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Tristan T. Timbrook
University of Rhode Island

Jacob B. Morton
University of Rhode Island

See next page for additional authors

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The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review & Meta-analysis

Tristan T. Timbrook[1,2], Jacob B. Morton[1,2], Kevin W. McConeghy[3], Aisling R. Caffrey[1,2,3], Eleftherios Mylonakis[4], Kerry L. LaPlante[1,2,3]

1. Rhode Island Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA
2. College of Pharmacy, University of Rhode Island, Kingston, RI, USA
3. Center of Innovation in Long Term Services and Supports, Providence Veterans Affairs Medical Center, Providence, RI, USA
4. Infectious Diseases Division, Warren Alpert Medical School of Brown University, Providence, RI, USA

Corresponding Author: Kerry L. LaPlante, Pharm.D., FCCP, Professor, University of Rhode Island College of Pharmacy, 7 Greenhouse Rd, Suite 295A, Kingston, RI 02881, (401) 874-5560 (office); KerryLaPlante@uri.edu

Alternative Corresponding Author: Aisling R. Caffrey, PhD, MS, Assistant Professor, University of Rhode Island College of Pharmacy, 7 Greenhouse Rd, Suite 265B, Kingston, RI 02881, (401) 874-5320 (office); Aisling_Caffrey@uri.edu

Summary: Molecular rapid diagnostic testing (mRDT) in bloodstream infections significantly decreased the risk of mortality overall and with stewardship but not without. Time to effective therapy, as well as length of stay, were decreased with mRDT.

Background: Previous reports on molecular rapid diagnostic testing (mRDT) do not consistently demonstrate improved clinical outcomes in bloodstream infections (BSIs). This meta-analysis seeks to evaluate the impact of mRDT in improving clinical outcomes in BSIs.

Methods: We searched PubMed, CINAHL, Web of science, and EMBASE through May 2016 for BSI studies comparing clinical outcomes by mRDT and conventional microbiology methods.

Results: Thirty-one studies were included with 5,920 patients. Risk of morality was significantly lower with mRDT as compared to conventional microbiology methods (OR 0.66, 95% CI 0.54-0.80) yielding a NNT of 20. The risk of mortality was slightly lower with mRDT in studies with antimicrobial stewardship programs (ASPs) (OR 0.64, 95% CI 0.51-0.79) and non-ASP studies failed to demonstrate a significant decrease in risk of mortality (OR 0.72, 95% CI 0.46-1.12). Significant decreases in mortality risk were observed with both Gram-positive (OR 0.73, 95% CI 0.55-0.97) and Gram-negative organisms (OR 0.51, 95% CI 0.33-0.78) but not yeast (OR 0.90, 95% CI 0.49-1.67). Time to effective therapy decreased by a weighted mean difference of -5.03 hours (95% CI -8.60 to -1.45) and length of stay decreased by -2.48 days (95% CI -3.90 to -1.06).

Conclusions: For BSIs, mRDT was associated with significant decreases in risk of mortality in the presence of a ASP, but not in its absence. Additionally, mRDT decreased time to effective therapy and length of stay. mRDT should be considered as part of the standard of care in patients with BSIs.

Background

Bloodstream infections (BSIs) are associated with significant morbidity, mortality, and increased length of stay (LOS) [1,2]. Delayed administration of effective antibiotics increases the risk of mortality and therefore correct selection of an antibiotic regimen early in the treatment process is paramount [3,4]. Delayed identification of the causative organism and culture susceptibilities may often be responsible for delays in optimal antimicrobial therapy. Molecular rapid diagnostic testing (mRDT), which includes tests such as polymerase chain reaction (PCR), matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS), and peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), has improved upon conventional microbiological methods, reducing time to organism identification, optimizing antimicrobial therapy, and subsequently improving clinical outcomes, including mortality [5].

Advancement of RDT is now one of five overarching goals from the National Action Plan for Combating Antibiotic-Resistant Bacteria [6]. Additionally, the 2016 Infectious Diseases Society of America (IDSA) antimicrobial stewardship program (ASP) guidelines recommend the use of rapid diagnostic testing with ASP support and intervention as an addition to conventional methods for blood specimens to improve clinical outcomes [7]. Widespread implementation of this technology has been limited due to inadequate outcomes data and high costs [8]. A recent meta-analysis included evaluations of the clinical benefits of molecular and phenotypic rapid diagnostics in BSIs, but was limited by the time frame of the literature included, with the most recent study being published in 2012 [9]. Additionally, the impact on LOS was not assessed, nor was the effect on mortality according to ASP presence. The objective of this systematic review and meta-analysis was to provide a comprehensive and up-to-date assessment of mRDT on mortality, time to effective therapy, and LOS, when compared to conventional microbiology methods in patients with BSIs.

Methods

Literature Search

We searched PubMed, CINAHL, Web of Science, and Embase from inception to May 31, 2016 for BSI studies in English comparing clinical outcomes by mRDT and conventional microbiology methods. The search query used was (bacteremia or “bloodstream infection”) AND (spectrometry OR "Matrix assisted laser desorption/ionization" OR MALDI-TOF OR microarray OR PCR OR "nucleic acid" OR PNA OR molecular OR "polymerase chain reaction") AND ("length of stay" OR mortality OR morbidity OR diagnosis OR outcome). Two authors (TTT and JBM) searched the literature and performed article selection independently. Differences were resolved through consensus involving a third author (KWM). A manual search of the included articles’ references was conducted to identify additional relevant studies. Unpublished studies were included through searching abstracts from IDWeek, Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), and European Congress of Clinical Microbiology and Infectious Diseases (ESCMID) from 2007 to 2015 using the keywords bacteremia or bloodstream infection.

Study Selection

All studies evaluating the differences in clinical outcomes between mRDT, either for organism identification and/or resistance mechanism detection, and conventional methods in BSIs were eligible for inclusion. mRDT was defined as commercially available molecular tests that are able to provide results in 24 hours or less. Studies were included if results were reported for clinical outcomes of interest. Studies were excluded if they were non-English studies, evaluated infections with mycobacterial, viral, or parasitic organisms, or if mRDT was utilized on negative blood cultures or direct blood specimens (e.g. Septifast).

Outcomes

Outcomes evaluated included overall mortality, mortality in studies with ASP, mortality by organism, time to effective therapy, and LOS. Mortality was defined as all-cause 30-day or in-hospital. Organism types were grouped by Gram positive, Gram negative, yeast, or if a combination thereof, were termed multiple. Time to effective therapy was defined as the time from either blood specimen obtainment or positive test to a therapy with *in vitro* activity against the infecting organism. LOS was defined as total hospital or from culture (collection or positivity) LOS among either survivors or all patients within the study. Studies were classified as ASP studies if the authors reported infectious diseases physician or pharmacist review of antimicrobial selection based upon culture or mRDT results.

Quality Assessments

Assessments of quality were made by two authors (TTT and JBM) using the Newcastle-Ottawa Scale (NOS) [10] for observation studies and the Risk of Bias (ROB) tool for randomized controlled trials (RCT) [11]. NOS evaluates for the selection of patients, comparability of patients, and assessment of outcomes. The ROB tool assess whether there is a low, high, or unclear level of bias based on five primary domains of bias in RCTs, including selection, performance, detection, attrition, and reporting bias [12]. Differences in quality assessment between the two authors were resolved through consensus involving a third author (KWM).

Data Extraction and Analysis

All meta-analyses were performed using Review Manager v.5.3. Mortality outcomes were assessed using a random effects model to estimate pooled odds ratios (OR) and 95% confidence intervals (CI) with Dersimonian and Laird weights [13]. To express the effect of

testing in clinical terms, the number needed to treat (NNT) to prevent one death was calculated. The effect of mRDT on time to effective therapy and LOS was evaluated using a random effects model and reported as weighted mean difference and 95% CI. Medians and interquartile ranges or ranges were converted to means and standard deviations according to Wan et al. [14]. Publication bias was assessed using funnel plots and Egger's test. Heterogeneity between studies was evaluated with the I^2 estimation and Cochran *Q* test [12]. For heterogeneity testing, $P < .10$ was considered significant as the *Q* test has low power. Random-effects univariate meta-regressions were performed for covariates that had possible effects on an outcome and were reported in ≥ 10 studies using the metaphor package in R v.3.2.3. This systematic literature review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1).

Results

The literature search resulted in 7,273 studies meeting the keyword criteria (Figure 1). After removing duplicates, titles and abstracts were reviewed for 5,426 studies. Studies not related to our search were removed yielding 40 studies for full text review. Full-text review identified 5 articles with data not relevant to our meta-analysis, 3 studies without clinical outcomes, 2 studies with mRDT in each comparison arm, and 2 studies that evaluated mRDT on blood specimens in septic patients without positive cultures. Review of the references of the included studies resulted in 4 additional studies being added to the meta-analysis. Data were extracted from 31 studies with 5,920 patients as two studies [15,16] contained overlapping data.

Characteristics of the included studies are shown in Table 1. Only 6 studies (19.4%) [17–22] were conducted outside of the United States. The majority of studies included (26/31, 83.9%) were designed as pre- post-intervention quasi-experimental studies when initiating mRDT. While most of the studies reporting study setting were academic medical centers, 2 included

studies (6.5%) [23,24] were from community hospitals. Among studies reporting patient population information, adult patients were the most common cohort studied (95.2%, 20/21). Gram-positive organisms were the most frequently reported BSI type included, occurring in 17 studies (54.8%), followed by Gram-negative organisms with 7 studies (22.6%). Multiple organism and yeast studies comprised the remainder with 5 (16.1%) and 2 studies (6.5%), respectively.

