Performance of BioFire Blood Culture Identification 2 Panel (BCID2) for the detection of bloodstream pathogens and their associated resistance markers: a systematic review and meta-analysis of diagnostic test accuracy studies

Anna Maria Peri1*, Weiping Ling1, Luis Furuya-Kanamori1, Patrick N. A. Harris1,2 and David L. Paterson1,3

Abstract

Background: Early identification of bloodstream pathogens and their associated antimicrobial resistance may shorten time to optimal therapy in patients with sepsis. The BioFire Blood Culture Identification 2 Panel (BCID2) is a novel multiplex PCR detecting 43 targets directly from positive blood cultures, reducing turnaround times.

Methods: We have performed a systematic review and meta-analysis of diagnostic test accuracy studies to assess the BCID2 performance for pathogen identification and resistance markers detection compared to gold standard culture-based methods (including phenotypic and/or genotypic characterization).

Results: Nine studies were identified reporting data to build $2 \times 2$ tables for each BCID2 target, including 2005 blood cultures. The pooled specificity of the assay was excellent (> 97%) across most subgroups of targets investigated, with a slightly broader confidence interval for S. epidermidis (98.1%, 95% CI 93.1 to 99.5). Pooled sensitivity was also high for the major determinants of bloodstream infection, including Enterobacteriales (98.2%, 95% CI 96.3 to 99.1), S. aureus (96.0%, 95% CI 90.4 to 98.4), Streptococcus spp. (96.7%, 95% CI 92.8 to 98.5), P. aeruginosa (92.7%, 95% CI 83.1 to 97.0), E. faecalis (92.3%, 95% CI 83.5 to 96.6), as well as blaCTX-M (94.9, 95% CI 85.7 to 98.3), carbapenemases (94.9%, 95% CI 83.4 to 98.6) and mecA/C & MREJ (93.9%, 95% CI 83.0 to 98.0). Sensitivity for less common targets was slightly lower, possibly due to their under-representation in the included studies.

Conclusions: BCID2 showed good performance for detecting major determinants of bloodstream infection and could support early antimicrobial treatment, especially for ESBL or carbapenemase-producing Gram-negative bacilli and methicillin-resistant S. aureus.

Keywords: Bloodstream infection, Sepsis, Blood culture, Molecular diagnostic techniques, BCID2, Meta-analysis

© The Author(s) 2022. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
the increasing burden of antimicrobial resistance often hamper a prompt management of affected patients [2].

The implementation of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) in clinical laboratories in recent years has substantially contributed to reducing the time to identify bloodstream pathogens. However, up to 12–24 h from blood culture positivity are still required for pathogen characterization, and even longer times are needed before antimicrobial susceptibility testing (AST) is available according to standard methods [3].

Therefore, other molecular technologies are emerging, based on the detection of pathogen DNA directly from positive blood cultures, aimed at further reducing time to results, and simplifying the laboratory workflow [4]. Limitations of such tests still apply, including the ability to detect a limited panel of pathogens and resistance genes only, making their clinical implementation challenging. Among these tests, the BioFire Blood Culture Identification Panel (BCID, bioMérieux) is a multiplex PCR applied on positive blood cultures whose original version was based on the identification of 24 microorganisms and 3 antimicrobial resistance genes (mecA, vanA/B and KPC), and whose use has been associated to early appropriate treatment [5, 6]. Some relevant targets were missing from the original panel of the assay, as highlighted by a study where a subset of bacteraemia cases caused by organisms not detected by the first version of the test were associated to adverse clinical outcomes and mainly caused by anaerobes [7].

To overcome this limitation, a new version of the BCID has been recently released (BioFire Blood Culture Identification 2 Panel, BCID2, bioMérieux) including 33 pathogens and 10 resistance markers, reaching a broad coverage of the most common determinant of bloodstream infection (and the broadest coverage among molecular tests applied on positive blood cultures), and making the implementation of the test in clinical practice more promising [8].

A few studies have been published so far assessing the performance of this test in real-life scenarios, showing relatively good agreement with conventional culture-based testing [9–14]. However, the limited sample size of these individual studies prevented a reliable assessment of the performance of BCID2, and results were often described as percentage of agreement or concordance with conventional testing rather than reporting diagnostic accuracy measures (e.g., sensitivity [Se], specificity [Sp]) that are used in clinical practice [9, 10, 13].

Considering the potential implementation of the BCID2 in clinical practice as a tool for guiding clinical decision making in patients with bloodstream infection in the close future, gaining a better understanding of its diagnostic accuracy in real-life settings could represent a valuable knowledge. Therefore, we have performed a systematic review and meta-analysis of diagnostic test accuracy studies to estimate the performance of the BCID2 for pathogen identification and resistance markers detection compared to conventional blood culture-based methods, including phenotypic and genotypic characterization on culture isolates.

**Methods**

These systematic review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guideline [15] (Additional file 1: Data 1).

**Search strategy**

The search strategy was built by an experienced librarian in Medline, Scopus, Embase as well as in pre-print databases (i.e., MedRxiv, BioRxiv and SSRN Electronic Journal) on February 4th, 2022, for studies that assessed the performance of the BCID2. The search terms included “BCID2”, “BIOFIRE Blood Culture Identification 2”, “Biofire Filmarray”, “Panel 2”, “BioFire FilmArray Blood Culture Identification 2”, “Blood culture Identification panel 2”.

After identifying eligible papers, a backward & forward citation search was performed in Scopus identifying further papers which also underwent blind screening by the two reviewers. Moreover, on April 12th, 2022, a search of the grey literature was performed using the terms “Biofire Filmarray” and “BCID2"; again, blind screening by the two reviewers was performed. Websites identified through the grey literature search were further searched for additional information.

No restriction in terms of publication date or language were introduced in the systematic search.

The search strategy details are available in the Additional file 1: Data 2.

**Inclusion criteria**

To be included the studies had to assess the performance of the BCID2 on prospectively or randomly collected clinical blood cultures samples flagging positive, or spiked blood cultures. Specifically, they had to report information to build a $2 \times 2$ diagnostic contingency table for each BCID2 target, with blood culture-based conventional methods as the gold standard comparator.

The BCID2 is manufactured by bioMérieux (France) and received Conformité Européenne In vitro Diagnostics (CE IVD), Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA) approvals in Europe, the U.S and Australia respectively, during 2020.
Both studies including the Research Use Only (RUO) versions (or Investigational Use Only, IUO) and the IVD commercial versions of the assay were eligible for inclusion in the meta-analysis since the RUO versions did not differ from the currently commercially approved ones [12]. Differently, studies based on the use of “RUO prototype” versions of the assay were not deemed eligible for inclusion since, as confirmed by the manufacturer, changes were made to the prototypes before developing the definitive RUO/IUO version which is identical to IVD cleared and commercially available one. Targets included in the BCID2 panel are listed in Table 1.

