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Rapid multiplex PCR for respiratory viruses reduces time to result and improves clinical care: Results of a systematic review and meta-analysis

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SUMMARY

Objectives: The clinical impact of rapid sample-to-answer "syndromic" multiplex polymerase chain reaction (PCR) testing for respiratory viruses is not clearly established. We performed a systematic literature review and meta-analysis to evaluate this impact for patients with possible acute respiratory tract infection in the hospital setting.

Methods: We searched EMBASE, MEDLINE, and Cochrane databases from 2012 to present and conference proceedings from 2021 for studies comparing clinical impact outcomes between multiplex PCR testing and standard testing.

Results: Twenty-seven studies with 17,321 patient encounters were included in this review. Rapid multiplex PCR testing was associated with a reduction of − 24.22 h (95% CI −28.70 to −19.74 h) in the time to results. Hospital length of stay was decreased by −0.82 days (95% CI −1.52 to −0.11 days). Among influenza positive patients, antivirals were more likely to be given (RR 1.25, 95% CI 1.06–1.48) and appropriate infection control facility use was more common with rapid multiplex PCR testing (RR 1.55, 95% CI 1.16–2.07).

Conclusions: Our systematic review and meta-analysis demonstrates a reduction in time to results and length of stay for patients overall along with improvements in appropriate antiviral and infection control management among influenza-positive patients. This evidence supports the routine use of rapid sample-to-answer multiplex PCR testing for respiratory viruses in the hospital setting.

Introduction

Respiratory tract infections (RTIs) place a significant burden on the healthcare system and are the third most common cause of mortality and morbidity, globally.[1] Respiratory viruses are the predominant causative agents responsible for most acute respiratory infections.[2] Rapid and accurate diagnosis of the underlying pathogen is critical for optimizing effective patient management decisions, such as the need for antibiotic or antiviral prescriptions and implementation of infection-control measures to prevent further transmission.[3,4]

Routine laboratory-based pathogen tests such as viral culture, immunofluorescence assays, and single-target reverse-transcription polymerase chain reaction (RT-PCR) techniques, do not generally provide results rapidly enough to have an impact on clinical decisions. Rapid antigen detection tests (RADTs) also have been shown to have poor sensitivity in detecting respiratory viruses in adults.[5,6] Conventional testing may be laborious, comprising multiple complex steps; require special instruments that may challenge the capacity of clinical laboratories; and involve delays due to transit of

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specimens, batch testing, and time in reporting or authorizing results.[7] Consequences of delays in accurate diagnosis may lead to longer hospital stays and worse health care outcomes.[8]

In contrast, rapid multiplex molecular testing platforms allow accurate detection of a wide range of viral pathogens simultaneously. Multiplex testing platforms also may be "sample-to-answer" in design, such that the extraction, amplification, and analysis of specimens are fully integrated within closed processes (e.g., individual cartridges). Rapid multiplex PCR testing with sample-to-answer systems provides an opportunity for the accurate detection of multiple respiratory targets with similar presenting symptoms (i.e., syndromic), in under one hour.[9–11] The potential benefits of rapid multiplex panels include earlier discharge and directed use of antimicrobials and isolation facilities.[12] However, recent guidelines lack recommendations or give limited support to the use of rapid multiplex molecular respiratory testing, noting either more research is needed or indicating use only in limited patient populations.[13–15]

The objective of this study was to conduct a systematic review and meta-analysis assessing the clinical impact of using rapid sample-to-answer multiplex PCR for patients with possible acute RTI in the hospital setting (emergency department (ED) or inpatient) compared with standard of care/routine testing.

Methods

This systematic review was conducted according to guidelines set forth in the Cochrane Handbook[16] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) statement.[17] A detailed protocol was developed and registered prospectively with PROSPERO (registration number CRD42021287852). The PRISMA checklist is provided in the Supplementary materials.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were pre-specified in the protocol using the PICOTS (population, interventions, comparators, outcomes, timing, and setting) framework.[18] Briefly, we included studies that enrolled adults ≥18 years of age with suspected acute respiratory tract infection and compared rapid sample-to-answer multiplex PCR tests versus standard-of-care diagnostic tests. Eligible rapid sample-to-answer multiplex PCR tests were defined as having 10 or more targets and included FilmArray (BioFire), ePlex and eSensor (GenMark), Verigene RV+ (Nanosphere/Luminex), and QIAstat-Dx (QIA GEN). Standard of care was defined broadly as any other test or intervention that was not considered a sample-to-answer multiplex PCR. Clinical impact outcomes included time to results, antibiotic use, neuraminidase inhibitor (NAI) use, length of stay (LOS), infection control facility use, mortality, investigations, ancillary testing, patient satisfaction, and provider satisfaction. There was no restriction for timing in regard to when the tests were administered or the duration of follow-up. Eligible studies had to be conducted in the hospital setting (emergency department (ED), inpatient, or both).

Additionally, only comparative studies were included: randomized clinical trials (RCTs), quasi-randomized controlled clinical trials (CCTs), and comparative observational studies. Non-comparative studies and case reports with less than five patients were excluded. Studies that compared two sample-to-answer multiplex PCR tests head-to-head or reported test performance results only (e.g., sensitivity, specificity) also were excluded.

Search strategy and screening process

A comprehensive search to identify relevant studies that assessed the clinical impact of multiplex PCR tests compared with standard diagnostic tests was performed in EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials databases using the OvidSP® platform. The databases were searched from 2012, when most commercially available rapid tests became available, to the date of the search (October 13, 2021). The complete search strategy is provided in Supplement Table S1.