Laboratory practices varied among studies, including mRDT technologies used, frequency of testing, and reporting processes. PCR or other microarray technologies were most frequently utilized (20/31, 64.5%), followed by PNA-FISH (6/31, 19.4%) and MALDI-TOF (4/31, 12.9%). One study (3.2%) utilized both a nanotechnology microarray system and confirmatory MALDI-TOF [25]. A distinction of MALDI-TOF analysis from direct blood specimen vs overnight solid media incubation was reported in 4 of 5 MALDI-TOF studies [15,24,26,35] with a single study [26] reporting the latter method. Of the 19 studies reporting the frequency of laboratory sample testing, 5 studies (26.3%) reported real-time testing, 10 studies (52.6%) batch testing between 1 to 4 times daily, and 3 studies (15.8%) reported real-time testing during limited time frames (e.g. 7am-7pm). Among the 5 studies performing 24x7 real-time testing, mRDT result notifications were reported as being performed in real time for two studies [27, 33] while another study [40] only notified of the results and in real time if resistance genes were detected. Finally, notification methods also varied between studies when reported, with the majority of the reporting studies (17/29, 58.6%) reporting directly to the primary team or physician, while 3 studies (10.3%) reported to the result to nurses.

ASP activities varied by study. The presence of an ASP facilitating mRDT represented the majority of the data (20/31, 64.5%). In the 14 studies reporting ASP notification processes, only half were 24x7 real-time. The remainder had set response hours (e.g., 8a-5p M-F) or once daily

review of results. Two studies [23,27], which were both quasi-experimental, explicitly stated whether the ASP was present in both periods with one [23] of the two having an ASP in the post period only.

Clinical outcomes in BSIs generally favored mRDT over conventional microbiology (Figures 2 and 3). Among 26 studies [5,15,17–20,23,24,26,28–44], the odds of mortality were significantly lower with mRDT (OR 0.66, 95% CI 0.54 to 0.80) yielding a NNT of 20. Stratification revealed that the odds of mortality were significantly lower for BSIs using mRDT with ASP (OR 0.64, 95% CI 0.51 to 0.79), but failed to achieve significance without ASP support (OR 0.72, 95% CI 0.46 to 1.12). Similar results were observed when a sensitivity analysis was performed using studies [17,20,26,29,36,40,43] which controlled for confounding (Supplementary Figure 1). When evaluating mortality by organism type (Figure 3), there was no significant difference in the odds of mortality among yeast isolates (OR 0.90, 95% CI 0.49 to 1.67). In contrast, the odds of mortality were reduced with mRDT among Gram-negative (OR 0.51, 95% CI 0.33 to 0.78), Gram-positive (OR 0.73, 95% CI 0.55 to 0.97), and multiple organism testing (OR 0.58, 95% CI 0.32 to 1.04). Mortality in multiple organism testing had significant heterogeneity (Cochran's Q P = .07, I^2 = 53%) due to a study [17] which used both mRDT and rapid susceptibility testing. Exclusion of that study yielded a 51% decreased odds of mortality in multiple organism testing (OR 0.49, 95% CI 0.33 to 0.71, Cochran's Q P = .56, I^2 = 0%). Sensitivity analysis using studies [17,20,26,29,36,40,43] controlling for confounding achieved non-significant reductions in risk of mortality by each organism group (Supplementary Figure 2). Meta-regressions of covariates by the presence of an ASP (P = .56), organism type (P = .42), real-time ASP (P = .82), or real-time mRDT (P = .34) as possible moderators for mortality were not significant.

Among 9 studies [20–22,25,26,33,34,37,44], time to effective therapy (Supplementary Figure 3) was significantly decreased by a weighted mean difference of -5.03 hours (95% CI -8.60 to -

1.45) with mRDT versus conventional microbiology. Time to effective therapy had significant heterogeneity (Cochran's Q P = .0002, I^2 = 74%) due to a study [33] which was limited to vancomycin resistant enterococci (VRE). Exclusion of that study yielded time to effective therapy with a decreased weighted mean difference of -1.89 hours (95% CI -2.43 to -1.36, Cochran's Q P = .48, I^2 = 0%). Evaluation of that study [33] and VRE subgroup data from 2 studies [25,36] yielded a time to effective therapy weighted mean difference of -26.65 h (95% CI -35.43 to -17.88, Cochran's Q P = .66, I^2 = 0%). Finally, LOS (Supplementary Figure 4) was significantly shorter with mRDT by -2.48 days (95% CI -3.90 to -1.06) and similar results were observed among subgroups by total hospital LOS and from culture LOS. Sensitivity analysis was performed using the only two studies [17,36] that controlled for confounding and reflected a decreased LOS by a WMD of -8.08 days (-20.59 to 4.44, Cochran's Q P < .0001, I^2 = 95%).

Analysis of the potential for publication bias with funnel plots (Supplementary Figures 5-7) suggested no evidence of publication bias for the analyses presented in Figures 2-3 and Supplementary Figure 3. Similarly, Egger's regression testing reflected an absence of publication bias for the analyses presented in Figures 2, 3, and Supplementary Figure 3 (P = .98, P = .98, P = .07, respectively). However, Egger's regression testing suggested possible publication bias with the LOS analysis (Supplementary Figure 4; P = .01).

Discussion

In this systematic review and meta-analysis of 31 studies and 5,920 BSI patients, mRDT was associated with a decreased risk of mortality and LOS, as well as improved time to effective therapy compared to conventional microbiological methods. The extent of adoption of mRDT for BSIs among acute care facilities in the United States is unknown, although use of rapid diagnostic tests for identification of drug resistant organisms and improving stewardship has been called for by the National Action Plan for Combating Antibiotic-Resistant Bacteria [6].

While a number of observational studies have supported the use of mRDT with ASPs for improving clinical outcomes, a recent randomized control trial has suggested these technologies have a limited impact [45]. However, it should be noted that the aforementioned study's definition of standard blood culture processing included MALDI-TOF, and therefore included mRDT in both comparator groups.

Clinical implications with the use of rapid diagnostics in BSIs has been evaluated in one meta-analysis [9]. While the previous meta-analysis evaluated the use of RDT with communication of results to providers, the role of ASP was not explored. Additionally, the meta-analysis was limited by its literature review time frame and did not focus solely on molecular technologies. In the current meta-analysis with 16 additional studies, we explored the relationship between mRDT and ASP specifically. We found that mortality decreased significantly with mRDT in the presence of ASP but not its absence. Thus, we believe our results support the IDSA ASP guideline recommendation to utilize rapid diagnostics with ASP facilitation in BSIs [7]. Moreover, our analysis approximates that mRDT would only need to be used in 20 patients with BSI in order to prevent one death within 30 days, which further supports mRDT as the standard of care in BSIs.

Compared to conventional microbiologic methods, mRDT was associated with significantly decreased risk of mortality among gram-negative organisms, gram-positive organisms, and multiple infection type studies, while yeast studies did not achieve significant mortality reductions. However, among studies [17,20,26,29,36,40,43] controlling for confounding, non-statistically significant reductions in risk of mortality were observed by organism groups. Failure to demonstrate the benefit of mRDT in yeast BSIs on risk of mortality or among studies in the sensitivity analysis may be due to the limited number of studies and corresponding sample sizes.

Detecting true mortality benefits may be difficult in pre-post studies that have not controlled for confounding. Therefore, the use of an outcome more directly related to mRDT, such as time to effective therapy, may be a better indicator of mRDT benefits. Despite few studies reported time to effective therapy, we did observe a significant decrease in time to effective therapy. However, the distribution of time to effective therapy varied both within and between studies. The importance of time to effective therapy has been recently demonstrated in a study of VRE bacteremia which reported a 3-fold increase in 30-day mortality in the absence of effective therapy in the first 48h of BSI, and speculated that rapid diagnostics may be beneficial in reducing time to effective therapy in the setting of VRE [3]. Our results suggest the particular utility of mRDT in VRE BSIs, improving time to effective therapy by over 24 hours. Furthermore, the mean time to effective therapy for all three VRE studies included in our analysis ranged from 43.7 hours to 50.2. As such, we believe mRDT may have profound benefits in patients with VRE bacteremia, and may help minimize risk of mortality.

Finally, significant decreases in LOS were observed. While we did not evaluate costs, the observed decreases in LOS have significant implications based on savings of cost per day for hospitalization. A study evaluating the economic impact of mRDT in BSI demonstrated an estimated $30,000 cost savings per 100 patients after accounting for mRDT costs [36]. However, the generalizability of decreased LOS reported are likely limited to large hospitals and medical centers as only two of the included studies were community hospitals. Additionally, LOS did not achieve significant reductions among the two studies [17,36] which controlled for confounding, although the significant heterogeneity in this analysis and small sample limit inference of these results.