Gold standard methods for pathogen identification included traditional culture-based biochemical techniques for phenotypic profiling (manual and automated), as well as the use of MALDI-TOF MS. The use of genotypic testing in the case of inconclusive or unclear results from conventional testing was also considered as an appropriate method to complement biochemical techniques or mass spectrometry when performed. Gold standard methods for the detection of antimicrobial resistance markers included phenotypic testing assessed by automated methods or by traditional phenotypic techniques, according to EUCAST and CLSI guidelines [16, 17]. Moreover, the genotypic confirmation of the antimicrobial resistance gene markers of interest on blood culture colonies, was also considered as an appropriate gold standard for comparison of resistance genes detected by the BCID2.

### Screening and selection of articles

Papers identified during the main database search strategy were exported into Endnote [18] and subsequently in Rayyan (https://www.rayyan.ai/) [19]. The screening of the papers was performed in Rayyan by two independent reviewers (A.M.P., W.L.), by screening title/abstract and the full text of the articles in one stage. The screening of the grey literature was performed by the two reviewers directly from the specific websites included in the search (see Additional file 1: Data 2).

Agreement between the two reviewers was assessed by the kappa coefficient. Discrepancies in the study selection were discussed after the screening; and if agreement could not be reached, a third reviewer was involved (L.F.K.).

### Data extraction

Data extracted included the number of true positives, false positives, false negatives, and true negatives, for each BCID2 target (Table 1), defined below, as well as time to pathogen identification and antimicrobial markers detection or AST availability according to the BCID2 and conventional culture-based methods.

For pathogen identification a true positive was defined as a result where the BCID2 panel and the gold standard comparator detected the same target organism. A false negative result was defined by the BCID2 failing to detect an organism target that was detected by the gold standard comparator, while a false positive result was defined by the BCID2 panel detecting an organism that was not detected by the gold standard methods. To be defined as a true negative result, the target organism should have not been detected by either method.

For antimicrobial resistance markers, a true positive was defined as a result where the BCID2 detected a specific resistance gene and the gold standard comparator showed a phenotypic resistant profile known to be associated with that genetic determinant and/or detected the genetic determinant of interest itself, by mean of standard genotypic testing performed on blood culture colonies.

### Table 1 Targets included in the BCID2 Panel

| Gram negatives | Gram positives | Yeast | Antimicrobial resistance markers |
|----------------|----------------|------|----------------------------------|
| *A. calcoaceticus-baumannii complex* | *Staphylococcus spp.* | *Candida albicans* | mecA/C |
| *Bacteroides fragilis* | *Staphylococcus aureus* | *Candida auris* | mecA/C and MREJ (MRSA) |
| *Haemophilus influenzae* | *Staphylococcus epidermidis* | *Candida glabrata* | van A/B |
| *Neisseria meningitidis* | *Staphylococcus lugdunensis* | *Candida krusei* | blacTX-M |
| *Pseudomonas aeruginosa* | *Streptococcus spp.* | *Candida parapsilosis* | blacKPC |
| *Stenotrophomonas maltophilia* | *Streptococcus agalactiae* | *Candida tropicalis* | blacIMP |
| *Enterobacteriales spp.* | *Streptococcus pyogenes* | *Cryptococcus neoformans/gattii* | blaoXA-48 |
| *Enterobacter cloacae complex* | *Streptococcus pneumoniae* | | blanNDM |
| *Escherichia coli* | *Enterococcus faecalis* | | blanVIM |
| *Klebsiella aerogenes* | *Enterococcus faeicium* | | mcr-1 |
| *Klebsiella oxytoca* | *Listeria monocytogenes* | | |
| *Klebsiella pneumoniae group* | | | |
| *Proteus spp.* | | | |
| *Salmonella* | | | |
| *S. marcescens* | | | |

MRSA = Methicillin Resistant *Staphylococcus aureus*
colonies. A false negative was defined as a result where the BCID2 did not detect a specific resistance gene and the gold standard culture-based comparator showed a phenotypic resistant profile normally induced by the genetic marker of interest and/or detected the presence of the gene of interest by mean of genotypic characterization on culture colonies. A false positive was defined as a result where the BCID2 detected a specific resistance gene, and the blood culture-based gold standard comparator showed a susceptible phenotype for those antimicrobials to which resistance is normally induced by the genetic determinant of interest and/or ruled out the presence of that resistance gene by mean of genotypic characterization on culture colonies. A true negative was defined as a result where the BCID2 did not detect a resistance marker of interest and the blood culture-based gold standard comparator showed a susceptible phenotype for those antimicrobials to which resistance is normally induced by the genetic determinant of interest and/or ruled out the resistance marker of interest by mean of genotypic characterization on culture colonies.

If both phenotypic and genotypic testing were performed by a study as gold standard comparators for assessing antimicrobial resistance and gave a discrepant result for a resistance profile of interest, the result from genotypic testing was chosen as gold standard comparator rather than the phenotypic result.

Of note, isolates showing intermediate resistance to specific antimicrobials at standard phenotypic testing were considered as resistant. Moreover, considering that the BCID2 panel no longer reports mecA/C for coagulase-negative staphylococci except for S. epidermidis and S. lugdunensis, accuracy of mecA/C was calculated for these two species only.

Blood cultures growing BCID2 off-panel pathogens were included in the analysis, while blood cultures resulting in BCID2 invalid runs were not included.

If information in the selected papers was unclear or incomplete, the authors were emailed for obtaining missing data. The manufacturer was also contacted to confirm whether any changes had been made from the “RUO prototype” versions to the RUO/IUO and IVD versions of the test.

Quality assessment
The QUADAS-2 scale was used to assess the quality of studies included in the meta-analysis [20], whose main domains were adapted to our specific clinical question. Specifically, the domain “patient selection” was modified into “sample selection”; consistently, in all domains the word “patients” was always replaced by “blood culture samples”. Moreover, in the index test domain we did not include the signalling question about whether the threshold was pre-specified, as the test does not have any threshold. For the study reporting data about time to results only [21] the signalling questions about blinding in the index and reference standard domains of the risk of bias assessment were deemed not applicable, as well as the signalling question about genotypic confirmation in the reference standard domain of the applicability concerns section.

The quality scores were inputted in the Quality effects model as part of the sensitivity analysis for the main BCID2 targets.

Statistical analyses
Contingency tables were built for each target of the BCID2, including bloodstream pathogens and resistance markers, by pooling results from monomicrobial and polymicrobial blood cultures, with the total number of samples for each table being equal to the number of blood cultures tested by each specific study.