In addition to searching bibliographic databases, we searched the websites of the following conferences held in 2021 for publications of eligible studies: American Society for Microbiology Microbe (ASM Microbe); European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); European Respiratory Society (ERS) International Congress; Infectious Diseases Society of America (IDWeek); and American College of Emergency Physicians (ACEP). Furthermore, we performed forward citation searches of included studies and screened the bibliographies of recently published reviews to look for additional studies which may not have been identified from the database searches.

All unique records identified through the systematic review were evaluated by a two-step process based on pre-defined inclusion and exclusion criteria. In Step 1, two reviewers working independently reviewed each record and records assessed by both reviewers as not relevant were excluded; records assessed by both reviewers as definitely or possibly relevant were retained for full-text review. In Step 2, two reviewers working independently assessed each full-text publication to determine eligibility and reasons for exclusion were documented. Any disagreement about inclusion/exclusion at either step was resolved by a third reviewer. Multiple reports from the same study were linked according to methods described in the Cochrane Handbook such that data extraction and analysis were study-based.[16] Specific criteria for linking studies included comparing trial identification numbers, author names, location and setting, details about the intervention, number of patients and baseline data, and the date and duration of the study. The overall process of review is summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1).

Data collection and quality assessment

Data from relevant studies were extracted by two independent reviewers. Any discrepancies were checked against the source document by a third reviewer. The data extraction template was developed and piloted to capture information on study design and methods, patient selection criteria and characteristics, intervention and comparator test descriptions, and outcomes and results from the included studies. Publications reporting results for the same study were grouped per study.

Outcomes were extracted for intervention and comparator test groups, and for both overall and pre-planned influenza subgroup populations. Ten clinical impact outcomes were included in this review: Time to results, defined as the mean time (in hours) from taking the sample to the time that the results were available to ready for the clinical team; Length of stay, defined as the mean days in hospital and mean hours in ED; Appropriate influenza antiviral (neuraminidase inhibitor, NAI) use, defined as the mean duration of use (in days) and the proportion of treated with NAIs for influenza positive patients; Infection control facility use, defined as the proportion with appropriate room placement to single room and/or shared cohort ward for influenza positive patients; Antibiotic use, defined as the mean duration of use (in days) and the proportion of patients treated with antibiotics; Mortality, defined as overall, inpatient, and 30-day; Change in investigations, defined as the number or proportion with a reduction or addition of tests or procedures used as part of the diagnostic workup; Change in ancillary testing, defined as the number or proportion with a reduction or addition in any testing performed after diagnosis; Patient satisfaction, defined

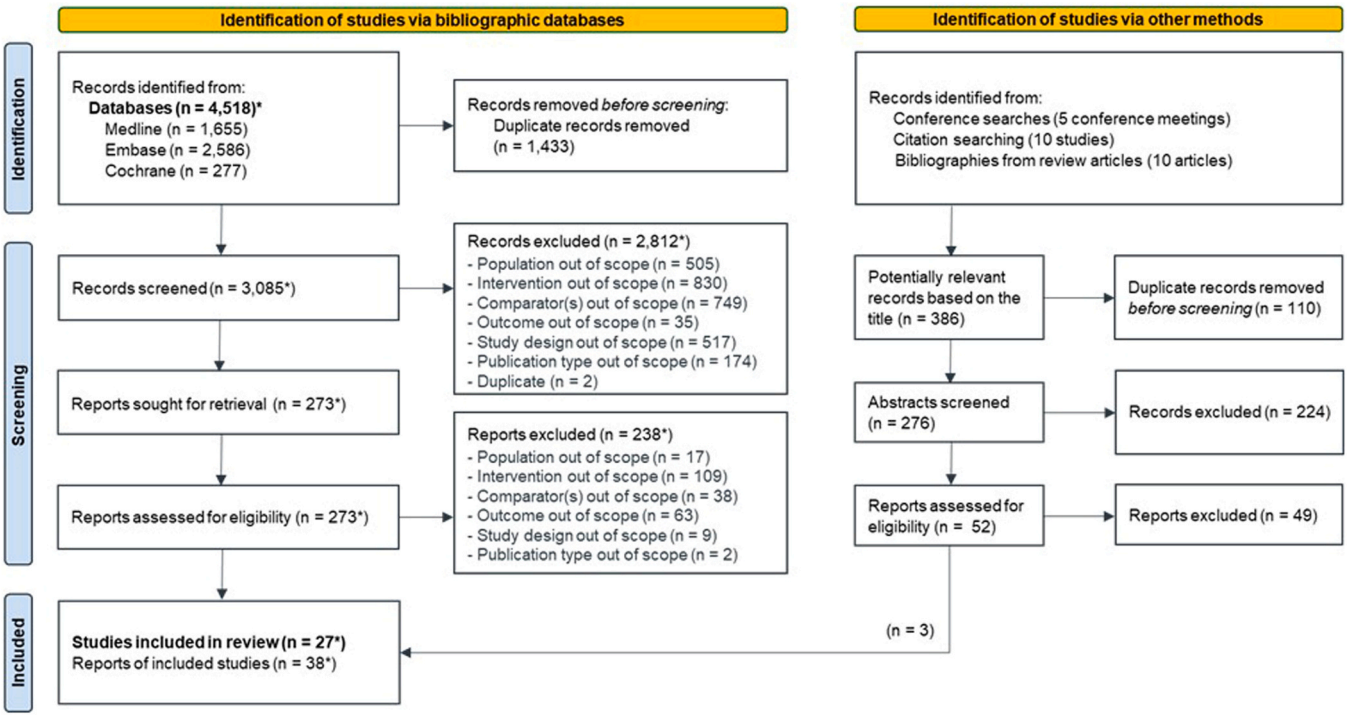

Fig. 1. Flow diagram of the search for studies on clinical impact of sample-to-answer multiplex PCR.

as reported by included study; Provider satisfaction, defined as reported by included study. In addition, based on reviewer feedback, we included cost-related outcomes.