There are several limitations to this systematic review and meta-analysis. For LOS, our analysis suggested possible publication bias. However, this may be related to the small number of studies reporting this outcome. While the generalizability of our findings for clinical outcomes may be limited to academic medical centers, it should be noted that two community hospital studies were included [23,24]. In one of the community hospital studies, while an ASP was present, non-ID trained pharmacists responded to the BSIs [24]. Future studies from the community hospital setting elucidating outcomes would help to clarify best practices in this area. Guidance for recording and reporting these outcomes when using RDT in BSIs has been described and should be utilized by researchers in the future [9]. In addition, we treated all interventions as equal with regards to technology type due to variability in laboratory practices such as batching of assays or performing MALDI-TOF either directly from blood culture bottles containing nutritional broth or from solid agar incubated overnight. Notification methods for mRDT results also varied which could have implications on clinical outcomes. While future evaluations may consider these variations and their relationship to clinical outcomes, our analysis supports mRDT as a group improves outcomes in BSIs. Additionally, we believe the implementation of mRDT should include an action plan to ensure correct interpretation, real-time reporting, and guidance on optimal therapy. Having 24x7 testing, with immediate notifications to the provider along with direction from an ASP team, will facilitate the initiation, escalation, or de-escalation of therapy in a meaningful timeframe.

Conclusion

mRDT was associated with significant decreases in morality in the presence of an ASP, but not in its absence. Significant decreases in risk of mortality were also seen for gram-positive organisms, gram-negative organisms, and multiple organism infection studies. Additionally, mRDT was associated with decreased time to effective therapy and LOS. The greatest benefit of mRDT for improving time to effective therapy may be for BSIs caused by resistant organisms,

particularly VRE. Additional studies in community hospitals are needed, as are additional studies elucidating the benefits of various microbiologic technologies in combination with ASP to define best practices. Based on the clinical outcomes, mRDT should be considered as part of the standard of care in patients with BSIs.

Notes

Potential conflicts of interest.

E.M. has received institutional grant support through T2 Biosystems. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Disclaimer.

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs.

References

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect **2013**; 19:501–509.
2. Vrijens F, Hulstaert F, Van de Sande S, Devriese S, Morales I, Parmentier Y. Hospital-acquired, laboratory-confirmed bloodstream infections: linking national surveillance data to clinical and financial hospital data to estimate increased length of stay and healthcare costs. J Hosp Infect **2010**; 75:158–162.
3. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ. Time Is of the Essence: The Impact of Delayed Antibiotic Therapy on Patient Outcomes in Hospital-Onset Enterococcal Bloodstream Infections. Clin Infect Dis **2016**; 62:1242–1250.
4. Marchaim D, Gottesman T, Schwartz O, et al. National Multicenter Study of Predictors and Outcomes of Bacteremia upon Hospital Admission Caused by Enterobacteriaceae Producing Extended-Spectrum -Lactamases. Antimicrob Agents Chemother **2010**; 54:5099–5104.
5. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of Rapid Diagnostic Tests Used by Antimicrobial Stewardship Programs. Clin Infect Dis **2014**; 59:S134–S145.
6. The White House. Fact Sheet: Obama Administration Releases National Action Plan to Combat Antibiotic-Resistant Bacteria. Available at: https://www.whitehouse.gov/the-press-office/2015/03/27/fact-sheet-obama-administration-releases-national-action-plan-combat-ant. Accessed 31 May 2016.
7. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis **2016**; 62:e51–e77.
8. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better Tests, Better Care: Improved Diagnostics for Infectious Diseases. Clin Infect Dis **2013**; 57:S139–S170.

9. Buehler SS, Madison B, Snyder SR, et al. Effectiveness of Practices To Increase Timeliness of Providing Targeted Therapy for Inpatients with Bloodstream Infections: a Laboratory Medicine Best Practices Systematic Review and Meta-analysis. Clin Microbiol Rev **2016**; 29:59–103.
10. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 7 May 2016.
11. Hartling L, Ospina M, Liang Y, et al. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. BMJ **2009**; 339:b4012–b4012.
12. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med **2002**; 21:1539–1558.
13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials **1986**; 7:177–188.
14. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol **2014**; 14:135.
15. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Arch Pathol Lab Med **2013**; 137:1247–1254.
16. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect **2014**; 69:216–225.
17. Beuving J, Wolffs PFG, Hansen WLJ, et al. Impact of same-day antibiotic susceptibility testing on time to appropriate antibiotic treatment of patients with bacteraemia: a randomised controlled trial. Eur J Clin Microbiol Infect Dis **2015**; 34:831–838.

18. Wang B, Jessamine P, Desjardins M, Toye B, Ramotar K. Direct mecA polymerase chain reaction testing of blood culture bottles growing Gram-positive cocci and the clinical potential in optimizing antibiotic therapy for staphylococcal bacteremia. Diagn Microbiol Infect Dis **2013**; 75:37–41.
19. Suzuki H, Hitomi S, Yaguchi Y, et al. Prospective intervention study with a microarray-based, multiplexed, automated molecular diagnosis instrument (Verigene system) for the rapid diagnosis of bloodstream infections, and its impact on the clinical outcomes. J Infect Chemother **2015**; 21:849–856.
20. Neuberger A, Oren I, Sprecher H. Clinical Impact of a PCR Assay for Rapid Identification of Klebsiella pneumoniae in Blood Cultures. J Clin Microbiol **2008**; 46:377–379.
21. Na SH, Kim C-J, Kim M, et al. Impact of the multiplex polymerase chain reaction in culture-positive samples on appropriate antibiotic use in patients with staphylococcal bacteremia. Diagn Microbiol Infect Dis **2016**; 84:353–357.
22. Cattoir V, Merabet L, Djibo N, et al. Clinical impact of a real-time PCR assay for rapid identification of Staphylococcus aureus and determination of methicillin resistance from positive blood cultures. Clin Microbiol Infect **2011**; 17:425–431.
23. Box MJ, Sullivan EL, Ortwine KN, et al. Outcomes of rapid identification for gram-positive bacteremia in combination with antibiotic stewardship at a community-based hospital system. Pharmacotherapy **2015**; 35:269–276.
24. Lockwood AM, Perez KK, Musick WL, et al. Integrating Rapid Diagnostics and Antimicrobial Stewardship in Two Community Hospitals Improved Process Measures and Antibiotic Adjustment Time. Infect Control Hosp Epidemiol **2016**; 37:425–432.
25. Roshdy DG, Tran A, LeCroy N, et al. Impact of a rapid microarray-based assay for identification of positive blood cultures for treatment optimization for patients with streptococcal and enterococcal bacteremia. J Clin Microbiol **2015**; 53:1411–1414.

26. Huang AM, Newton D, Kunapuli A, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis **2013**; 57:1237–1245.

27. Bauer KA, West JE, Balada-Llasat J, Pancholi P, Stevenson KB, Goff DA. An Antimicrobial Stewardship Program's Impact with Rapid Polymerase Chain Reaction Methicillin-Resistant *Staphylococcus aureus* / *S. aureus* Blood Culture Test in Patients with *S. aureus* Bacteremia. Clin Infect Dis **2010**; 51:1074–1080.

28. Bias T, Jain A, Beil E, et al. Use of the Nanosphere Verigene Gram-negative blood culture (BC-GN) systemfor more rapid bacterial identification and antimicrobial optimization in patientswith Gram-negative rod bacteraemia [abstract EP033]. In: Program and abstracts of the 25th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, **2015**.

29. Forrest GN, Mehta S, Weekes E, Lincalis DP, Johnson JK, Venezia RA. Impact of rapid in situ hybridization testing on coagulase-negative staphylococci positive blood cultures. J. Antimicrob Chemother **2006**; 58:154–158.

30. Forrest GN, Mankes K, Jabra-Rizk MA, et al. Peptide nucleic acid fluorescence in situ hybridization-based identification of Candida albicans and its impact on mortality and antifungal therapy costs. J Clin Microbiol **2006**; 44:3381–3383.

31. Forrest GN, Roghmann M-C, Toombs LS, et al. Peptide nucleic acid fluorescent in situ hybridization for hospital-acquired enterococcal bacteremia: delivering earlier effective antimicrobial therapy. Antimicrob Agents Chemother **2008**; 52:3558–3563.

32. Heil EL, Daniels LM, Long DM, Rodino KG, Weber DJ, Miller MB. Impact of a rapid peptide nucleic acid fluorescence in situ hybridization assay on treatment of Candida infections. Am J Health-Syst Pharm **2012**; 69:1910–1914.

33. MacVane SH, Hurst JM, Boger MS, Gnann JW. Impact of a rapid multiplex polymerase chain reaction blood culture identification technology on outcomes in patients with vancomycin-resistant *Enterococcal* bacteremia. Infect Dis **2016**; :1–6.
34. Macvane SH, Nolte FS. Clinical Impact of Adding a Rapid PCR-based Blood Culture Identification Panel (BCID) to an Established Antimicrobial Stewardship Intervention (ASI) Program for Patients with Gram-negative Bacteremia (GNB). [abstract 123]. In: Program and abstracts of the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, **2015**.
35. Nagel JL, Huang AM, Kunapuli A, et al. Impact of antimicrobial stewardship intervention on coagulase-negative Staphylococcus blood cultures in conjunction with rapid diagnostic testing. J Clin Microbiol **2014**; 52:2849–2854.
36. Pardo J, Klinker KP, Borgert SJ, Butler BM, Giglio PG, Rand KH. Clinical and economic impact of antimicrobial stewardship interventions with the FilmArray blood culture identification panel. Diagn Microbiol Infect Dis **2016**; 84:159–164.
37. Revolinski S, Huang A, Peppard W, Ledeboer N. Outcomes Utilizing Rapid Diagnostic Technology Coupled with Pharmacist Intervention in Patients with Gram-Positive Bloodstream Infections [abstract P0429]. In: Program and abstracts of the 25th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, **2015**.
38. Sango A, McCarter YS, Johnson D, Ferreira J, Guzman N, Jankowski CA. Stewardship approach for optimizing antimicrobial therapy through use of a rapid microarray assay on blood cultures positive for Enterococcus species. J Clin Microbiol **2013**; 51:4008–4011.
39. Sothoron C, Ferreira J, Guzman N, Aldridge P, McCarter YS, Jankowski CA. A Stewardship Approach To Optimize Antimicrobial Therapy through Use of a Rapid Microarray Assay on Blood Cultures Positive for Gram-Negative Bacteria. J Clin Microbiol **2015**; 53:3627–3629.