Results were then assessed for specific targets and groups of targets of interest. The split component synthesis (SCS) method [22] using the inverse variance heterogeneity model [23] was utilised to estimate the pooled diagnostic odds ratio (DOR) and calculate the heterogeneity ($I^2$). The SCS method then splits the DOR into its component parts, the logit sensitivity (Se) and logit specificity (Sp), and from there derives the negative and positive likelihood ratios (LR − and LR +). The area under the curve (AUC) was derived from the DOR using the following equation logit (AUC) = ln(DOR)/2.

Sensitivity analyses were conducted using the Quality effects model to assess the impact of the quality of the individual studies [24], the quality scores were taken from the quality assessment. Publication bias was assessed using of the Doi plot and the LFK index [25]. The funnel plot and existing tests for asymmetry (e.g. Egger, Begg) where not used as the standard errors of DOR could be misleading, and thus not suitable for meta-analyses of test accuracy [26]. The statistical analysis was performed with STATA/SE 16.1 using the diagma [27] and I FK modules [28].

Time to results were defined as the time from blood culture collection to pathogen identification and antimicrobial resistance markers detection or AST availability according to the BCID2 and conventional culture testing.

Results
Yield of search strategy
The search strategy resulted in 163 papers and the backward & forward literature citation search performed in Scopus in 180 papers. The grey literature search identified further 284 records. As a result of the literature screening, ten studies met the inclusion criteria [9–14,
Agreement between the two reviewer was substantial with a $k$ correlation coefficient 0.7959 (95% CI 0.6178 to 0.9740). The PRISMA flow diagram reporting the steps of the study selection is shown in the Fig. 1 [30].

**Study characteristics**

Eight out of ten included reports were published as original studies [9–14, 21, 29], one was a conference report [31], and one was a multicentric study whose results had both been published as a conference report as well as submitted by the manufacturer for obtaining FDA approval [32, 33].

Nine out of the ten selected studies reported data about the BCID2 accuracy in identifying pathogens and resistance genes markers compared to culture-based methods [8–14, 29, 31, 32]; of them two also reported data about time to results [12, 29]. One study reported data about time to results only [21].

Four of the selected studies were from Europe [9, 11, 13, 31], two from Australia [12, 29], one from the U.S [10], one from Hong Kong [14], one from India [21] and one was a multicentric study including sites both from the U.S. and Europe [32, 33]. Three out of ten studies were multicentric in design. All the 9 studies reporting data about the BCID2 accuracy for pathogens and resistance markers identification included fresh clinical blood culture samples [9–12, 29, 31–33], except one which included spiked samples only [14], and another one which assessed archived clinical samples [13]. Some studies including clinical samples, also included a subgroup of spiked blood cultures [9, 11]. One study included both data about clinical, archived and seeded samples but only the data from the clinical prospective group was included in our analysis as the other two groups were not eligible due to the comparator used [32, 33]. The number of samples assessed by each study ranged from 30 to 1074 and all studies included both monomicrobial and polymicrobial isolates. One study focused on paediatric blood cultures and three studies specifically on blood cultures collected from the Intensive Care Unit and/or Emergency Department. Table 2 summarizes the characteristics of the studies included in the metanalysis.

Two studies were funded by the manufacturer (either bioMérieux or Biofire diagnostics, which has currently been acquired by bioMérieux) [10, 32, 33], while in other cases the manufacturer supplied the laboratory kit consumables only [9, 12–14, 29]. In the study funded by Biofire diagnostics, it was disclosed that the funder had no role in study design, data collection and interpretation. In two cases funding was not disclosed [21, 31].
Pathogen identification was performed in 9/10 studies according to MALDI-TOF [9–14, 21, 29, 31], while different methods were used for AST according to local practices, including semi-automated methods (VITEK-2) and conventional phenotypic testing such as disk and gradient diffusion testing and broth microdilution in line with EUCAST and CLSI guidelines [16, 17]. Among the 9 studies reporting data to build 2 × 2 tables, genotypic confirmation of antimicrobial resistance genes in case of detection of phenotypic resistance was performed by all except one study [10]. One study reported data about pathogen identification and not about antimicrobial resistance markers detection [31]. Table 3 summarizes the conventional culture methods used as gold standard for pathogen identification and resistance detection by the different studies.

Overall, the 9 studies reporting data about the BCID2 accuracy in identifying bloodstream pathogens and resistance markers compared to culture-based methods, included 2005 blood cultures assessed with both methods, after excluding BCID2 invalid runs (n=3). Of these, 1913 were blood culture clinical samples (95.4%) and 92 (4.6%) spiked samples; moreover 268 (13.4%) yielded a polymicrobial result according to either conventional culture methods or the BCID2. Overall, 839 BCID2 on-panel Gram negative bacteria, 1159 Gram positives and 86 yeasts grew from the included samples. All BCID2 on-panel pathogens grew according to conventional culture methods on the blood cultures samples, including: Enterobacterales (n=678), of which the most common species were E. coli (n=354), Klebsiella spp. (n=183), E. cloacae complex (n=51), Proteus spp. (n=31), S. marcescens (n=25), and Salmonella (n=24), non-fermenting bacilli (P. aeruginosa n=73, A. baumannii n=24, and S. maltophilia, n=21), B. fragilis (n=24), Gram negative encapsulated bacteria (N. meningitidis n=7, and H. influenzae, n=12), E. faecalis (n=79), E. faecium (n=76), L. monocytogenes (n=13), Staphylococcus spp. (n=750), including S. epidermidis (n=338), S. aureus (n=238) and S. lugdunensis (n=17), Streptococcus spp. (n=241)