Risk of bias was assessed using accepted tools per study type; Cochrane's Risk of Bias Tool (RoB2)[19] was used for RCTs and CCTs, and Newcastle Ottawa scale (NOS)[20] for observational studies.

Statistical analysis

Following a feasibility assessment to evaluate the comparability of included studies, we performed frequentist meta-analysis using the metafor package in R 3.6.1.[22] The random effects model was prespecified as the primary model for all analyses and the fixed effect model was secondary. Results for all analyses were presented as a risk ratio (RR) with 95% CI for binary outcomes and as a mean difference (MD) with 95% CI for continuous outcomes. Absolute risks (ARs) were calculated using the following formula: AR = the number of events in the intervention or comparator groups, divided by the number of people in that group per 100 persons.[23] Results were reported overall and by study design, interventional (RCTs/CCTs) or observational.

Mean and standard deviation (SD) values were calculated for studies reporting outcomes as median and interquartile range or minimum-maximum range.[24] For studies with missing variance data (e.g., SD, SE), values were imputed as per the statistical formula in Cochrane Handbook.[25] Statistical heterogeneity was evaluated using Cochran's Q statistic and the I^2 statistic based on inverse-weighting; a p-value of less than 0.1 for the test for heterogeneity indicated presence of heterogeneity.[16] Small study effects, which may be due to reporting bias, were examined using funnel plots and the Egger's test for asymmetry for meta-analyses with 10 or more studies.[21] The consistency of results and confidence intervals were used to ascertain the certainty of evidence for each outcome.

Subgroup analyses were planned for the following prespecified subgroups of interest: (1) influenza-positive vs. influenza-negative populations, (2) pneumonia vs. non-pneumonia populations, and (3) point-of-care vs. non-point-of-care testing. Sensitivity analyses were planned to exclude studies which were reported only as conference abstracts or studies for which variance estimates were imputed.[16] Sensitivity analyses were conducted using continuity correction for outcomes with zero events.

Results

Results of the search

A total of 4518 publications were identified through database searches. After de-duplication, 3085 unique records were retained for title and abstract review. Of which, 273 records were potentially relevant for full-text screening. After full-text review, 24 eligible studies (from 35 records) were included for data extraction. Additionally, from supplemental searches of conference proceedings, citations of included studies, and bibliography screening, 3 additional eligible studies were identified. Overall, 38 publications reporting 27 unique studies[26–52] with 17,321 patient encounters were included in this review [Fig. 1].

Characteristics of included studies

Of the 27 studies meeting the inclusion criteria, 8 studies were RCTs,[26–33] 2 were CCTs,[34,35] and 17 were observational cohort studies.[36–52] Most studies (n = 24) evaluated the BioFire® Respiratory Pathogen (RP) Panels (this included any of the following: BioFire® FilmArray® RP 1.6 Panel, BioFire® FilmArray® RP 1.7 Panel, BioFire® FilmArray® RP 2.0 Panel, BioFire® FilmArray® RP 2.0 plus Panel, BioFire® RP 2.1 Panel, and BioFire® RP 2.1 plus Panel) with or without other tests.[26–34,36,38–51] Others evaluated the QIAstat-Dx Respiratory SARS-CoV-2 Panel,[35] GenMark respiratory viral panel (RVP),[37] and ePlex RPP[52] [one study each]. The comparator groups included laboratory-based PCR tests (n = 15), conventional laboratory tests unspecified (n = 6), and routine diagnostic tests unspecified (n = 2). Two studies used Luminex xTAG RVP, and one study each used indirect immunofluorescence assay and direct fluorescent antibody staining

followed by culture as the comparator group. Characteristics of included studies are detailed in Table 1.

The majority of the studies included in our review were conducted in United States (12 studies), followed by Europe (8 studies), Asia (3 studies), Argentina (2 studies), and Australia and Canada with one study each. The sample size of studies varied from 45 patients[33] to 2523 patients.[49] Eleven studies assessed the clinical impact of multiplex PCR tests in an inpatient hospital setting, 9 studies in an emergency department (ED), and 7 studies evaluated outcomes in both inpatient and ED settings. Baseline characteristics, including age and gender, were comparable across studies and test groups [Supplement Fig. S1 and Fig. S2].

Quality assessment of included studies

Using the Cochrane RoB2 tool to assess 10 included trials, we judged 5 to be at low risk of bias [Supplement Figure S3].[26–29,32] Three trials had some concerns of bias as no information was reported about the randomization process and allocation concealment.[30,31,33] Two CCTs were assessed at high risk of bias for using quasi-random allocation methods.[34,35]

Using the NOS to assess 17 observational studies, the majority of observational studies published as full-length journal articles (7 of 8) were considered to be of moderate quality (score of 5–6 stars) [Supplement Figure S4].[39,40,44,46,50–52] The majority of studies published only as conference abstracts (8 of 9) were considered low quality (score ≤3 stars) due to lack of information.