40. Walker T, Dumadag S, Lee CJ, et al. (2016) Clinical impact after laboratory implementation of the Verigene gram-negative bacteria microarray for positive blood cultures. J. Clin. Microbiol. [in press].
41. Felsenstein S, Bender JM, Sposto R, Gentry M, Takemoto C, Bard JD. Impact of a Rapid Blood Culture Assay for Gram-Positive Identification and Detection of Resistance Markers in a Pediatric Hospital. Arch Pathol Lab Med **2016**; 140:267–275.
42. Frye AM, Baker CA, Rustvold DL, et al. Clinical impact of a real-time PCR assay for rapid identification of staphylococcal bacteremia. J Clin Microbiol **2012**; 50:127–133.
43. Ly T, Gulia J, Pyrgos V, Waga M, Shoham S. Impact upon clinical outcomes of translation of PNA FISH-generated laboratory data from the clinical microbiology bench to bedside in real time. Ther Clin Risk Manag **2008**; 4:637–640.
44. Maslonka M, Freifeld AG, Rupp ME, et al. Impact of Rapid Bloodstream Pathogen Identification in Hospitalized Patients [abstract P171]. In: Program and abstracts of IDWeek, Philadelphia, PA, **2014**.
45. Banerjee R, Teng CB, Cunningham SA, et al. Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing. Clin Infect Dis **2015**; 61:1071–1080.
46. Holtzman C, Whitney D, Barlam T, Miller NS. Assessment of impact of peptide nucleic acid fluorescence in situ hybridization for rapid identification of coagulase-negative staphylococci in the absence of antimicrobial stewardship intervention. J Clin Microbiol **2011**; 49:1581–1582.
47. Nguyen DT, Yeh E, Perry S, et al. Real-time PCR testing for mecA reduces vancomycin usage and length of hospitalization for patients infected with methicillin-sensitive staphylococci. J Clin Microbiol **2010**; 48:785–790.

Figure 1: Flow diagram.

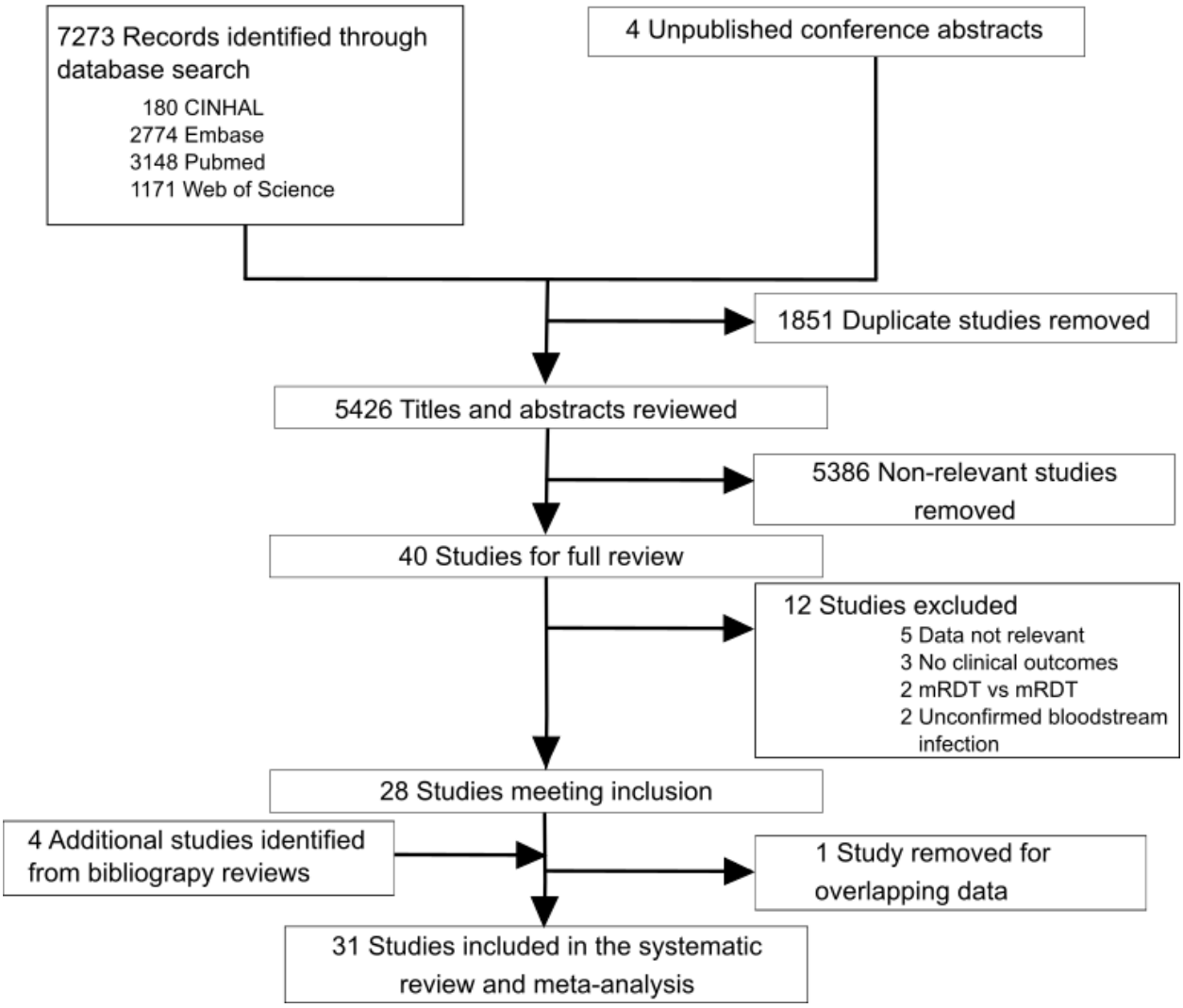
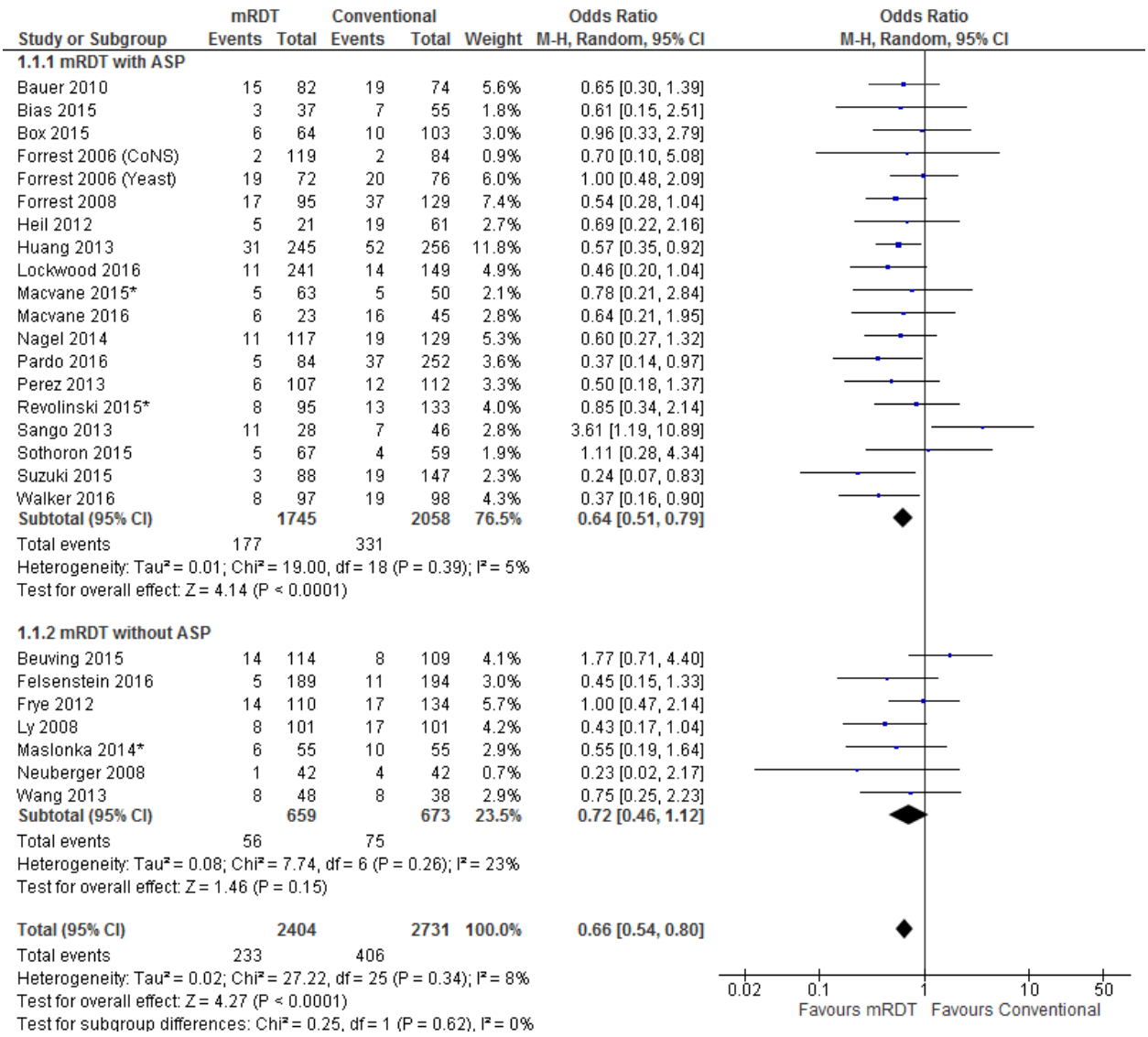
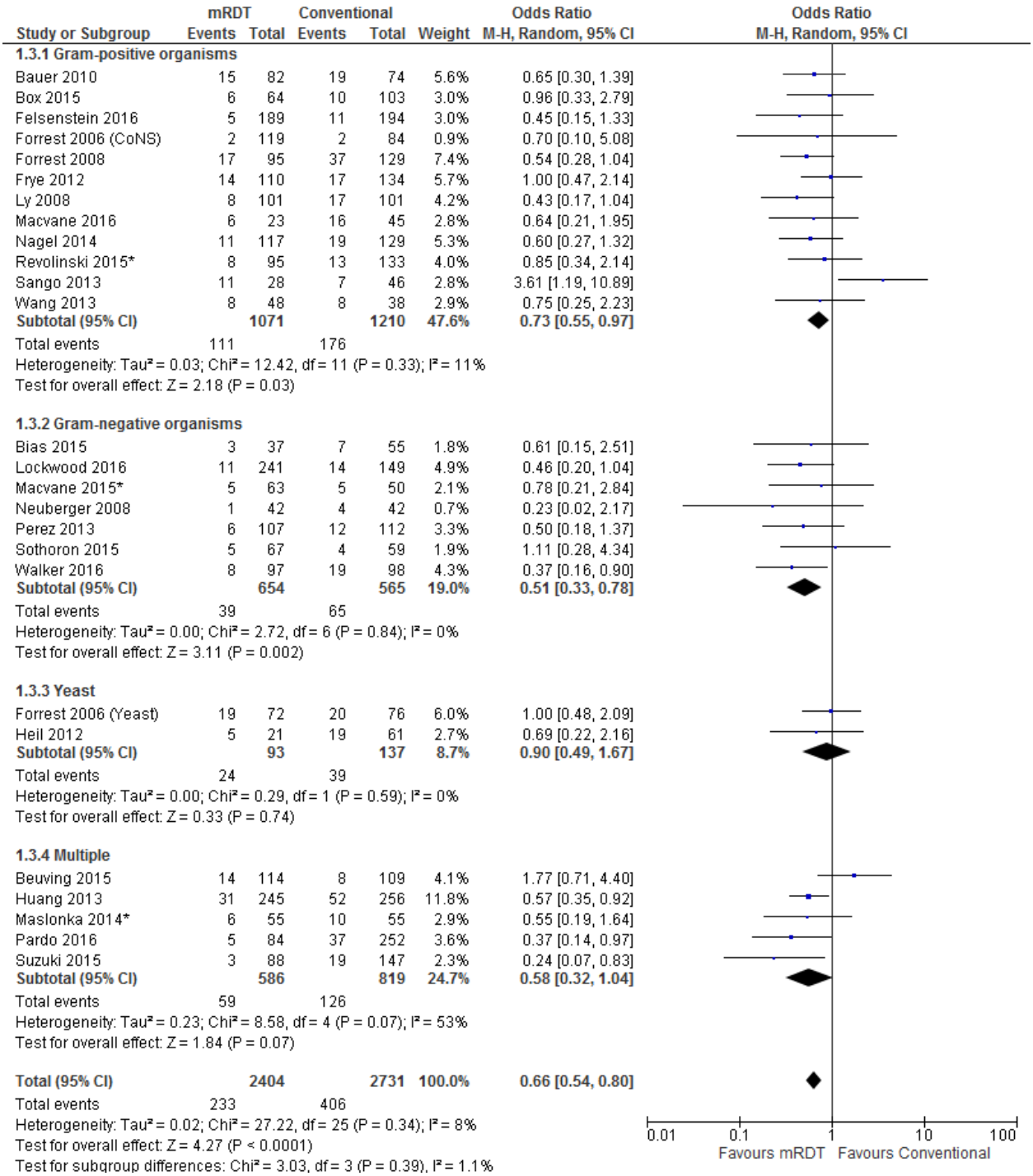