### Table 2 Characteristics of studies included in the meta-analysis

| Author, year      | Study design       | Country          | Population                  | Type of samples (n) | Blood culture samples growth  | Total samplesa | Diagnostic accuracy | TAT |
|-------------------|--------------------|------------------|-----------------------------|---------------------|------------------------------|---------------|---------------------|-----|
| Berinson et al. 2021 [9] | Prospective, single centre | Germany          | ICU, ED, adults             | Clinical (182) + spiked (10) | Monomicrobial (161); polymicrobial (31) | 192           | Yes                 | No  |
| Graff et al. 2021 [10] | Prospective, single centre | U.S              | Any ward, paediatric       | Clinical (191)      | Monomicrobial (167); polymicrobial (24) | 191           | Yes                 | No  |
| Holma et al. 2021 [11] | Prospective, single centre | Finland          | Any ward                    | Clinical (102) + spiked (21) | Monomicrobial (71); polymicrobial (29); negative (23) | 123           | Yes                 | No  |
| Sparks et al. 2021 [12] | Prospective, multi centre  | Australia        | Any ward                    | Clinical (49)       | Monomicrobial (42); polymicrobial (7) | 49            | Yes                 | Yes |
| Cortazzo et al. 2021 [13] | Assessment of archived samples, single centre | Italy            | Not specified               | Archived (90)      | Monomicrobial (55); polymicrobial (33) | 90            | Yes                 | No  |
| Peri et al. 2022 [29] | Prospective, single centre | Australia        | ICU, ED, adults             | Clinical (62)       | Monomicrobial (60); polymicrobial (2) | 62            | Yes                 | Yes |
| Sze et al. 2021 [14] | Assessment of seeded samples, single centre | Hong Kong        | Not specified               | Spiked (61)        | Monomicrobial (46); polymicrobial (15) | 61            | Yes                 | No  |
| Lu et al. 2019 [32, 33] | Prospective, multi centre  | U.S., Europe     | Not specified               | Clinical (1074)     | NA b                        | 1074          | Yes                 | No  |
| Camelena 2021 [31] | Prospective, multi centre  | France           | ICU, ED, haematology, surgery, adults and paediatrics | Clinical (163)     | Monomicrobial (153); polymicrobial (10) | 163           | Yes                 | No  |
| Shah et al. 2022 [21] | Prospective, single centre | India            | ICU, adults and paediatrics | Clinical (30)      | Monomicrobial (23); polymicrobial (7) | 30            | No                  | Yes |

* Excluding invalid runs; a125/1074 samples had multiple analytes detected by BCID2
** TAT = Turnaround Time; ICU = Intensive Care Unit; ED = Emergency Department; NA = Not available
Table 3  Culture-based methods used by the different studies, serving as gold standard comparators for the BCID2

| Study                  | Comparator for pathogen ID | Methods used for AST | Comparator for blaCTX-M | Comparator for carbapenemases | Comparator for mcr-1 | Comparator for mecA/C | Comparator for mecA/C & MREJ | Comparator for vanA/B |
|------------------------|----------------------------|-----------------------|--------------------------|------------------------------|----------------------|------------------------|-----------------------------|-------------------------|
| Berinson et al. [9]    | MALDI-TOF MS               | VITEK-2               | 3rd gen. cephalosporin resistance at VITEK-2 confirmed by combination disk test; PCR⁴ if cephalosporin-R / BCID2-blaCTX-M negative isolates | Carbapenem resistance confirmed by PCR⁵ | Not specified | Oxacillin resistance confirmed by PCR | Oxacillin resistance confirmed by immunochromatographic assay and GeneXpert SA/ MRSA | Glycopeptide resistance confirmed by vanA/B PCR and GeneXpert vanA-vanB |
| Graff et al. [10]      | MALDI-TOF MS               | Phenotypic methods according to CLSI | 3rd gen. cephalosporin resistance | Carbapenem resistance | Phenotypic resistance | Oxacillin resistance | Oxacillin resistance | Glycopeptide resistance |
| Holma et al. [11]      | MALDI-TOF MS confirmed by 16S rDNA seq if unclear results | Disk and/or MIC-gradient diffusion | Genotypic characterization | Genotypic characterization | Genotypic characterization | Genotypic characterization | Genotypic characterization | |
| Sparks et al. [12]     | MALDI-TOF MS               | VITEK-2 and/or disk diffusion, Etest | 3rd gen. cephalosporin resistance + phenotypic confirmation of ESBL and/or PCR | Carbapenem resistance confirmed by PCR for blaIMP⁶ | Not specified | Oxacillin resistance confirmed by PCR | Oxacillin resistance confirmed by PCR | Glycopeptide resistance confirmed by PCR |
| Cortazzo et al. [13]   | MALDI-TOF MS               | PCR                   | PCR                       | PCR                         | Not specified | Oxacillin resistance confirmed by PCR | Oxacillin resistance confirmed by PCR | Glycopeptide resistance |
| Peri et al. [29]       | MALDI-TOF MS               | VITEK-2, disk diffusion, E-test | 3rd gen. cephalosporin resistance (disk test and BMD) confirmed by PCR | Carbapenem resistance | Not specified | Oxacillin resistance confirmed by PCR | Oxacillin resistance confirmed by PCR | Glycopeptide resistance |
| Sze et al. [14]        | MALDI-TOF MS               | BMD                   | 3rd gen. cephalosporin resistance (disk test and BMD) confirmed by PCR | PCR                         | Colistin resistance confirmed by PCR | Oxacillin resistance confirmed by PCR | Oxacillin resistance confirmed by PCR | Glycopeptide resistance confirmed by PCR |
| Lu et al. [32, 33]     | Standard manual and automated microbiological/biochemical methods | Manual and automated methods according to CLSI | Genotypic characterization | Genotypic characterization | Phenotypic resistance (BMD) | Genotypic characterization | Genotypic characterization | Genotypic characterization |
| Camelenac [31]        | MALDI-TOF MS               | Not performed         | -                         | -                           | -                     | -                      | -                           | -                       |
| Shah et al. [21]       | MALDI-TOF MS               | VITEK-2               | VITEK-2                   | VITEK-2                    | VITEK-2               | VITEK-2               | VITEK-2                    | VITEK-2                  |

⁴ For blaCTX-M, blaTEM, and blaSHV; ⁵ For spiked samples: genotypic profile assessed by PCR and Whole Genome Sequencing; ⁶ Data about pathogen identification only reported; ⁷ Data about time to results only reported.

ID = identification; MALDI-TOF MS = matrix-assisted laser desorption/ionization time of flight mass spectrometry; BMD = Broth Microdilution
and Candida spp. (n = 79). Among these isolates, the major resistance patterns detected according to conventional testing were: ESBL production in Enterobacterales (n = 114), resistance to carbapenems and/or production of carbapenemases in Gram-negatives (n = 59), resistance to oxacillin and/or genotypic detection of mecA/C (n = 212) and mecA/C & MREJ in Staphylococcus spp. (n = 76) and resistance to vancomycin and/or detection of vanA/B in Enterococcus spp. (n = 44). Resistance to colistin was rarely tested in carbapenem susceptible isolates as per local practices, and colistin isolates were always avoided. Moreover, in the index and gold standard test domains, it was unclear for some studies (7/9, 78%) [9, 11, 13, 14, 29, 31–33] whether the index test interpreter was blind to the results of the gold standard and vice versa (5/9 studies, 56%) [9–11, 31–33]. Overall, the main reason for high risk of bias was found in the flow and timing domain and was due to the use by most studies (5/9, 56%) of different gold standards on different samples, mainly when performing PCR sequencing only on phenotypically resistant isolates [9, 12, 14, 29]. Nonetheless, most studies (5/9, 56%) reported a good score relatively to all the applicability domains (see Additional file 1: Data 3a and 3b).