Time to result

Time to result was reported in 15 studies, demonstrating a significant reduction in the mean time to results with rapid sample-to-answer multiplex PCR tests compared with routine testing (MD −24.22 h, 95% CI −28.70 to −19.74 h, I^2 98.7%) [Fig. 2]. Although there was considerable statistical heterogeneity ($I^2 > 75\%$), the direction of effect was the same for all studies. Subgroup analysis by study design also demonstrated significantly lower time to results for rapid sample-to-answer multiplex PCR tests compared with routine testing (MD −25.98 h, 95% CI −30.01 to −21.96 h, I^2 97.3% for 8 RCTs/CCTs and MD −22.04 h, 95% CI −32.76 to −11.32 h, I^2 99.3% for 7 observational studies). The funnel plot did not suggest small study effects due to potential reporting bias (Egger's test p-value = 0.0533) [Supplement Fig. S5].

Length of stay

Length of hospital stay was reported from 14 studies (7 RCTs/CCTs and 7 observational studies). Length of hospital stay was significantly shorter among patients tested with rapid sample-to-answer multiplex PCR tests compared with routine testing (MD −0.82 days, 95% CI −1.52 to −0.11 days, I^2 91.9%). Similar trends were observed within study design subgroups; however, the difference was not statistically significant (MD −0.44 days, 95% CI −1.08 to 0.21 days for RCTs/CCTs) and (MD −1.14 days, 95% CI −2.38 to 0.11 days for observational studies) [Fig. 3]. The funnel plot did not suggest small study effects due to potential reporting bias (Egger's test p-value = 0.6052) [Supplement Fig. S6].

Data on length of ED stay were available from only three observational studies. No significant difference in mean LOS between rapid sample-to-answer multiplex PCR test versus routine testing groups was observed (MD −3.14 h, 95% CI −14.59 to 8.3 h, I^2 24.3%) [Supplement Fig. S7].

Appropriate NAI use and appropriate infection prevention control (IPC)

Appropriate NAI use, expressed as the proportion of influenza-positive patients treated with NAIs, was reported from 7 studies (3 RCTs/CCTs and 4 observational studies). Influenza-positive patients were 1.25 times more likely to be appropriately treated with NAIs when tested with rapid sample-to-answer multiplex PCR tests compared with routine testing (RR 1.25, 95% CI 1.06–1.48, I^2 67.7%) (Fig. 4A). The absolute risk of appropriate NAI use was 71 versus 61 per 100 influenza-positive patients with multiplex PCR versus routine testing, respectively. Among interventional studies, a statistically significant beneficial effect of multiplex PCR tests over routine tests in reducing the NAI prescriptions was demonstrated across three studies (RR 1.53, 95% CI 1.35–1.73, I^2 0%). The absolute risk was 95 versus 63 per 100 influenza-positive patients.

Appropriate infection prevention and control (IPC) among influenza-positive patients was reported from 3 interventional studies. Influenza-positive patients were 1.55 times more likely to undergo appropriate IPC when tested with rapid sample-to-answer multiplex PCR tests compared with routine testing (RR 1.55, 95% CI 1.16–2.07, I^2 70.4%) (Fig. 4B). The absolute risk of appropriate IPC was 58 versus 42 per 100 influenza-positive patients with multiplex PCR versus routine testing, respectively. One study assessed IPC measures for patients with suspected COVID-19 and found that 73% (313 of 428) of patients in the multiplex PCR test group versus 57% (242 of 421) of patients in the routine testing group were transferred to the correct clinical area based on infection status (difference 15.7%, 95% CI 9.1–22.0, $p < 0.0001$).[35] No study reported IPC measures for RSV or any other non-influenza virus.

Antibiotic use, proportion and duration

Antibiotic use, expressed as the proportion of patients treated with antibiotics, was reported from 12 studies (7 RCTs/CCTs and 5 observational studies). No significant difference in antibiotic use was observed for multiplex PCR testing versus routine testing (RR 0.92, 95% CI 0.78–1.09, I^2 97.4%) (Fig. 5A). The absolute risk of antibiotic use was 68 vs. 76 per 100 individuals in the multiplex PCR group versus the routine testing group, respectively. The funnel plot did not suggest small study effects due to potential reporting bias (Egger's test p-value = 0.4127) [Supplement Fig. S8].

No significant difference was demonstrated when the results were analyzed separately for RCTs/CCTs in different settings: inpatient (RR 0.98, 95% CI 0.95–1.01), ED (RR 1.71, 95% CI 0.81–3.63), and mixed (RR 1.06, 95% CI 0.93–1.20) settings. However, observational studies showed a significant reduction of antibiotic use with rapid multiplex PCR tests compared with routine testing in inpatient (RR 0.40, 95% CI 0.34–0.46) and ED (RR 0.85, 95% CI 0.75–0.96) settings (Fig. 5A).

Duration of antibiotic use was reported from 9 studies, demonstrating no significant difference between rapid sample-to-answer multiplex PCR testing and routine testing overall (MD −0.41, 95% CI −1.11 to 0.29 days, I^2 92.2%). Significantly shorter duration of antibiotic use was observed in the multiplex PCR test group compared with the routine testing group in the mixed (inpatient and emergency department) setting, as reported from two studies (MD −0.44, 95% CI −0.75 to −0.13 days, I^2 0%) (Fig. 5B).

