: Rapid versus standard antibiotic susceptibility testing, Outcome 3: Mortality (subgroups: rapid ID and AST, AST alone

Study or Subgroup	Rapid susceptibility Events	Total	Standard method Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 Rapid AST and ID vs standard						
Banerjee 2020	25	222	18	226	26.0%	1.47 [0.78 , 2.77]
Beuving 2015	14	114	8	109	12.7%	1.77 [0.71 , 4.40]
Emonet 2015	6	48	9	41	8.2%	0.51 [0.16 , 1.57]
Kim 2021	3	56	3	60	3.9%	1.08 [0.21 , 5.56]
Subtotal (95% CI)		**440**		**436**	**50.8%**	**1.25 [0.77 , 2.03]**
Total events:	48		38			
Heterogeneity: Tau² = 0.02; Chi² = 3.26, df = 3 (P = 0.35); I² = 8%						
Test for overall effect: Z = 0.89 (P = 0.37)						
1.3.2 Rapid AST alone vs standard						
Allaouchiche 1999	15	72	12	73	14.9%	1.34 [0.58 , 3.10]
Banerjee 2015	38	410	22	207	34.3%	0.86 [0.49 , 1.49]
Subtotal (95% CI)		**482**		**280**	**49.2%**	**0.98 [0.62 , 1.56]**
Total events:	53		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)		**922**		**716**	**100.0%**	**1.12 [0.81 , 1.54]**
Total events:	101		72			
Heterogeneity: Tau² = 0.00; Chi² = 4.58, df = 5 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.49), I² = 0%						



Analysis 1.4. Comparison 1: Rapid versus standard antibiotic susceptibility testing, Outcome 4: Time-to-appropriate antibiotic (phenotypic testing)

Study or Subgroup	Rapid susceptibility Mean	SD	Total	Standard method Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Banerjee 2020	19	22.9	222	24.7	24.6	226	59.9%	-5.70 [-10.10 , -1.30]
Kim 2021	38.2	38.2	56	72.8	93	60	40.1%	-34.60 [-60.17 , -9.03]
Total (95% CI)			**278**			**286**	**100.0%**	**-17.29 [-45.05 , 10.47]**
Heterogeneity: Tau² = 329.98; Chi² = 4.77, df = 1 (P = 0.03); I² = 79%								
Test for overall effect: Z = 1.22 (P = 0.22)								
Test for subgroup differences: Not applicable								



ADDITIONAL TABLES

Table 1. Rates of antibiotic-resistant organisms

Studies	Rates of antibiotic-resistant organisms (%)	Organisms	Antibiotic-resistance
Allaouchiche 1999	31%	*Staphylococcus aureus*	oxacillin, vancomycin
Banerjee 2015	49%	*Staphylococcus* spp	oxacillin, vancomycin
		Enterococcus spp	vancomycin

Table 1. Rates of antibiotic-resistant organisms *(Continued)*

		Enterobacteriaceae	broad-spectrum – beta-lactam (amoxicillin–clavulanic, piperacillin–tazobactam, cefepime)
Banerjee 2020	19%	Enterobacteriaceae, *Acinetobacter baumannii, Pseudomonas aeruginosa*	Broad-spectrum – beta-lactam (amoxicillin-clavulanic, piperacillin-tazobactam, cefepime, ceftazidime, carbapenems)
Beuving 2015	4%	*Staphylococcus* spp	oxacillin, vancomycin
		Streptococcus spp	penicillin
		Enterococcus spp	beta-lactam
		Enterobacteriaceae	broad-spectrum – beta-lactam (amoxicillin–clavulanic, piperacillin–tazobactam)
Emonet 2015	13%	*Staphylococcus aureus*	oxacillin, vancomycin
Kim 2021	49%	*Staphylococcus* spp	oxacillin, vancomycin
		Enterococcus spp	vancomycin
		Enterobacteriaceae	broad-spectrum – beta-lactam
		Pseudomonas aeruginosa	piperacillin–tazobactam