Time to results
Three studies only reported the time from blood culture collection to results according to the BCID2 and conventional culture methods [12, 21, 29], including time to pathogen identification and time markers detection and/or AST.

Specifically, according to Sparks et al. [12] mean time (± standard deviation [SD]) from blood culture collection to pathogen identification with the BCID2 and conventional culture methods were 24.6 (± 16.8) h and 38.32 (± 21.9) h respectively; moreover, mean time (± SD) to resistance detection for blood cultures containing blaCTX-M alleles with the BCID2 was 21.3 (± 0.4) h while mean time (± SD) to culture-based PCR and conventional AST for the same samples was 50.7 (± 0.4) h. A second study [29] estimated that if the BCID2 had been implemented in the clinical workflow, pathogen identification and resistance markers detection would have been available 9.69 h (95% CI: 7.85 to 11.53) and 27.8 h (95% CI: 23.05 to 32.55) sooner compared to conventional testing. However, these were only estimated times as the BCID2 was not run real time.

According to a third study median time to BCID2 results was 21 h while median times to pathogen identification and AST according to culture-based methods were 42 and 49 h respectively [21].

A fourth study [10] reported time to results according to the BCID2 but not according to conventional culture methods, and the remaining studies did not report any time to results. Therefore, overall, data about time to results were not considered enough to be assessed in the meta-analysis.

Quality assessment
Low quality assessment in the sample selection domain was mainly due to the exclusion by some studies (2/9, 22%) of some blood culture samples based on the time to positivity [9, 14] as well as to the lack of disclosure of whether consecutive samples were included (7/9 studies, 78%) [11–14, 29, 31–33], despite case control design was always avoided. Moreover, in the index and gold standard test domains, it was unclear for some studies (7/9, 78%) [9, 11, 13, 14, 29, 31–33] whether the index test interpreter was blind to the results of the gold standard and vice versa (5/9 studies, 56%) [9–11, 31–33]. Overall, the main reason for high risk of bias was found in the flow and timing domain and was due to the use by most studies (5/9, 56%) of different gold standards on different samples, mainly when performing PCR sequencing only on phenotypically resistant isolates [9, 12, 14, 29]. Nonetheless, most studies (5/9, 56%) reported a good score relatively to all the applicability domains (see Additional file 1: Data 3a and 3b).

Performance of BCID2
Figure 2a–f and Additional file 1: Data 4 summarize the performance of the assay for the most relevant on-panel determinants of bloodstream infection, including Enterobacterales, S. aureus, Streptococcus spp., blacTX-M, carbapenemases and mecA/C & MREJ [34, 35].

Overall, the BCID2 panel showed good performances for the detection of such targets. Specifically, the pooled sensitivity and specificity of the BCID2 for the detection of Enterobacterales were 98.2% (95% CI 96.3 to 99.1) and 98.3% (95% CI 96.5 to 99.2) respectively, with an Area Under the Curve (AUC) of 0.982 (95% CI 0.972 to 0.989) (Fig. 2a). Of note, among 58 false positive results for Enterobacterales detected in all studies, 53 were attributed to the presence of nucleic acid from non-viable E. coli in specific lots of blood culture bottles in the multicentric pivotal study [32, 33]. For S. aureus sensitivity and specificity were 96.0% (95% CI 90.4 to 98.4) and 99.5% (95% CI 98.7 to 99.8) respectively, with an AUC of 0.986 (95% CI 0.974 to 0.993) (Fig. 2b) and for Streptococcus spp. sensitivity was 96.7% (95% CI 92.8 to 98.5), specificity 99.5% (98.8 to 99.8) and the AUC 0.978 (95% CI 0.978 to 0.992) (Fig. 2c). The performance of the BCID2 for the detection of the main on-panel antimicrobial resistance markers was also high, with a pooled sensitivity and specificity of 94.9% (95% CI 85.7 to 98.3) and 99.4% (95% CI 97.8 to 99.8) for blacTX-M, 94.9% (95% CI 83.4 to 98.6) and 99.7% (95% CI 98.9 to 99.9) for carbapenemases, and 93.9% (95% CI 83.0 to 98.0) and 99.6% (95% CI 98.6–99.9) for mecA/C & MREJ (Fig. 2d–e).

Table 4 summarizes the performance of the assay for the other BCID2 targets or subgroups of targets of interest. Overall, specificity was above 98% for all targets or subgroups of targets assessed, with a narrow confidence interval. Few false positive results were reported, mainly for S. epidermidis, where the lower limit of the confidence interval for specificity was 93.1%, and for mecA/C [9, 32, 33]. Of note, in one of the 2 studies were most false positive results were reported, S. epidermidis was
not unfrequently detected by the BCID2 panel in place of other coagulase-negative staphylococci [9].

In regard to pooled sensitivity, this was overall inversely proportional to the frequency the targets or subgroups of targets were detected in the whole samples’ population. Specifically, sensitivity was > 95% for *E. coli* and *Staphylococcus* spp. Moreover, for other targets commonly detected in the setting of bloodstream infections (including *Klebsiella* spp., enterococci, *P. aeruginosa*, *Candida* spp., and meCA/C) sensitivity values where > 90%, with the lower limit of confidence intervals > 80% (slightly lower for *S. epidermidis* and *vanA/B*). Other relevant but less common pathogens (such as *Proteus* spp., *Salmonella*, *A. baumannii*, *B. fragilis* and *S. lugdunensis*) maintained a sensitivity > 80% (with 95% CI > 60%), while for rarer targets (such as *H. influenzae*, *N. meningitidis*, *L. monocytogenes*, and *mcr-1*) sensitivity ranged from 73 to 86% with the lower limit of confidence intervals between 39 and 55%.

The AUC of the targets and subgroups of targets of interest were > 96% in most cases, with narrow confidence intervals.

The rate of invalid results reported by the studies was low as 3 samples only were excluded due to this reason. Heterogeneity was absent for all the targets and subgroups of targets considered except for *S. epidermidis*, where a moderate heterogeneity was found (52.7%), likely due to the relatively high number of false positives detected by some studies compared to others, as discussed [9, 32, 33], and for *H. influenzae*, where a low heterogeneity was found (31.9%) (Table 4).

The Doi plots for *Enterobacterales*, *S. aureus*, *Streptococcus* spp., *blaCTX-M* and carbapenemases showed no asymmetry, and for meCA/C & MREJ minor asymmetry was found, overall excluding publication bias for the 6 major determinants of bloodstream infection (Additional file 1: data 5). Among the other targets assessed, major asymmetry of the Doi plots favouring studies with higher discretionary capacity suggesting the presence of publication bias was observed for *B. fragilis* (LFK index = 2.82), *S. epidermidis* (LFK index = 3.19) and meCA/C (LFK index ~ -2.29) (data not shown). This finding is not surprising considering some studies report a slightly less accurate performance of these targets compared to others [9, 32, 33].