Mortality

Inpatient mortality was reported from four interventional studies and two observational studies. No significant differences were observed in the multiplex PCR test group compared with the routine

Table 1
Summary of characteristics of studies included in the systematic literature review.

Author, year Trial ID, location	Article type	Sample size (Setting)	Patient characteristics	Rapid sample-to-answer multiplex PCR	Comparator test (s)	Outcomes reported	Study dates
Randomized controlled trials (RCTs)							
Branche, 2015 NCT01907659, US	Journal article	300 (Inpatient)	Men: 44% Median age: 62.5 years Current smokers: NR Pneumonia: 19%	BioFire® RP Panels + VIDAS BRAHMS PCT	Standard care: Hospital influenza/RSV duplex PCR, and urine legionella antigen analysis	Time to results; Antibiotic prescription; LOS; Mortality	October 2013 to April 2014
Brendish, 2017 ISRCTN90211642, UK	Journal article	720 (Inpatient & ED)	Men: 48% Median age: 62.5 years Current smokers: 25% Pneumonia: 27%	BioFire® RP Panels	Routine care: Testing for respiratory viruses by laboratory PCR	Time to results; Antibiotic prescription; NAIs prescription; LOS; Infection control; Mortality	January 15, 2015 to April 30, 2015, and October 1, 2015 to April 30, 2016
Clark, 2021 ISRCTN17197293, UK	Journal article	613 (Inpatient)	Men: 46% Median age: 62.5 years Current smokers: 23% Pneumonia: 26%	BioFire® RP Panels	Routine care: Laboratory PCR by conventional methods in the on-site laboratory facilities	Time to results; Antibiotic prescription; NAIs prescription; LOS; Infection control; Mortality	December 12, 2017, to May 3, 2018, and December 3, 2018, to May 3, 2019
Echavarría, 2018 Argentina	Journal article	432 (ED)	Men: 41% Median age: 43.5 years Current smokers: NR Pneumonia: 22%	BioFire® RP Panels	Indirect Immunofluorescence assay with specific monoclonal antibodies for RSV, FluA, FluB, PIV 1–3 and AdV	Time to results; Antibiotic prescription; NAIs prescription; LOS; Mortality; Investigations	April 2016 to November 2016 and April 2017 to October 2017
Gelfer, 2015 US	Journal article	142 (ED)	Men: 41% Mean age: 64 years Current smokers: 35% Pneumonia: 100%	BioFire® RP Panels	Standard diagnostic testing: PPMC laboratory-generated PCR panel probe	Time to results; Antibiotic prescription	January 2014 to March 2014
Gilbert, 2016 US	Journal article	127 (ED)	Men: 49% Mean age: 70 years Current smokers: 23% Pneumonia: 100%	BioFire® RP Panels	PPMC laboratory-generated PCR RP	Time to results; Antibiotic prescription	December 4, 2014, to March 6, 2015
Shengchen, 2019 NCT03391076, China	Journal article	800 (Inpatient)	Men: 57% Mean age: 61 years Current smokers: 20% Pneumonia: 57%	BioFire® RP Panels+ RTPCR	Routine RT-PCR and others (blood gas analysis, C reactive protein, erythrocyte sedimentation rate, procalcitonin and routine microbiological testing)	Time to results; Antibiotic prescription; LOS; Mortality	October 2017 to July 2018
Wong, 2017 Canada	Conference abstract	45 (Inpatient)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Routine diagnostic testing: influenza A/B/RSV in-house PCR followed by Luminex NxTag RPP	Infection control	December 2016 to January 2017
Quasi-randomized controlled clinical trials (CCTs)							
Andrews, 2017 ISRCTN10470967, UK	Journal article	545 (Inpatient & ED)	Men: 52% Median age: 64 years Current smokers:	BioFire® RP Panels	Standard diagnostic assay: In-house developed RT-PCRs with 4 separate multiplex assays and an adenovirus monoplex	Time to results; Antibiotic prescription; NAIs prescription; LOS; Mortality	January 2015 to July 2015

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Table 1 (*continued*)