Table 2. Participants on inadequate empiric antimicrobial

Studies	Participants on inadequate empiric antimicrobial (%)
Allaouchiche 1999	25%
Banerjee 2015	49%
Banerjee 2020	not provided
Beuving 2015	26%
Emonet 2015	28%
Kim 2021	16%

Appropriate empiric antibiotic is defined as an agent to which the blood culture organism was susceptible by antimicrobial susceptibility testing. The time window for the initiation of empiric antibiotic varied between different studies: (i) from conduct of Gram-staining: 4 to 11

hours (Banerjee 2015); 6 to 8 hours (Emonet 2015)); (ii) from blood culture drawing: 27 to 28 hours (Beuving 2015); 17 to 42 hours (Banerjee 2020); 48 to 83 hours (Kim 2021).

Table 3. Time-to-discharge

Study	Average time to discharge (in days)			P value
	Conventional, control group	Rapid, comparison group		
Studies using genotypic rapid susceptibility testing				
Banerjee 2015	Median 8 days IQR 5 to 15 N = 207	*Rapid susceptibility alone* Median 8 days IQR 5 to 15 N = 198	*Rapid susceptibility with stewardship* Median 8 days IQR 5 to 16 N = 212	0.60
Beuving 2015	Median 11 days Range 1 to 133 N = 109	Median 11 days Range 0 to 75 N = 114		0.82
Emonet 2015	Median 27 days IQR 10 to 39 N = 41	Median 23.5 days IQR 15 to 36 N = 48		0.71
Studies using phenotypic rapid susceptibility testing				
Banerjee 2020	Mean 8.2 days SD 8.7 N = 226	Mean 9.8 days SD 9.8 N = 222		0.17
Studies using rapid AST and antimicrobial stewardship				
Banerjee 2015	Median 8 days IQR 5 to 15 N = 207	*Rapid susceptibility alone* Median 8 days IQR 5 to 15 N = 198	*Rapid susceptibility with stewardship* Median 8 days IQR 5 to 16 N = 212	0.60
Banerjee 2020	Mean 8.2 days SD 8.7 N = 226	Mean 9.8 days SD 9.8 N = 222		0.17
Beuving 2015	Median 11 days Range 1 to 133 N = 109	Median 11 days Range 0 to 75 N = 114		0.82

Table 3. Time-to-discharge *(Continued)*

Studies using rapid AST without antimicrobial stewardship				
Emonet 2015	Median 27 days IQR 10 to 39 N = 41	Median 23.5 days IQR 15 to 36 N = 48		0.71
Studies using rapid AST and rapid ID				
Banerjee 2020	Mean 8.2 days SD 8.7 N = 226	Mean 9.8 days SD 9.8 N = 222		0.17
Beuving 2015	Median 11 days Range 1 to 133 N = 109	Median 11 days Range 0 to 75 N = 114		0.82
Emonet 2015	Median 27 days IQR 10 to 39 N = 41	Median 23.5 days IQR 15 to 36 N = 48		0.71
Studies using rapid AST (alone) without rapid ID				
Banerjee 2015	Median 8 days IQR 5 to 15 N = 207	*Rapid susceptibility alone* Median 8 days IQR 5 to 15 N = 198	*Rapid susceptibility with stewardship* Median 8 days IQR 5 to 16 N = 212	0.60

AST: antimicrobial susceptibility testing; **IQR**: interquartile range;**SD**: standard deviation

Table 4. Time-to-appropriate antibiotic

Study	**Average time-to-appropriate antibiotic change to targeted or definitive therapy (in hours)**			**P value**
	Conventional or control group	**Rapid or comparison group**		
Studies using genotypic rapid susceptibility testing				
Banerjee 2015	Median 11 hours IQR 2 to 51 N = 207	*Rapid susceptibility alone* Median 6 hours IQR 2 to 31 N = 198	*Rapid susceptibility with stewardship* Median 4 hours IQR 2 to 20 N = 212	0.55
Beuving 2015*	Mean 26.9 hours	Mean 28.2 hours		0.96