The sensitivity analyses for the 6 main determinants of bloodstream infection (*Enterobacterales, S. aureus, Streptococcus* spp., *blaCTX-M*, carbapenemases and meCA/C) using the Quality effects models are shown in the Additional file 1: data 6 and confirm a good performance of the assay.

Five out of nine studies reported data about concordance between culture-based methods and BCID2 on polymicrobial blood cultures samples (see Table 5).
Overall, full concordance between the 2 methods was 75/90 (83%) polymicrobial samples, including pathogen identification and resistance marker detection.

686 new BCID2 targets (not included in the previous version of the test) were detected in 1913 clinical blood culture samples. Of those 335 were S. epidermidis and 112 antimicrobial resistance markers.

### Discussion

The results of our meta-analysis confirm overall a good performance of the BCID2 in detecting bloodstream pathogens and associated resistance markers. In particular, the specificity of the assay was excellent across all targets investigated. Regarding the BCID2 sensitivity, this was high (>95%) for targets which have
a major role in the aetiology of bloodstream infection, including *Enterobacterales*, *S. aureus*, *Streptococcus* spp., *P. aeruginosa*, enterococci and *Candida* spp., as well as some major resistance determinants such as *bla* <sub>CTX-M</sub>, carbapenemases and *mecA/C* and *MREJ* (> 90% with 95% CI ranging from 80 to 99%). In settings like sepsis, where early appropriate antimicrobial treatment is associated with survival [36], these performance values my help to optimise early patient management improving clinical outcomes.

Nonetheless, overall, few studies were included in our meta-analysis, due to the recent release of the BCID2 panel, partially preventing a robust assessment of the sensitivity of those pathogens or resistance markers which are less common in the setting of bloodstream infections.

The ten selected studies did not report enough information about turnaround times to be assessed in the meta-analysis. Available data suggest that the BCID2 can identify bloodstream pathogens and some antimicrobial resistance markers up to 10 h and 28 h earlier than conventional culture-based testing respectively, although this may vary according to local practices (i.e., use of MALDI-TOF on early subcultures) and further studies are needed to better define times to result compared to traditional techniques. Yet, the turnaround time of the BCID2 from a positive blood culture is well defined (1 h), and each centre could easily estimate the potential time gained with the implementation of the test based on their laboratory workflow and local practices.

Reduced turnaround time, however, is not sufficient to indicate the utility of a diagnostic test for bloodstream infection, and several additional factors should be considered. Among these, the possibility of running the test 24/7 rather than during business hours, based on the resources of the clinical laboratory, is likely going to affect the impact of the test on timely antimicrobial prescriptions. Moreover, despite the scarcity of randomized controlled trial in this field, a recent meta-analysis has shown that the impact of rapid diagnostic tests for bloodstream infection on patients’ outcome is dependent on the real-time implementation of the tests’ results by mean of antimicrobial stewardship programs [37]. Several rapid tests for the diagnosis of bloodstream infection have become available in the recent years, and the advantages of implementing one test over the other in a specific setting should also take into account the local epidemiology of antimicrobial resistance, as well as health economic endpoints. As compared to the previous version of the test, in our meta-analysis the BCID2 was able to detect up to 686 of the new targets (of which 335 where *S. epidermidis*) in 1913 clinical blood culture samples, likely proving an increased diagnostic usefulness compared to the prior panel.

Our study has some limitations that should be acknowledged. The first limitation is the lack of assessment of polymicrobial BC as a separate group from monomicrobial samples. Some studies reported how the agreement of the BCID2 results with conventional methods was lower for polymicrobial than monomicrobial samples [9, 12, 29], and this was not assessed in our analysis by means of diagnostic accuracy measures, since 2 × 2 tables could not be calculated for specific targets on polymicrobial samples. Specifically, Berinson et al. reported a concordance for polymicrobial samples of 63% (19/31) with the most common discrepancies due to the misidentification of coagulase-negative staphylococci species or additional growth of coagulase-negative staphylococci undetected by the BCID2 [9]. Moreover, in the study from Sparks et al. 2/7 polymicrobial samples had discordant results between the two methods, although in one case the additional growth observed according to conventional testing was thought to be due to a laboratory contamination, and the second discrepant case consisted in the lack of detection of *K. oxytoca* on a sample where *K. pneumoniae* also grew and was appropriately identified [12]. In a third study 1 out of 2 polymicrobial sample was found to have discordant results according to the two methods but whole genome sequencing confirmed results from the BCID2 rather than those from conventional culture [29]. Lastly, in the multicentric pivotal study 125/1074 positive blood cultures samples had multiple targets detected by BCID2 of which 43/125 (34.4%) had perfect agreement with conventional testing; notably, when omitting the 53 false positive results due to the presence of nucleic acid from non-viable *E. coli* in specific lots of blood culture bottles, agreement with conventional testing was 43/84 (51.2%).

| Study            | Concordant results / total polymicrobial samples (%) |
|------------------|-----------------------------------------------------|
| Berinson et al.  | 19/31 (61.3)                                        |
| Sparks et al.    | 5/7 (71.4)                                          |
| Cortazzo et al.  | 35/35 (100)                                         |
| Peri et al.      | 1/2 (50)                                            |
| Sze et al.       | 15/15 (100)                                         |
| Total            | 75/90 (83)                                          |

In the study by Lu et al. [32, 33] 125/1074 positive blood cultures samples had multiple targets detected by BCID2 of which 43/125 (34.4%) had perfect agreement with conventional testing. When omitting the 53 false positive results due to the presence of nucleic acid from non-viable *E. coli* in specific lots of blood culture bottles, agreement with conventional testing was 43/84 (51.2%).
Differently, other studies reported an agreement of 100% on polymicrobial samples.

The high number of false positives detected in the pivotal study due to the presence of non-viable E. coli in some blood cultures bottles highlights a limitation of tests based on the detection of pathogen DNA rather than conventional cultures, which can falsely detect non-viable pathogens.

Another limitation of our meta-analysis relates to our definition of the “I” category as “intermediate resistance”. Current EUCAST guidelines now use the definition of “I” as “susceptible, increased exposure” [38], rather than as “intermediate”, as we have done, following the approach used by the papers we have included. As such, our classification of isolates into resistant (including the previously defined intermediate isolates) or susceptible should be interpreted according to the former guidelines. Overall, very few isolates were classified as “intermediate” (n = 7).