Figure 2: Mortality with mRDT vs conventional testing in BSI.



*Conference abstract. Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; ASP, antimicrobial stewardship program; M-H, Mantel-Haenszel method; CI, confidence interval.

Figure 3: Mortality with mRDT vs conventional testing by organism type in BSI.



*Conference abstract. Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; M-H, Mantel-Haenszel method; CI, confidence interval.

Table 1. Characteristics of Included Studies of Included in Systematic Review and Meta-analysis

Author Year	Study Design	Setting	Patient Population	Sample Size, mRDT/Control, No. of Patients	BSI Type	Laboratory Tests	mRDT Testing & Notification Recipient	ASP Presence	ASP Notification Process	NOS Score
Bauer [27] 2010	Quasi-experimental	1150-bed tertiary care facility	Adult	82/74	*S. aureus*	Conventional vs PCR	24x7; Physician	Yes	Real-time M-F 8a-5p	9
Beuving [17] 2015	RCT	750-bed hospital	Adult	129/121	Multiple	Conventional vs PCR	NR; Physician	No	NA	NA
Bias [28] 2015	Quasi-experimental	NR	Adult	49/65	Gram-negative organisms	Conventional vs BC-GN	NR; Physician & ASP	Yes	NR	7
Box [23] 2015	Quasi-experimental	5 Community hospitals	Adult	64/103	Gram-positive organisms	Conventional vs BC-GP	7a-7p; Nurse	Yes	Real-time 7a-7p	7
Cattoir [22] 2011	Quasi-experimental	900-bed teaching hospital	Adult	49/48	*Staphylococcus spp.*	Conventional vs PCR	NR; Physician	No	NA	9
Felsenstein [41] 2016	Quasi-experimental	Children's hospital	Pediatric	219/221	Gram-positive organisms	Conventional vs BC-GP	24x7 testing but not real-time; Physician	No	NA	8
Forrest [30] 2006	Quasi-experimental	Medical center	NR	72/76	Yeast	Conventional vs PNA-FISH	1x/day; Team & ASP	Yes	Real-time	7
Forrest [29] 2006	Case-control	740-bed medical center	NR	119/84	CoNS	Conventional vs PNA-FISH	1x/day; Team & ASP	Yes	Real-time	9
Forrest [31] 2008	Quasi-experimental	600-bed teaching hospital	Adult	95/129	*Enterococcus spp.*	Conventional vs PNA-FISH	2x/day; Physician & ASP	Yes	Real-time	7
Frye [42] 2012	Quasi-experimental	Two 500-bed medical centers	Adult	110/134	*Staphylococcus spp.*	Conventional vs PCR	2x/day M-F, 1x/day SS; MRSA results to floor	No	NA	9
Heil [32] 2012	Quasi-experimental	NR	Adult	21/61	Yeast	Conventional vs PNA-FISH	7a-9:30p; Physician & PharmD	Yes	Real-time	7
Holtzman [46] 2011	Quasi-experimental	Medical center	Adult	99/100	CoNS	Conventional vs PNA-FISH	1x/day; EHR only	No	NA	9

Table 1 continued.

Author Year	Study Design	Setting	Patient Population	Sample Size, mRDT/Control, No. of Patients	BSI Type	Laboratory Tests	mRDT Testing & Notification Recipient	ASP Presence	ASP Notification Process	NOS Score
Huang [26] 2013	Quasi-experimental	Health system	Adult	245/256	Multiple	Conventional vs MALDI-TOF	NR; Ordering clinician & ASP	Yes	6a-11:30p	9
Lockwood [24] 2016	Quasi-experimental	2 community hospitals	Adult	241/149	Gram-negative organisms	Conventional vs MALDI-TOF	NR; Nurse & ASP	Yes	Real-time	7
Ly [43] 2008	RCT	907-bed tertiary care center	Adult	101/101	*Staphylococcus spp.*	Conventional vs PNA-FISH	2x/day; Treating clinician	No	NA	NA
Macvane [34] 2015	Quasi-experimental	NR	Adult	63/50	Gram-negative organisms	Conventional vs PCR	NR; NR	Yes	NR	7
Macvane [33] 2016	Quasi-experimental	709-bed academic center	Adult	23/45	*Enterococcus spp.*	Conventional vs PCR	24x7; Nurse and PharmD	Yes	Real-time 8a-5p M-F	7
Maslonka [44] 2014	Case-Control	NR	NR	55/55	Multiple	Conventional vs PCR	NR; NR	No	NA	7
Na [21] 2016	Quasi-experimental	Academic hospital	NR	97/94	*Staphylococcus spp.*	Conventional vs PCR	1x/day M-Sat; EHR only	No	NA	7
Nagel [35] 2014	Quasi-experimental	Health system	Adult	117/129	CoNS	Conventional vs MALDI-TOF	NR; Physician & ASP	Yes	6a-11:30p	7
Neuberger [20] 2008	Quasi-experimental	Tertiary care medical center	NR	42/42	*Klebsiella pneumoniae*	Conventional vs PCR	11p-11a M-F; Physician	No	NA	9
Nguyen [47] 2010	Quasi-experimental	Academic hospital	Adult	94/65	*Staphylococcus spp.*	Conventional vs PCR	NR; EHR only	No	NA	9
Pardo [36] 2016	Case-control	939-bed academic medical center	Adult	84/252	Multiple	Conventional vs PCR	1x/day; ASP	Yes	NR	9

Table 1 continued.