Table 4. Time-to-appropriate antibiotic *(Continued)*

	SD 30.1 N = 109	SD 32.5 N = 114		
Emonet 2015	Median 8 hours IQR 1 to 36 N = 41	Median 6 hours IQR 3.8 to 10 N = 48		0.13
Studies using phenotypic rapid susceptibility testing				
Banerjee 2020	Mean 24.7 hours (SD 24.6) Median 14.9 (IQR 3.3 to 41.1) N = 226	Mean 19 hours (SD 22.9) Median 8.6 hours (IQR 2.6 to 27.6) N = 222		0.0125
Kim 2021	Mean 72.8 hours SD 93.0 N = 60	Mean 38.2 hours SD 38.2 N = 56		< 0.001
Studies using rapid AST and antimicrobial stewardship				
Banerjee 2015	Median 11 hours IQR 2 to 51 N = 207	*Rapid susceptibility alone* Median 6 hours IQR 2 to 31 N = 198	*Rapid susceptibility with stewardship* Median 4 hours IQR 2 to 20 N = 212	0.55
Banerjee 2020	Mean 24.7 hours (SD 24.6) Median 14.9 hours (IQR 3.3 to 41.1) N = 226	Mean 19 hours (SD 22.9) Median 8.6 hours (IQR 2.6 to 27.6) N = 222		0.0125
Beuving 2015*	Mean 26.9 hours SD 30.1 N = 109	Mean 28.2 hours SD 32.5 N = 114		0.96
Kim 2021	Mean 72.8 SD 93.0 N = 60	Mean 38.2 SD 38.2 N = 56		< 0.001
Studies using rapid AST without antimicrobial stewardship				
Emonet 2015	Median 8 hours IQR 1 - to 36 N = 41	Median 6 hours IQR 3.8 to 10 N = 48		0.13

Table 4. Time-to-appropriate antibiotic *(Continued)*

Studies using rapid AST and rapid ID				
Banerjee 2020	Mean 24.7 hours (SD 24.6) Median 14.9 hours (IQR 3.3 to 41.1) N = 226	Mean 19 hours (SD 22.9) Median 8.6 hours (IQR 2.6 to 27.6) N = 222		0.0125
Beuving 2015*	Mean 26.9 hours SD 30.1 N = 109	Mean 28.2 hours SD 32.5 N =114		0.96
Emonet 2015	Median 8 hours IQR 1 to 36 N = 41	Median 6 hours IQR 3.8 to 10 N = 48		0.13
Kim 2021	Mean 72.8 hours SD 93.0 N = 60	Mean 38.2 hours SD 38.2 N = 56		< 0.001
Studies using rapid AST (alone) without rapid ID				
Banerjee 2015	Median 11 hours IQR 2 to 51 N = 207	*Rapid susceptibility alone* Median 6 hours IQR 2 to 31 N = 198	*Rapid susceptibility with stewardship* Median 4 hours IQR 2 to 20 N = 212	0.55

*Beuving 2015 reported time-to-appropriate antibiotic from time of blood draw; other studies reported time from positive Gram stain
AST: antimicrobial susceptibility testing; **IQR**: interquartile range;**SD**: standard deviation

APPENDICES

Appendix 1. Included interventions

Molecular: matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MS) based resistance test (MALDI-TOF MS); fluorescence in situ hybridization with peptide nucleic acid (PNA-FISH); multiplex polymerase chain reaction (PCR); FilmArray; GenoType blood culture; GeneXpert MRSA Cepheid; Verigene Nanosphere; BD Gene Ohm StaphSR Becton Dickinson; BDMax Staph; Eazyplex; AID; LightMix; Check-Direct CPE; MyCycler; Sepsis FlowChip; CheckPoints; Prove-it Sepsis; B-lacta test.