A third limitation of our meta-analysis is the heterogeneity of the microbiological methods used as gold standard comparators for the detection of antimicrobial resistance, which included both phenotypic and genotypic testing. Overall, in one study only [10] antimicrobial resistance was assessed by means of phenotypic methods only, not accompanied by any genotypic confirmation, with, however, no major discrepancies observed with the BCID2 results. However, it should be acknowledged that most of the other studies used the genotypic characterization only to confirm a resistant phenotype detected by conventional culture methods or an antimicrobial resistance marker detected by the BCID2, or to investigate discordant results between phenotypic AST and BCID2 [9, 12, 14, 29], without performing a blind genotypic assessment of all samples. Given resistance genes can sometimes be expressed at clinically insignificant levels, the lack of an extended genotypic characterization of all samples might have affected the assessment of the performance of the BCID2 for antimicrobial markers detection.

Nevertheless, it must be acknowledged that the interaction between genotypic and phenotypic resistance is complex [39], and the use of molecular methods for the detection of resistance markers in the setting of clinical infections always requires critical thinking, both in the case of negative results (where phenotypic resistance might still be possible due to underlying different genetic determinants) and positive ones (where the genes detected might not be expressed, leading to a susceptible phenotype). Moreover, in the case of the BCID2, while for some genetic markers the association with the phenotypic resistance is univocal and very well established (i.e., meca for oxacillin resistance in Staphylococcus spp.) [40], in other cases, the on-panel genetic markers only explain a fraction of a specific phenotypic profile. This is for example the case of the detection of blaCTX-M, which cannot itself explain all the cases of 3rd generation cephalosporin resistance, whose genotypic determinants are more numerous within the setting of the Extended Spectrum Beta Lactamases and AmpC enzymes [41]. Moreover, as known, the BCID2 is not able to detect all CTX-M variants (i.e., CTX-M-151) although it does detect the majority of them [8].

The accuracy of an assay in terms of sensitivity and specificity lacks the capacity to capture all these complex scenarios, which are extremely relevant from the clinical point of view. Diagnostic accuracy is an important component in the assessment of the utility of a rapid diagnostic test but should be complemented by an evaluation of its real-life impact in clinical practice, incorporating the confidence of acting upon the results provided. This might best be performed by undertaking a cluster randomised trial in which laboratories are randomly assigned to use of BCID2 or conventional methods. The impact on clinically relevant outcomes associated to the use of the system combined with appropriate antimicrobial stewardship could then be determined.

**Conclusions**

The BCID2 showed good performance for the detection of on-panel targets including bloodstream pathogens and antimicrobial resistance determinants, making the assay a promising tool to implement in clinical practice. Nonetheless, in the clinical scenario, the use of molecular methods for the detection of antimicrobial resistance should always be interpreted carefully when used for clinical decision making, due to the complex interaction between genetic determinants and phenotypic profiles.

**Abbreviations**

BCID2: BioFire blood culture identification 2 panel; MALDI-TOF MS: Matrix-assisted laser desorption/ionization time of flight mass spectrometry; AST: Antimicrobial susceptibility testing; SE: Sensitivity; SP: Specificity; PRISMA-DTA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies; CE-IVD: Conformité Européenne In vitro Diagnostics; FDA: Food and drug administration; TGA: Therapeutic goods administration; RUO: Research use only (RUO); IUO: Investigational use only; SCS: Split component synthesis; DOR: Diagnostic odds ratio; LR: Likelihood ratios; AUC: Area under the curve; CI: Confidence interval; SD: Standard deviation.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07772-x.

**Additional file 1.** Supplementary data.

**Acknowledgements**

We thank Lars Eriksson for his support in during the systematic search, Prof Kelly Graff for sharing data of their previously published study, and Dr Usha...
Spaulding and Green Murray from bioMerieux for providing information about the assay.

Author contributions
AMP, DLP, and LFK designed the study. AMP and WL performed the blind screening of the literature. AMP performed the statistical analysis and wrote the paper; LFK supervised and advised on the appropriateness of the methods; WL, LFK, PNAH and DLP revised the paper for important intellectual content and agreed on the final version of the manuscript. All authors read and approved the final manuscript.

Funding
This research received no specific Grant from any funding agency in the public, commercial, or not-for-profit sectors. WL and AMP are receiving scholarship support from the University of Queensland for their Doctor of Philosophy candidature. LFK is supported by Australian National Health and Medical Research Council Early Career Fellowships (APP1158469). PH was supported by an Early Career Research Fellowship from the NHMRC (GNT1157530).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
DLP has received honoraria for speaking for bioMerieux. The other authors declare no conflict of interest.

Author details
1 University of Queensland Centre for Clinical Research, Herston, QLD 4029, Australia. 2 Central Microbiology, Pathology Queensland, Royal Brisbane and Women’s Hospital, Herston, QLD 4029, Australia. 3 Infectious Diseases Unit, Royal Brisbane and Women’s Hospital, Herston, QLD 4029, Australia.