Author Year	Study Design	Setting	Patient Population	Sample Size, mRDT/Control, No. of Patients	BSI Type	Laboratory Tests	mRDT Testing & Notification Recipient	ASP Presence	ASP Notification Process	NOS Score
Perez [15] 2013	Quasi-experimental	1000-bed quaternary care academic hospital	Adult	107/112	Gram-negative organisms	Conventional vs MALDI-TOF	3-4x/day; ASP	Yes	Real-time	9
Revolinksi [37] 2015	Quasi-experimental	NR	Adult	95/133	Gram-positive organisms	Conventional vs BC-GP	NR; Provider & PharmD	Yes	NR	7
Roshdy [25] 2015	Quasi-experimental	Academic medical center	NR	74/65	*Streptococcus / Enterococcus spp.*	Conventional vs BC-GP + MALDI-TOF	NR; PharmD	Yes	NR	7
Sango [38] 2013	Quasi-experimental	695-bed academic medical center	NR	28/46	*Enterococcus spp.*	Conventional vs BC-GP	24x7; ASP	Yes	M-F 7:30a-5p	7
Sothoron [39] 2015	Quasi-experimental	NR	Adult	67/59	Gram-negative organisms	Conventional vs BC-GN	24x7; ASP	Yes	Real-time	7
Suzuki [19] 2015	Quasi-experimental	413-bed tertiary medical center	NR	88/147	Multiple	Conventional vs BC-GP/GN	NR; Hospital physician and ID physician	Yes	NR	7
Walker [40] 2016	Quasi-experimental	401-bed tertiary care & 60-bed cancer hospitals	NR	97/98	Gram-negative organisms	Conventional vs BC-GN	24x7; Physician if resistant organism	Yes	Daily	9
Wang [18] 2013	Quasi-experimental	1200-bed tertiary care hospital	NR	48/38	*Staphylococcus spp.*	Conventional vs PCR	1x/day; Physician	No	NA	7

Note. MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization Time-of-Flight; BC-GP, blood culture gram positive nanotechnology microarray system; BC-GN blood culture gram negative nanotechnology microarray system; NR, not reported; NA, not applicable; NOS, Newcastle-Ottawa Scale; ROB, Risk of Bias; AST, antibiotic susceptibility testing; EHR, electronic health record.

Appendix

Supplementary Table 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5

Supplementary Table 1: PRISMA Checklist (Cont.)

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-3, Supplementary Figures 1-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8, Figures 2-3, Supplementary Figures 1-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, Supplementary Figures 5-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8, Figures 2-3, Supplementary Figures 1-2,4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

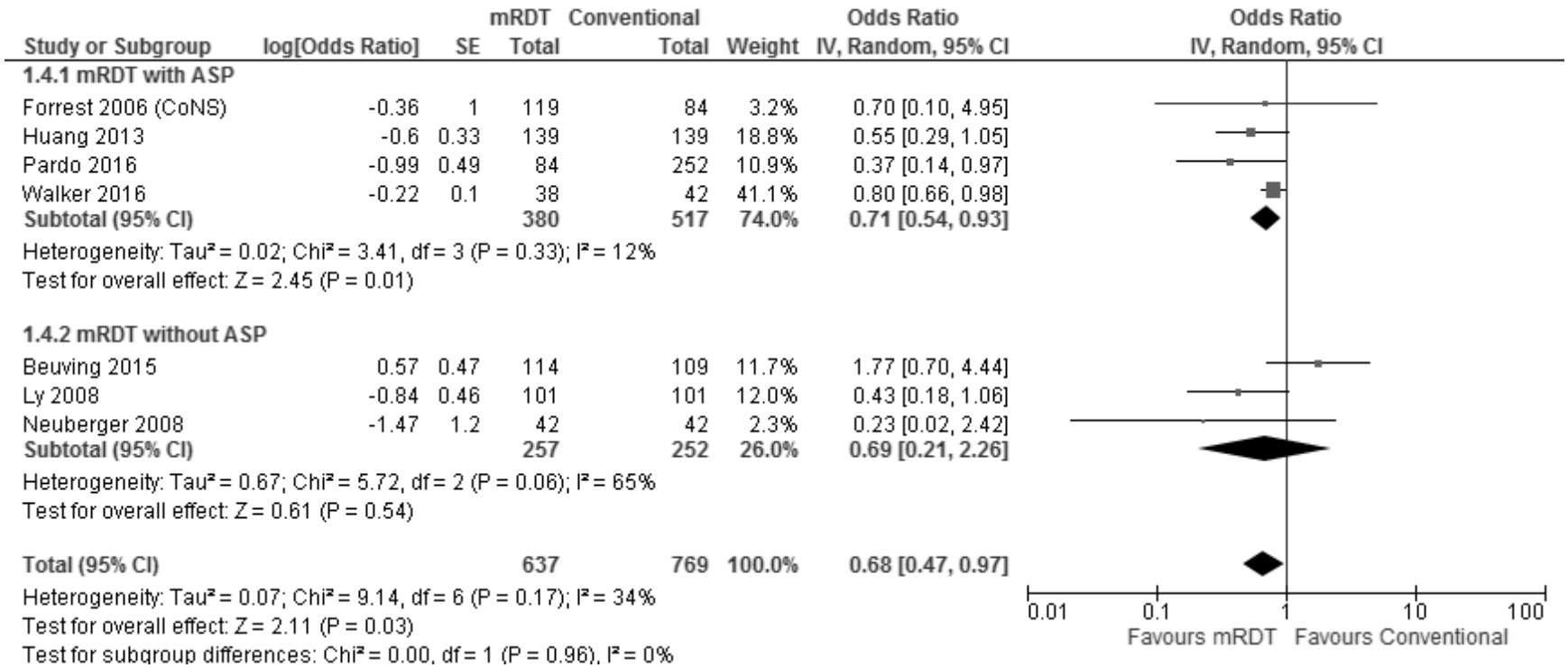
Supplementary Table 2: Newcastle-Ottawa Scale Quality Assessment Scores

Author	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	Total Score
Bauer [27]	****	**	***	9
Bias [28]	****		***	7
Box [23]	****		***	7
Cattoir [22]	****	**	***	9
Felsenstein [41]	****	*	***	8
Forrest [30]	****		***	7
Forrest [29]	****	**	***	9
Forrest [31]	****		***	7
Frye [42]	****	**	***	9
Heil [32]	****		***	7
Holtzman [46]	****	**	***	9
Huang [26]	****	**	***	9
Lockwood [24]	****		***	7
Macvane [34]	****		***	7
Macvane [33]	****		***	7
Maslonka [44]	****		***	7
Na [21]	****		***	7
Nagel [35]	****		***	7
Neuberger [20]	****	**	***	9
Nguyen [47]	****	**	***	9
Pardo [36]	****	**	***	9
Perez [15]	****	**	***	9
Revolinski [37]	****		***	7
Roshdy [25]	****		***	7
Sango [38]	****		***	7
Sothoron [39]	****		***	7
Suzuki [19]	****		***	7
Walker [40]	****	**	***	9
Wang [18]	****		***	7