Author, year Trial ID, location	Article type	Sample size (Setting)	Patient characteristics	Rapid sample-to-answer multiplex PCR	Comparator test (s)	Outcomes reported	Study dates
			NR Pneumonia: NR				
Brendish, 2020 ISRCTN14966673, UK	Journal article	1055 (Inpatient & ED)	Men: 54% Median age: 69 years Current smokers: NR Pneumonia: NR	QIAstat-Dx SARS-CoV-2 RP	Laboratory-based PCR testing for SARS-CoV-2	Time to results; Antibiotic prescription; LOS; Infection control; Mortality	March 20, 2020, to April 29, 2020
Observational studies							
Bergese, 2021 Argentina	Conference abstract	116 (Inpatient)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Pre- BioFire®RP Panels: Direct immunofluorescence, antibodies, and RT-PCR	NAIs prescription; LOS; Infection control; Mortality	April 2017 to July 2019
Ciccone, 2018 US	Conference abstract	677 (Inpatient)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	GenMark RVP	Rapid influenza or RSV/influenza Cepheid Xpert PCR	Antibiotic prescription	September 1, 2015, to April 15, 2016
Esber, 2017 US	Conference abstract	387 (Inpatient)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Laboratory-based PCR testing for influenza	Antibiotic prescription; LOS	January to February 2015 and January to February 2016
Lee, 2020 Taiwan	Journal article	676 (ED)	Men: 67% Mean age: 82 years Current smokers: NR Pneumonia: 74%	BioFire® RP Panels+ Serum PCT	PS-matched historical cohort: Laboratory tests including respiratory panel and PCT test.	Antibiotic prescription; NAIs prescription; LOS; Mortality	January 2016 to March 2018
Madigan, 2018 Australia	Journal article	324 (Inpatient & ED)	Men: 51% Mean age: 64.5 years Current smokers: NR Pneumonia: NR	BioFire® RP Panels + in-house PCR	In-house RT-PCR processing eight samples in single run	Time to results; LOS; Infection control	July 2, 2016, to August 30, 2016, and September 21, 2016, to October 20, 2016
Mansour, 2015 US	Conference abstract	165 (Inpatient & ED)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	Nucleic acid tests (Genmark eSensor, BioFire® RP Panels)	DFA staining + culture	Antibiotic prescription; NAI prescription; LOS	NR
Mehta, 2017 US	Conference abstract	1468 (ED)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	RSV and Influenza rapid antigen + PCR	Antibiotic prescription; NAIs prescription; Investigations	RSV or influenza tests: July to December 2015, and BioFire®RP Panels: July to December 2016
Pettit, 2015 US	Letter to editor	1102 (Inpatient)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Luminex xTAG RVP	Time to results; NAIs prescription	December 1, 2011, to February 28, 2013
Poelman, 2020 Netherlands	Journal article	492 (ED)	Men: 51% Median age: 62 years	BioFire® RP Panels	Laboratory developed test was a multiplex RT-PCR assay that included the same viral targets as the FilmArray RP	Time to results; Antibiotic prescription; NAIs	Mid December 2014 to early April 2015

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Table 1 (*continued*)

Author, year Trial ID, location	Article type	Sample size (Setting)	Patient characteristics	Rapid sample-to-answer multiplex PCR	Comparator test (s)	Outcomes reported	Study dates
			Current smokers: NR Pneumonia: NR			prescription; LOS; Infection control	
Qian, 2020 China	Journal article	182 (Inpatient)	Men: 60% Mean age: 55 years Current smokers: NR Pneumonia: 100%	BioFire® RP Panels	Conventional method: laboratory diagnostic tests including smears, cultures, and serological tests (PNEUMOSLIDE IgM, Vircell)	Time to results; NAIs prescription; LOS; Infection control	October 2016 to March 2018 and October 2014 to March 2016
Rappo, 2016 US	Journal article	337 (Inpatient & ED)	Men: 42% Mean age: 58 years Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Conventional testing: Rapid antigen testing (BD Directigen EZ Flu A+B and BD Directigen EZ RSV), Prodesse ProFlu+PCR, Luminex PCR, direct fluorescent- antibody testing, and viral culture (consisting of a combination of R-mix [Diagnostic Hybrids] and conventional tube cell culture).	Time to results; Antibiotic prescription; NAIs prescription; LOS; Investigations	November 1, 2010, to March 31, 2011, and February 29, 2012, to June 2, 2012
Roy, 2018a UK	Conference abstract	1075 (Inpatient & ED)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Conventional laboratory tests	Time to results	January 15, 2018, to May 1, 2018
Roy, 2018b UK	Conference abstract	155 (ED)	Men: NR Mean age: NR Current smokers: NR Pneumonia: NR	BioFire® RP Panels	Microbiology laboratory tests: Testing by traditional method in microbiology lab	Time to results; Infection control	NR
Shadowen, 2019 US	Poster	2523 (Inpatient)	Men: NR Mean age: NR Current smokers: NR Pneumonia: 100%	BioFire® RP Panels	Before BioFire®RP Panels	LOS	Control group: 2014–2015 and intervention group: 2016–2017
Timbrook, 2015 US	Journal article	789 (Inpatient)	Men: 43% Median age: 55 years Current smokers: NR Pneumonia: NR	BioFire® RP Panels+ VIDAS BRAHMS PCT	Culture + procalcitonin test (VIDAS BRAHMS PCT automated test)	Time to results; Antibiotic prescription; LOS	January 01, 2012, to January 01,2014
Vos, 2019 Netherlands	Journal article	570 (ED)	Men: 53% Median age: 62 years Current smokers: NR Pneumonia: 43%	BioFire® RP Panels	In-house RT-PCR	Antibiotic prescription; NAIs prescription; LOS; Infection control; Mortality; Investigations	2016/2017 season (19 weeks) and 2017/2018 season (22 weeks)
Weiss, 2019 US	Journal article	1504 (ED)	Men: 45% Mean age: 70 years Current smokers: NR Pneumonia: NR	ePlex RPP	Luminex xTAG RVP	Time to results; Antibiotic prescription; NAIs prescription; Mortality; Investigations	November 2016 to February 2017 (RVP) and November 2018 to February 2019 (RPP)

CCT=Controlled clinical trial, ED=Emergency department, LOS=Length of stay, mPOCT=Molecular point of care testing, NAIs=Neuraminidase inhibitors; NR=Not reported; PCR=Polymerase chain reaction, PCT=Procalcitonin test, RP=Respiratory panel, RPOCT=Respiratory point of care testing; RPP=Respiratory pathogen panel, RSV=Respiratory syncytial virus, RT-PCR: real-time polymerase chain reaction, RVP: respiratory viral panel, UK: United Kingdom, US: United States