Received: 23 May 2022 Accepted: 9 October 2022 Published online: 20 October 2022

References
1. Ferrer R, Martin-Lloechs I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42(8):1749–55.
2. Lamy B, Sundqvist M, Iledevich EA, Escmid Study Group for Bloodstream Infections E, Sepsis. Bloodstream infections—standard and progress in pathogen diagnostics. Clin Microbiol Infect. 2020;26(2):142–50.
3. Opota O, Croxatto A, Prod’hom G, Greub G. Blood culture-based diagnosis of bacteremia: state of the art. Clin Microbiol Infect. 2015;21(4):313–22.
4. Peker N, Couto N, Sinha B, Rossen JW. Diagnosis of bloodstream infections from positive blood cultures and directly from blood samples: recent developments in molecular approaches. Clin Microbiol Infect. 2018;24(9):944–55.
5. Banerjee R, Teng CB, Cunningham SA, Ihde SM, Steckelberg JM, Morarty JP, Shah ND, Mandrekar JN, Patel R. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. Clin Infect Dis. 2015;61(7):1071–80.
6. Bluss BA, Baures TJ, Yoo M, Hansen KE, Alexander DP, Benefield RJ, Spivak ES. Impact of a multiplex PCR assay for bloodstream infections with and without antimicrobial stewardship intervention at a cancer hospital. Open Forum Infect Dis. 2018;5(10):ofy258.
7. Ny P, Ozaki A, Pallares J, Nieberg P, Wong-Beringer A. Antimicrobial stewardship opportunities in patients with bacteremia not identified by BioFire FilmArray. J Clin Microbiol 2019; 57(5).
8. BIOFIRE Blood Culture Identification 2 Panel (BCID2). https://www.biomerieux.com/biofire-bcid-panel.
9. Berinson B, Both A, Bemekling L, Christner M, Lutgehetmann M, Aepfelbacher M, Rohde H. Usefulness of BioFire FilmArray BCID2 for Blood Culture Processing in Clinical Practice. J Clin Microbiol. 2021;59(8): e0054321.
10. Graff KE, Palmer C, Anaestani T, Velasquez D, Hamilton S, Pretty K, Parker S, Dominguez SR. Clinical impact of the expanded BioFire blood culture identification 2 panel in a U.S. Children’s Hospital. Microbiol Spectr. 2021;9(1):e0042921.
11. Holma T, Torvikoski J, Friberg N, Nevalaainen A, Tarikka E, Antikainen J, Martinell JJ. Rapid molecular detection of pathogenic microorganisms and antimicrobial resistance markers in blood cultures: evaluation and utility of the next-generation FilmArray Blood Culture Identification 2 panel. Eur J Clin Microbiol Infect Dis. 2021.
12. Sparks R, Balgahom R, Janto C, Polkinghorne A, Braney AJ. Evaluation of the BioFire Blood Culture Identification 2 panel and impact on patient management and antimicrobial stewardship. Pathology 2021.
13. Cortazzo V, D’Inzeo T, Giordano L, Menchinelli G, Loiti FM, Fiori B, De Maio F, Luzzaro F, Sanguinetti M, Posteraro B et al. Comparing BioFire FilmArray BCID2 and BCID panels for direct detection of bacterial pathogens and antimicrobial resistance genes from positive blood cultures. J Clin Microbiol. 2021; 59(4).
14. Sze DTT, Lau CYY, Chan TM, Ma ESK, Tang BSF. Comparison of novel rapid diagnostic of blood culture identification and antimicrobial susceptibility testing by Accelerate Pheno system and BioFire FilmArray Blood Culture Identification and BioFire FilmArray Blood Culture Identification 2 panels. BMJ Microbiol. 2021;21(1):350.
15. McInnes MDF, Moher D, Thoms B, Moher M, Collins J, McAuley DL, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA. 2018;319(4):388–96.
16. EUCAST guideline for the selection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. http://www.eucast.org/resistance_mechanisms/
17. Performance Standards for Antimicrobial Susceptibility Testing, 31st edition. CLSI Supplement M100. https://clsi.org/standards/products/microbiology/documents/m100/.
18. Team TE. EndNote X9 edn. Philadelphia, PA: Clarivate; 2013.
19. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
20. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leflay MM, Sterne JA, Bossuyt PM, Group Q-UADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36.
21. Shah S, Davar N, Thakkar P, Sawant C, Jadhav L. Clinical utility of the FilmArray blood culture identification 2 panel in identification of microorganisms and resistance markers from positive blood culture bottles. Indian J Microbiol Res. 2022;9(1):28–33.
22. Furuya-Kanamori L, Kostoulas P, Dori SA. A new method for synthesizing test accuracy data outperformed the bivariate method. J Clin Epidemiol. 2021;132:51–8.
23. Furuya-Kanamori L, Kostoulas P, Dori SA. A new method for synthesizing test accuracy data outperformed the bivariate method. J Clin Epidemiol. 2021;132:51–8.
24. Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials I: the inverse variance heterogeneity model. Contemp Clin Trials. 2015;45(Pt A):130–8.
25. Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model. Contemp Clin Trials. 2015;45(Pt A):123–9.
26. Furuya-Kanamori L, Barendregt JJ, Dori SA. A new improved graphical and quantitative method for detecting bias in meta-analysis. Int J Evid Based Healthc. 2018;16(4):195–203.
27. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005;58(9):882–93.
28. Furuya-Kanamori L, Dori SA, 2020. DIAGMA: Stata module for the split component synthesis method of diagnostic meta-analysis. Statistical Software Components: S458815, Boston College Department of Economics, revised 16 Oct 2021.
28. Furuya-Kanamori L, Doi SAR. 2020. LFK: Stata module to compute LFK index and Doi plot for detection of publication bias in meta-analysis. Statistical Software Components S458762, Boston College Department of Economics, revised 16 Oct 2021.

29. Peri AM, Bauer MJ, Bergh H, Butkiewicz D, Paterson DL, Harris PN. Performance of the BioFire Blood culture identification 2 panel for the diagnosis of bloodstream infections on blood cultures from the intensive care unit and emergency department. SSRN Electronic J 2022.

30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.

31. Camelena F. Performances et impact thérapeutique du BioFire Blood Culture Identification 2 (BCID2) Panel au cours du sepsis. In: 23es Journées Nationales d’Infectiologie. Monpellier, France, 2021.

32. Lu Y, Hatch J, Holmberg K, Hurlock A, Drobyshева D, Spaulding U, Vourli S, Pouran S, Everhart K, Leber A et al. Multi-center Evaluation of the BioFire® FilmArray® Blood Culture Identification 2 Panel for the Detection of Microorganisms and Resistance Markers in Positive Blood Cultures. In: IDWeek Washington DC, U.S.; 2019.

33. BioFire® Blood Culture Identification 2 (BCID2) Panel, Instructions for use and manual https://www.biofiredx.com/e-labeling/ITI0048.

34. Diekema DJ, Huiehl PR, Mendes RE, Pfaffer MA, Rolston KV, Sader HS, Jones RN. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrob Agents Chemother. 2019; 63(7).

35. Douglas NM, Hennessy JN, Currie BJ, Baird RW. Trends in bacteremia over 2 decades in the top end of the northern territory of Australia. Open Forum Infect Dis. 2020;7(11):ofaa472.

36. Sherwin R, Winters ME, Vike GM, Wardi G. Does early and appropriate antibiotic administration improve mortality in emergency department patients with severe sepsis or septic shock? J Emerg Med. 2017;53(4):588–95.

37. Timbrook TT, Morton JB, McConeghy KW, Caffrey AR, Mylonakis E, LaPlante KL. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: a systematic review and meta-analysis. Clin Infect Dis. 2017;64(1):15–23.

38. EUCAST To clinical colleagues: On recent changes in clinical microbiology susceptibility reports ‑ new interpretation of susceptibility categories S, I and R. In; 2021.

39. Hughes D, Andersson DI. Environmental and genetic modulation of the phenotypic expression of antibiotic resistance. FEBS Microbiol Rev. 2017;41(3):374–91.

40. Williams MC, Dominguez SR, Prinzi A, Lee K, Parker SK. Reliability of mecA in predicting phenotypic susceptibilities of coagulate-negative staphylococci and Staphylococcus aureus. Open Forum Infect Dis. 2020;7(12):ofaa553.

41. Stewart AG, Price EP, Schabacker K, Birikmen M, Harris PNA, Choong K, Subedi S, Sarovich DS. Molecular epidemiology of third-generation-cephalosporin-resistant enterobacteriaceae in Southeast Queensland, Australia. Antimicrob Agents Chemother. 2021;65(6):e00130-e221.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.