Phenotypic: Accelerate Pheno; Alfred 60/AST; forward laser light scatter; qMAC-sRAST; ViteK2

Appendix 2. Detailed search strategies

MEDLINE Pubmed

#1 Search “bloodstream infection*” or “blood-stream infection*” Field: Title/Abstract

#2 Search bacteremia [Mesh]

#3 Search bacteremia or bacteraemia Field: Title/Abstract

#4 Search “blood culture” Field: Title/Abstract

#5 Search sepsis Field: Title/Abstract

#6 Search Sepsis [Mesh]

#7 Search ((#6) or (#5) OR (#4) OR #3) or #2) or #1)

#8 Search (Streptococci or “Streptococcus pneumoniae” or “Streptococcus agalactiae” or “Streptococcus pyogenes” or “Streptococcus viridans” or Staphylococci or “Staphylococcus aureus” or MSSA or MRSA or “Staphylococcus epidermidis” or “Staphylococcus saprophyticus” or “Coagulase negative Staphylococci” or Enterococci or “Enterococcus faecium” or “Enterococcus faecalis” or Listeria or “Listeria monocytogenes”or Clostridium or Fusobacterium or Peptostreptococcus or Bacillus or Haemophilus or “Haemophilus influenzae” or Brucella or Enterobacteriaceae or “Escherichia coli” or Klebsiella or Proteus or Enterobacter or Salmonella or Citrobacter or Pseudomonas or “Pseudomona aeruginosa” or Serratia or Acinetobacter or Stenotrophomonas or Legionella or Helicobacter or Moraxella or Neisseria or “Neisseria meningitidis”or “Neisseria gonorrhoeae” or “Gram-negative” or “Gram-positive”) AND blood* Field: Title/Abstract

#9 Search (#7) OR #8)

#10 Search “antimicrobial susceptibility test” or “antimicrobial susceptibility testing” or “antibiotic susceptibility testing” or “susceptibility testing” Field: Title/Abstract

#11 Search “rapid” Field: Title

#12 Search “MALDI-TOF” OR “PNA-FISH” Field: Title/Abstract

#13 Search PCR Field: Title/Abstract OR “Polymerase Chain Reaction” [Mesh]

#14 Search FilmArray or **Microarray** or **“molecular test”** or “GenoType Blood Culture” or GeneXpert or Cepheid or “Verigene Nanosphere” Field: Title/ Abstract

#15 Search “BD Gene Ohm” or “BDMax Staph” or Eazyplex or LightMix or “Check-Direct CPE” Field: Title/ Abstract

#16 Search FlowChip or “Prove-it” or “B-lacta test” or “BetaLACTA”Field: Title/Abstract

#17 Search (“Pheno Accelerate” or “Alfred 60 AST” or “Light scattering” or “BacterioScan” or “qMAC-sRAST” or “Vitek2”) Field: Title/Abstract

#18 Search “antimicrobial stewardship” or “antimicrobial prescription**”** Field: Title/Abstract

#19 Search (#18 OR (17) OR #16) OR #15) OR #14) OR #13) OR #12) OR #11) OR #10) OR #9

#20 Search #9 AND #19

#21 Search “Randomized Controlled Trial” [Publication Type] OR “Controlled Clinical Trial” [Publication Type]

#22 Search (random* or placebo or single-blind* or double-blind*) Field: Title/Abstract

#23 Search impact or “clinical impact” or outcomes or clinical or “clinical outcomes” or effect Field: Title/Abstract

#24 Search evaluation or performance AND (impact* or outcome*) Field: Title/Abstract

#25 Search ((#24) OR (#23) OR #22) OR #21

#23 Search #20 AND #25

CENTRAL 2019, Issue 11

ID Search Hits

#1 “bloodstream infections”