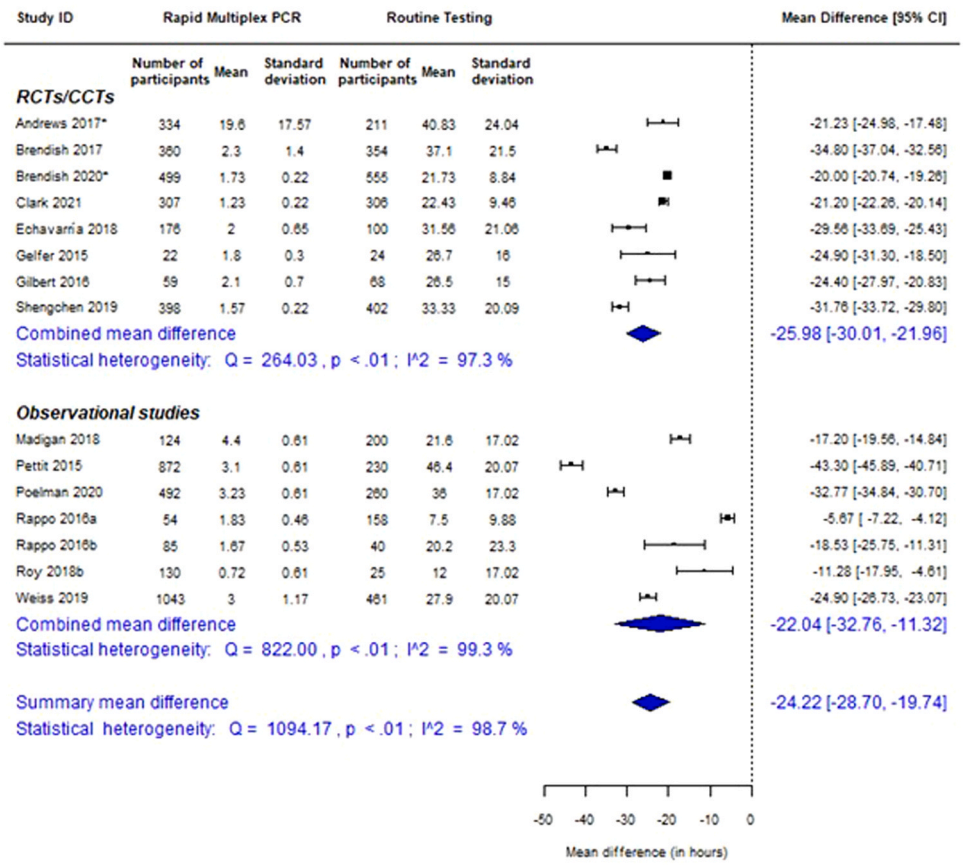

Fig. 2. Forest plot of time to results (in hours) with rapid sample-to-answer multiplex PCR versus routine testing. *denotes CCTs, Abbreviations: RCT, randomized clinical trial; CCT, quasi-randomized controlled clinical trial; CI, confidence interval.

testing group overall (RR 0.82, 95% CI 0.57–1.18, I^2 25.8%) or within interventional (RR 1.02, 95% CI 0.74–1.41, I^2 0.8%) or observational (RR 0.68, 95% CI 0.46–1.02, I^2 0%) study design subgroups (Fig. 6). The absolute risk was 6 versus 9 per 100 individuals.

Results of 30-day mortality also showed no significant difference and crossed the line of no effect (RR 0.89, 95% CI 0.70–1.14, I^2 6.2%) [Supplement Fig. S9]. The absolute risk was 6 versus 8 per 100 individuals.

Other outcomes

Other planned clinical impact outcomes, including change in planned investigations, change in ancillary testing, patient satisfaction, and provider satisfaction, were not reported by the included studies. In addition, the planned sub-group analyses on patients with and without pneumonia and in patients tested at the point of care or in the laboratory was not performed due to insufficient data from the reviewed studies. Cost-related outcomes were reported by nine studies: four studies reported overall cost savings due to shorter length of stay in the multiplex PCR test group compared with the routine testing group;[32,34,41,52] four studies reported lower medication costs with antivirals or antibiotics in the multiplex PCR test group compared with the routine testing group;[30,31,43,49] and one study reported a favorable results for the multiplex PCR test group compared with the routine testing group in terms of the "euro–hour", which incorporates labor costs, costs for reagents and run controls, depreciation and maintenance of equipment, external quality control as well as a 20% overhead.[44]Secondary and sensitivity analysis.

Secondary analyses using fixed effect models yielded similar, yet more precise, confidence intervals compared with primary analyses using the random effects model (Supplement Figs. S10-S18). Sensitivity analyses were planned to exclude studies which were reported only as conference abstracts or studies for which variance estimates were imputed; however, due to the limited of studies with these characteristics included in meta-analysis, these analyses were not performed.