Supplementary Table 3. Risk of Bias Quality Assessments

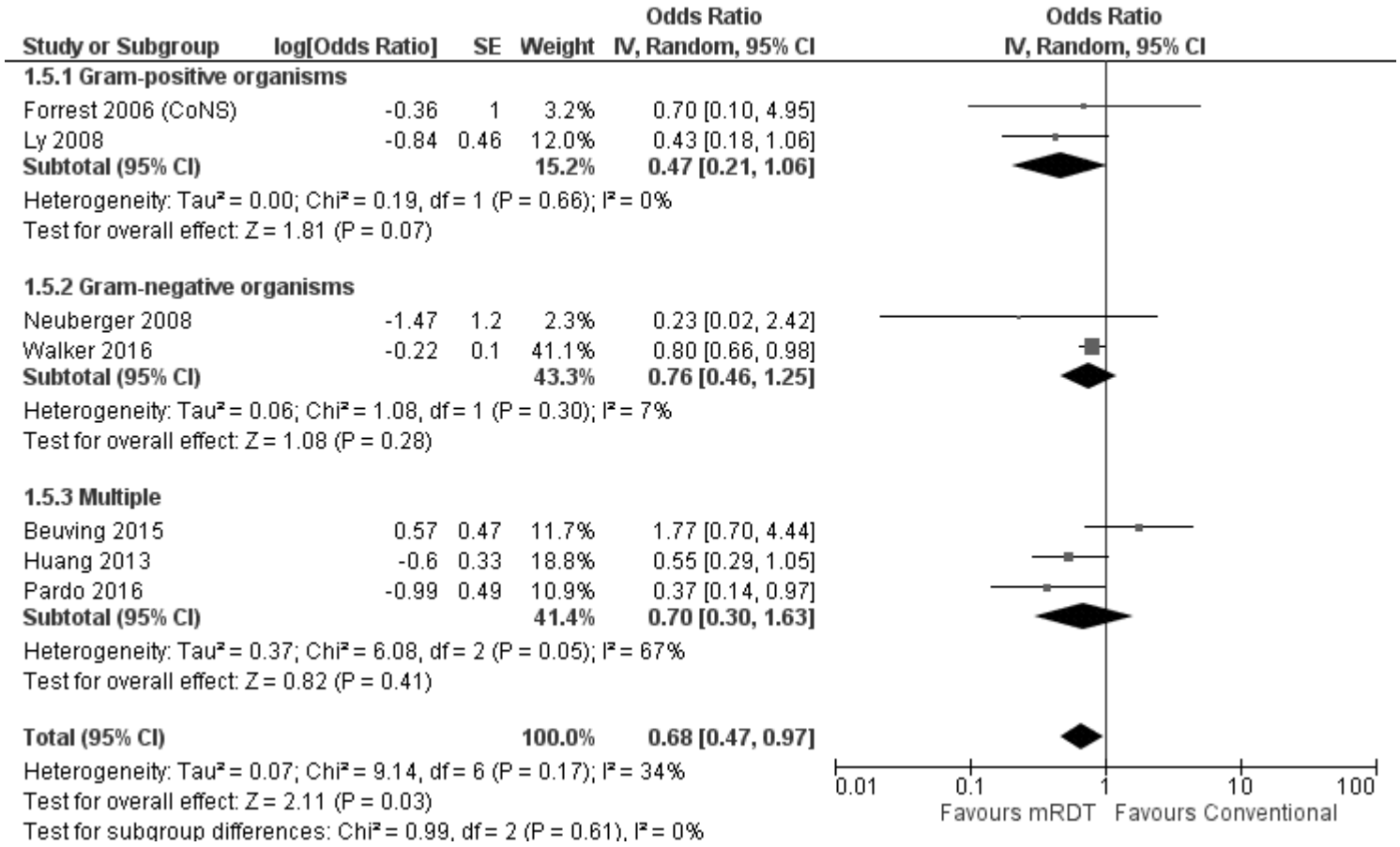
Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Beuving [17]	Low	Low	High	High	Low	Low	Unclear
Ly [43]	High	High	High	High	Low	Low	High

Supplementary Figure 1. Mortality with mRDT vs conventional testing in BSI among studies controlling for confounding.



Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; ASP, antimicrobial stewardship program; M-H, Mantel-Haenszel method; CI, confidence interval.

Supplementary Figure 2. Mortality with mRDT vs conventional testing by organism type in BSI among studies controlling for confounding.



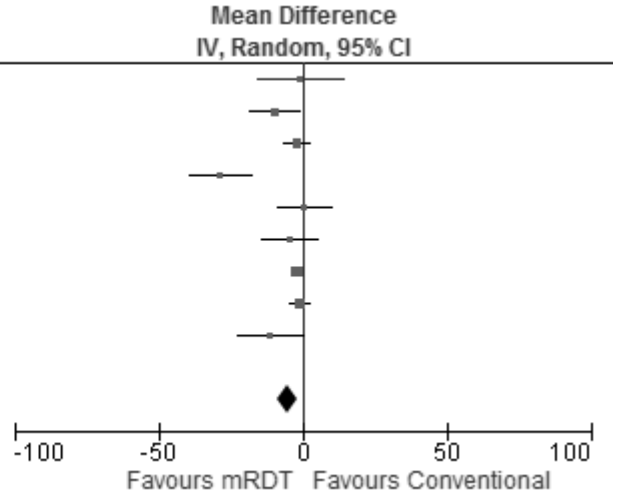
Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; M-H, Mantel-Haenszel method; CI, confidence interval.

Supplementary Figure 3. Time to effective therapy with mRDT vs conventional testing in BSI.

	mRDT			Conventional				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Cattoir 2011	24.3	36.7	49	25.3	38.2	48	4.5%	-1.00 [-15.91, 13.91]
Huang 2013	20.4	20.7	245	30.1	67.7	256	9.4%	-9.70 [-18.39, -1.01]
Macvane 2015*	7.3	12.67	63	9.33	11.07	50	16.1%	-2.03 [-6.41, 2.35]
Macvane 2016	21.43	7.98	23	50.2	35.15	45	7.2%	-28.77 [-39.55, -17.99]
Maslonka 2014*	14.9	26	55	14.3	22.9	55	8.9%	0.60 [-8.56, 9.76]
Na 2016	41.8	27.2	97	46.1	40.5	94	8.2%	-4.30 [-14.11, 5.51]
Neuberger 2008	1.64	1	25	3.5	1.2	38	21.1%	-1.86 [-2.41, -1.31]
Revolinski 2015*	8.2	12.27	95	9.3	14.2	133	17.7%	-1.10 [-4.55, 2.35]
Roshdy 2015	1.9	7.2	74	13.2	46	65	6.8%	-11.30 [-22.60, 0.00]
Total (95% CI)			**726**			**784**	**100.0%**	**-5.03 [-8.60, -1.45]**

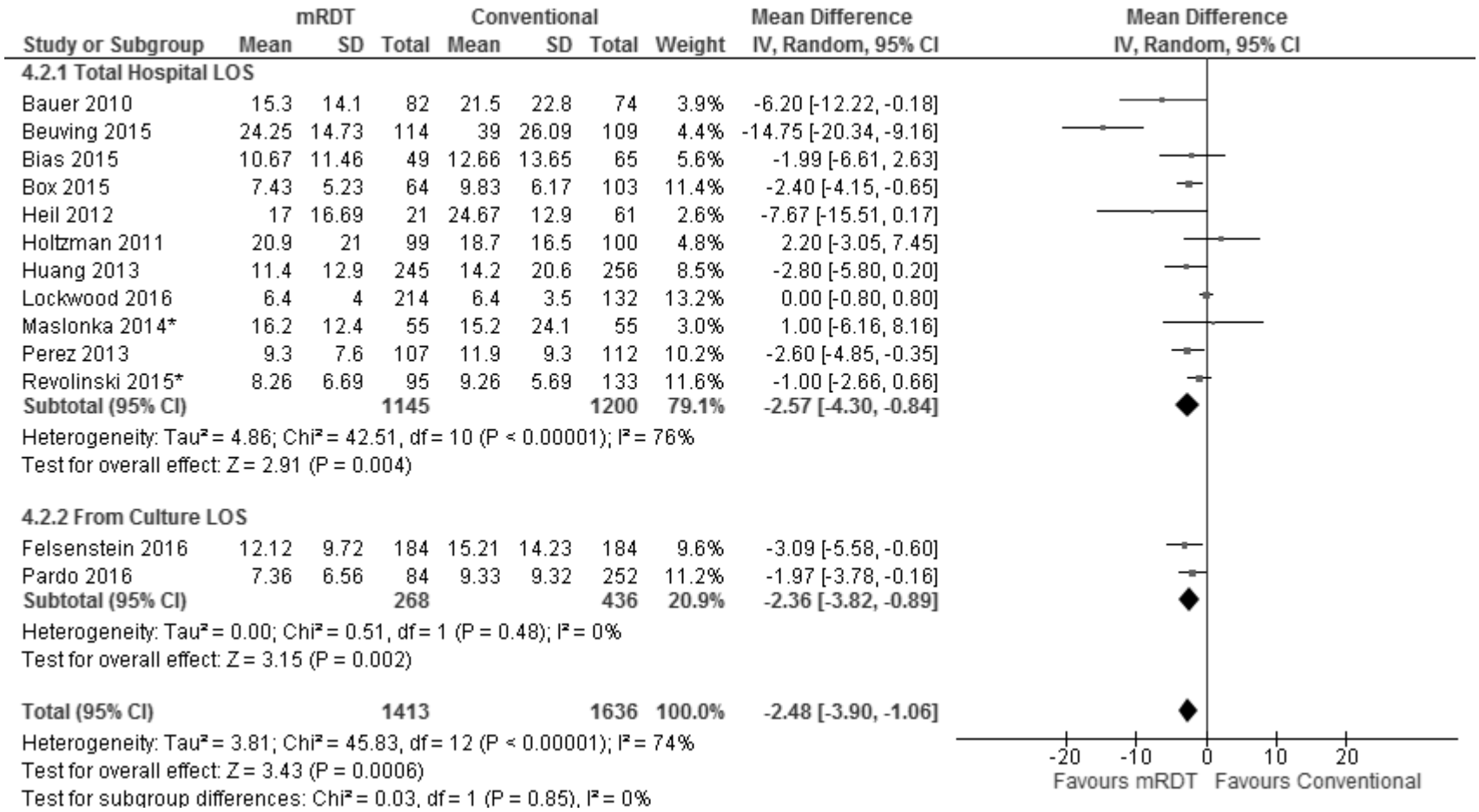
Heterogeneity: $Tau^2 = 15.66$; $Chi^2 = 30.36$, df = 8 (P = 0.0002); $I^2 = 74\%$

Test for overall effect: Z = 2.76 (P = 0.006)