#2 MeSH descriptor: [Sepsis] explode all trees

#3 MeSH descriptor: [Bacteremia] explode all trees

#4 bacteremia or bacteraemia

#5 “blood culture”

#6 sepsis

#7 (Streptococci or “Streptococcus pneumoniae” or “Streptococcus agalactiae” or “Streptococcus pyogenes” or “Streptococcus viridans” or Staphylococci or “Staphylococcus aureus” or MSSA or MRSA or “Staphylococcus epidermidis” or “Staphylococcus saprophyticus” or “Coagulase negative Staphylococci”)

#8 (Enterococci or “Enterococcus faecium” or “Enterococcus faecalis”)

#9 Listeria

#10 Clostridium or Fusobacterium or Peptostreptococcus

#11 Bacillus or Haemophilus or “Haemophilus influenzae” or Brucella or Enterobacteriaceae or “Escherichia coli” or Klebsiella or Proteus

#12 Enterobacter or Salmonella or Citrobacter or Pseudomonas or “Pseudomona aeruginosa” or Serratia or Acinetobacter

#13 Stenotrophomonas or Legionella or Helicobacter or Moraxella or Neisseria or “Neisseria meningitidis”

#14 “Neisseria gonorrhoeae” or “Gram-negative” or “Gram-positive”

#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 blood

#17 #15 and #16

#18 #1 or #2 or #3 or #4 or #5 or #6 or #17

#19 “antimicrobial susceptibility test” or “antimicrobial susceptibility testing” or “antibiotic susceptibility testing” or “susceptibility testing”

#20 rapid

#21 “MALDI-TOF” OR “PNA-FISH”

#22 PCR OR “Polymerase Chain Reaction”

#23 FilmArray or Microarray or “molecular test” or “GenoType Blood Culture” or GeneXpert or Cepheid or “Verigene Nanosphere”

#24 “BD Gene Ohm” or “BDMax Staph”

#25 Eazyplex

#26 LightMix

#27 Check-Direct CPE

#28 (“Pheno Accelerate” or “Alfred 60 AST” or “Light scattering” or “BacterioScan” or “qMAC-sRAST” or “Vitek2”)

#29 “antimicrobial stewardship” or “antimicrobial prescription”

#30 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

#31 #30 and #18

Embase <1947 to 2019 Week 47>

1 bloodstream infections.mp. or bloodstream infection/

2 sepsis.mp. or sepsis/

3 staphylococcal bacteremia/ or bacteremia/ or bacteremia.mp.

4 (Streptococci or "Streptococcus pneumoniae" or "Streptococcus agalactiae" or "Streptococcus pyogenes" or "Streptococcus viridans" or Staphylococci or "Staphylococcus aureus" or MSSA or MRSA or "Staphylococcus epidermidis" or "Staphylococcus saprophyticus" or "Coagulase negative Staphylococci" or Enterococci or "Enterococcus faecium" or "Enterococcus faecalis").mp.

5 (Listeria or "Listeria monocytogenes" or Clostridium or Fusobacterium or Peptostreptococcus or Bacillus or Haemophilus or ""Haemophilus influenzae" or Brucella or Enterobacteriaceae or "Escherichia coli" or Klebsiella).mp.

6 (Proteus or Enterobacter or Salmonella or Citrobacter or Pseudomonas or "Pseudomonas aeruginosa" or Serratia or Acinetobacter or Stenotrophomonas or Legionella or Helicobacter or Moraxella or Neisseria or "Neisseria meningitidis" or "Neisseria gonorrhoeae" or "Gram-negative" or "Gram-positive").mp.

7 4 or 5 or 6

8 blood.mp.

9 7 and 8

10 1 or 2 or 3 or 9

11 ("antimicrobial susceptibility test* " or "antibiotic susceptibility testing" or "susceptibility testing").mp.

12 rapid.m_titl.

13 ("MALDI-TOF" or "PNA-FISH").mp.

14 (PCR or "Polymerase Chain Reaction").mp.

15 (FilmArray or Microarray or "molecular test" or "GenoType Blood Culture" or GeneXpert or Cepheid or "Verigene Nanosphere").mp.

16 ("BD Gene Ohm" or "BDMax Staph").mp.

17 Eazyplex.mp.

18 LightMix.mp.

19 Check-Direct CPE.mp.

20 ("Pheno Accelerate" or "Alfred 60 AST" or "Light scattering" or "BacterioScan" or "qMAC-sRAST" or "Vitek2").mp

21 antimicrobial stewardship.mp. or antimicrobial stewardship/

22 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23 10 and 22

24 randomized controlled trial/ or controlled clinical trial/

25 (randomized or randomised or placebo or double-blind* or single-blind*).ti. or (randomized or randomised or placebo or double-blind* or single-blind*).ab.

26 ("clinical impact" or "clinical outcomes" or effect).mp.

27 evaluation.mp. or evaluation study/

28 (performance adj2 (impact* or outcome*)).mp.

29 24 or 25 or 26 or 27 or 28

30 23 and 29

LILACS

"bloodstream infection$" or sepsis [Words] and "rapid test$" or PCR [Words]

Appendix 3. Definitions

- **Rapid susceptibility technique**: an in vitro laboratory test used to determine if an antimicrobial agent will be active in inhibiting the growth of an organism, performed directly from a positive blood culture bottle, producing results in < 8 hours or same working day
- **Phenotypic susceptibility test**: the basis of phenotypic method is the minimum inhibitory concentration (MIC). Clinical MIC breakpoints determine whether the organism is categorized as susceptible, intermediate or resistant.
- **Molecular or genotypic susceptibility test**: a diagnostic test that analyzes the presence or absence of resistant genes in bacteria

- **Appropriate antimicrobial therapy**: antimicrobial treatment directed specifically to a micro-organism based on in vitro susceptibility test results
- **Time-to-result**: the time that it takes to perform and report a laboratory susceptibility test result from the time that the sample is received in the laboratory
- **Bloodstream infection (BSI) or bacteraemia**: positive blood culture result with systemic manifestations of infection

HISTORY

Protocol first published: Issue 12, 2018
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CONTRIBUTIONS OF AUTHORS

Vanesa Anton (VA) and Paul Hine (PH) undertook the study selection, data extraction and risk of bias assessment, and led the writing of the review.

Marty Chaplin (MC) undertook data extraction and risk of bias assessment, and contributed to editing this review.

Sanjeev Krishna (SK) and Timothy Planche (TP) contributed to review and editing of the review.

The final manuscript was approved by all authors.

DECLARATIONS OF INTEREST

VA has no known conflicts of interest.

PH was previously employed full-time by Cochrane Infectious Diseases Group (CIDG), and currently works full-time within the UK National Health Service (NHS). He received a Registration Scholarship to attend the 23rd Annual British HIV Association Conference 2017 from ViiV healthcare. ViiV had no involvement in the selection of recipients of the scholarship. In 2018, he attended a CPD-certified clinical research training programme, organized and funded by Gilead Sciences Europe Ltd. To the best of his knowledge, neither financial or non-financial conflicts of interests have influenced the current submitted work.

SK is a scientific advisor and shareholder in QuantuMDx, a company that is developing rapid diagnostic tests for several infections, and is a scientific advisor to Foundation for Innovative New Diagnostics (FIND). The opinions in this review are personal opinions, and do not represent views of either organization.

MC has no known conflicts of interest.

TP is the clinical lead of a NHS diagnostic microbiology laboratory at South West London Pathology. He is on advisory boards for Roche, Pfizer, and Singulex for diagnostics.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were unable to extract data to allow time-to-event analysis, so instead presented narrative synthesis.