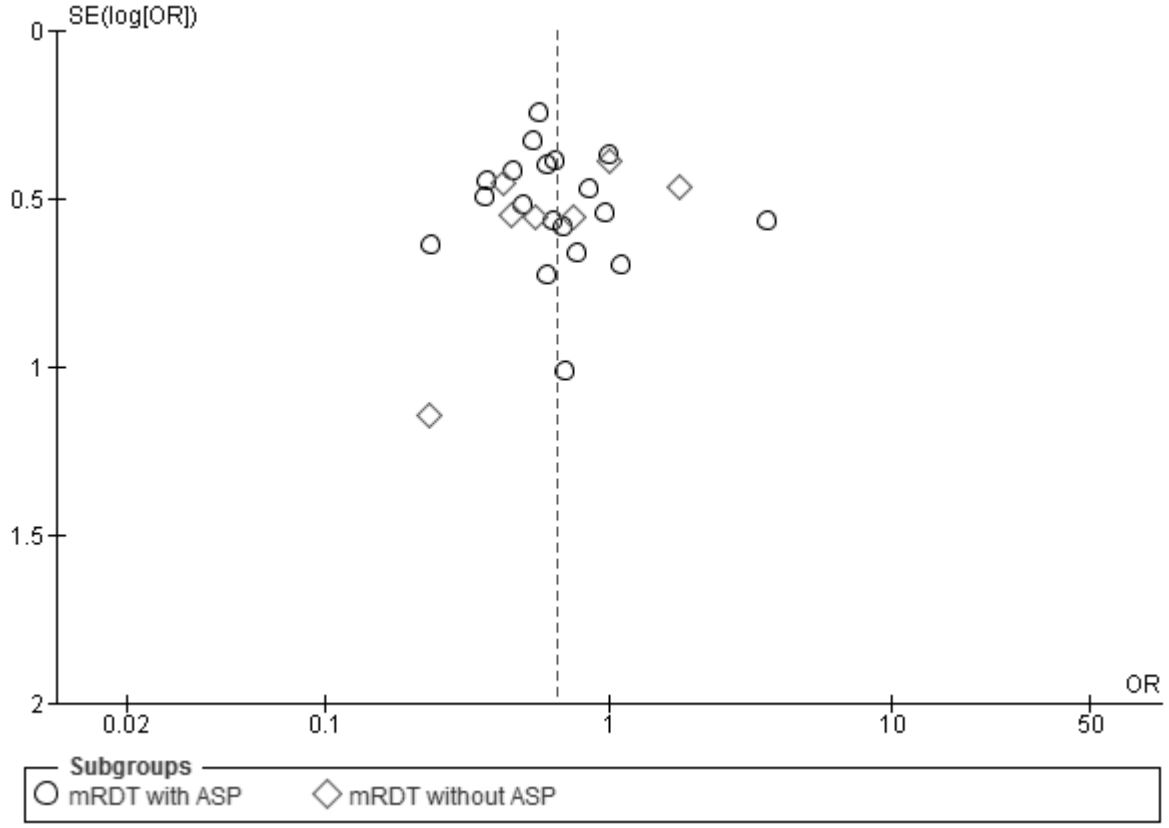
*Conference abstract. Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; IV, Inverse variance method; CI, confidence interval.

Supplementary Figure 4. Length of stay with mRDT vs conventional testing in BSI.



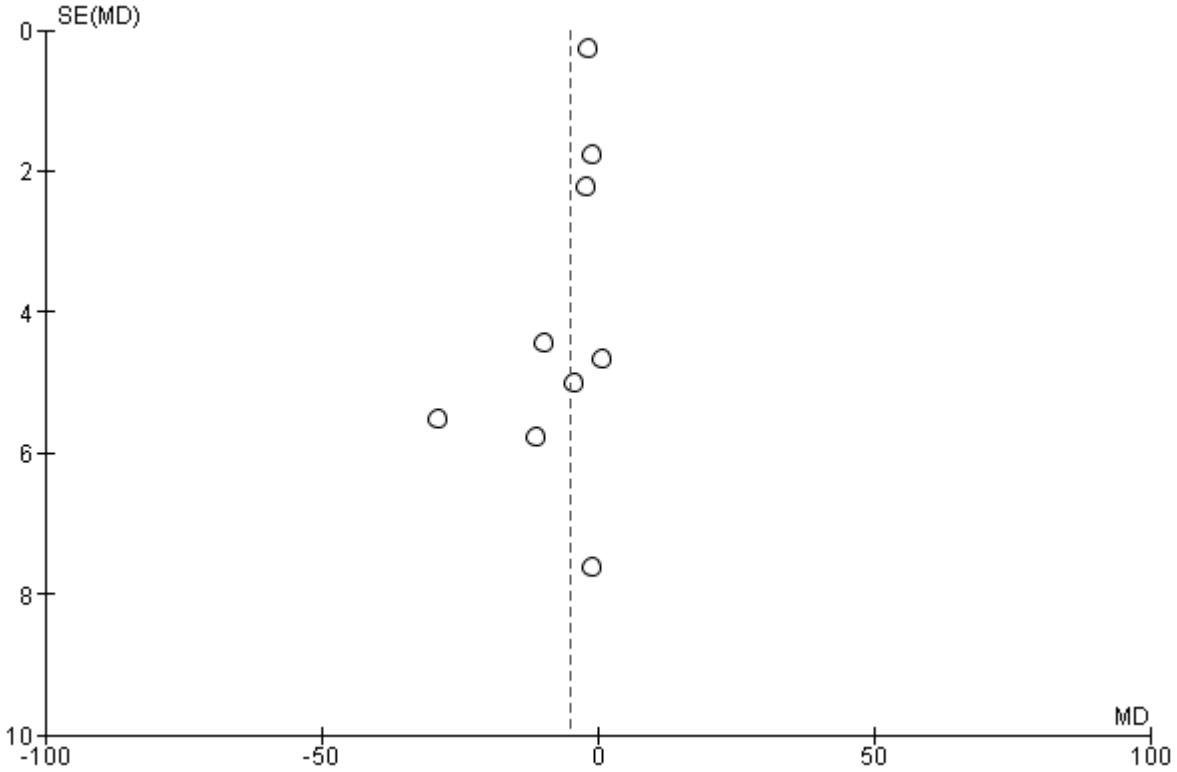
*Conference abstract. Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; LOS, length of stay; IV, Inverse variance method; CI, confidence interval.

Supplementary Figure 5. Funnel plot of included studies for mortality of mRDT vs conventional testing in BSI.



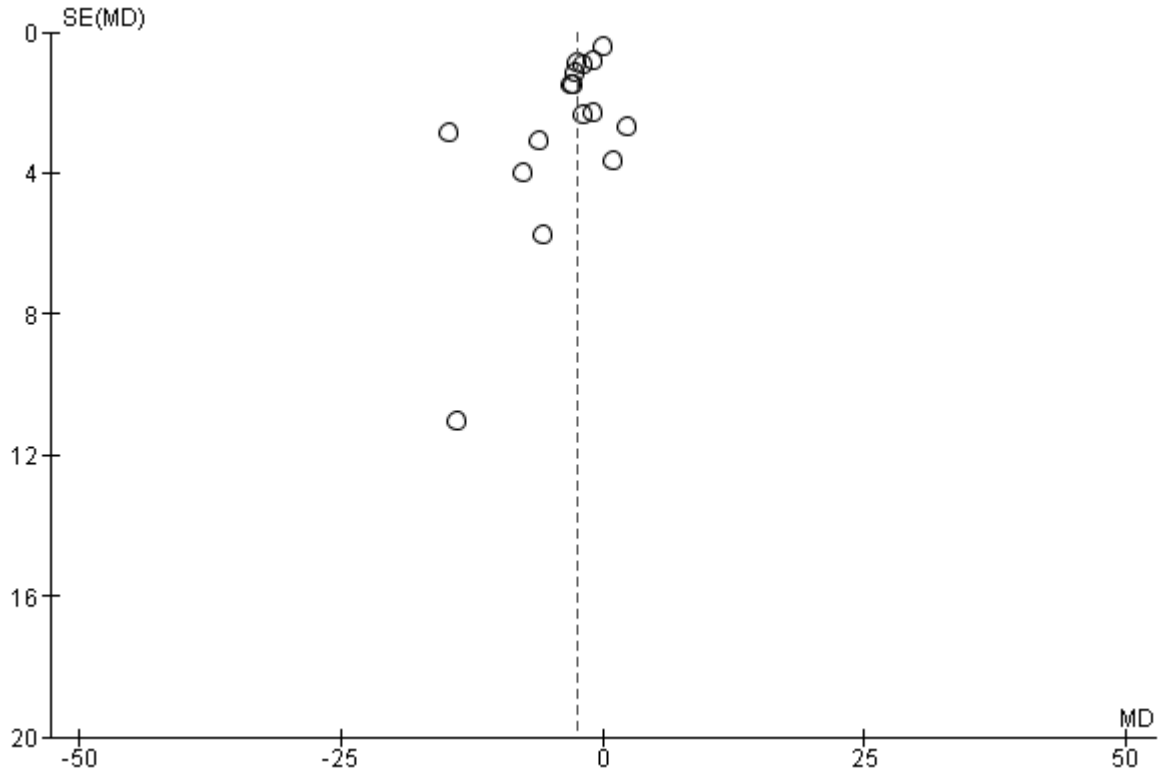
Abbreviations: mRDT, molecular rapid diagnostic testing; ASP, antimicrobial stewardship program; BSI, bloodstream infection; SE, standard error; OR, odds ratio.

Supplementary Figure 6. Funnel plot of included studies for time to appropriate therapy of mRDT vs conventional testing in BSI.



Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; SE, standard error; MD, mean difference.

Supplementary Figure 7. Funnel plot of included studies for length of stay of mRDT vs conventional testing in BSI.



Abbreviations: mRDT, molecular rapid diagnostic testing; BSI, bloodstream infection; SE, standard error; MD, mean difference.