Discussion

Based on 27 included studies with 17,321 patient encounters, this systematic review and meta-analysis showed that the use of rapid, sample-to-answer multiplex PCR testing for respiratory viruses was associated with clinically meaningful improvements in patient care. A large reduction in time to results was observed across studies when compared with routine testing in the hospital setting.[27–32,34,35,40,43,44,46–48,52] The typical time to results with rapid sample-to-answer multiplex PCR was within two hours from when the tests were requested, compared with one full day with routine laboratory-based tests. The importance of faster time to results in improving clinical outcomes, which includes shorter length of stay, reduced antibiotic use, and use of infection control facilities has been demonstrated in previous studies.[53]

In addition to improvement in time to results, rapid sample-to-answer multiplex PCR was associated with a reduction in hospital LOS. The reduction in LOS was approximately one day with sample-to-answer multiplex PCR compared with routine testing. Shorter LOS could equate to reduced chances of acquiring nosocomial infection,

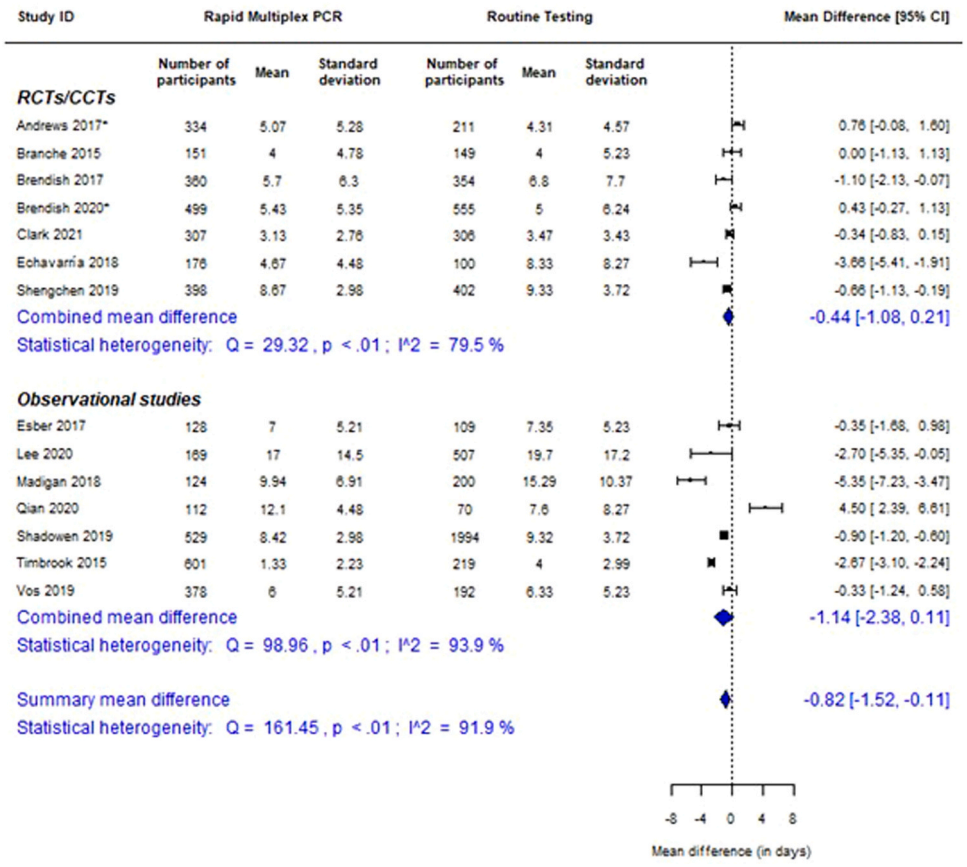

Fig. 3. Forest plot of hospital length of stay (in days) with rapid sample-to-answer multiplex PCR versus routine testing. *denotes CCTs, Abbreviations: RCT, randomized clinical trial; CCT, quasi-randomized controlled clinical trial; CI, confidence interval.

improved patient satisfaction, and an estimated minimum cost saving of approximately US$2873 per day.[29]

The appropriate use of NAI antivirals and infection control facilities among influenza-positive patients increased with rapid sample-to-answer multiplex PCR compared with routine testing. Rapid sample-to-answer multiplex PCR tests were also associated with an increased detection rate of influenza-positive patients in addition to the improvements in antiviral use, suggesting that more influenza-positive patients are identified then correctly prescribed appropriate antivirals. Although we did not evaluate time to treatment with NAIs among patients with influenza, the time to results for the multiplex PCR groups was within a few hours of admission. These findings on the impact of multiplex PCR testing are important as early administration (< 6 h from admission) of neuraminidase inhibitors for treatment of influenza among hospitalized adults has been associated with both decreased length of stay and mortality.[54,55] Additionally, rapid sample-to-answer multiplex PCR tests were associated with appropriate assignment of isolation facilities for influenza-positive patients. Based on studies identified in this systematic review, the appropriate use of infection control measures holds noteworthy importance for hospitals in preventing nosocomial transmission of respiratory infection and maintaining the patient flow through these facilities during periods of intense respiratory virus circulation.[28] In a Canadian study of respiratory syncytial virus infections in a pediatric population, the cost of nosocomial transmission was estimated at $993 per admission.[56] Rapid sample-to-answer multiplex PCRs have also been shown in other studies to reduce time to isolation for positive cases and time to de-isolation for isolated cases subsequently testing negative.[27] A randomized trial noted that laboratory-based PCR tests were associated with longer time to results, which led to a delay of 1.5 days in isolation facility use for influenza-positive patients (compared with a few hours in sample-to-answer multiplex PCR test).[28] Only a few studies reported quantifiable data for infection control measures among influenza-positive patients and there was variation in the definitions used, resulting in only three studies being eligible for inclusion in the meta-analysis. Standardization of outcome definitions for infection control measures would be useful for future research. The three studies reported that appropriate use of side room isolation for confirmed influenza cases was more common in the rapid sample-to-answer PCR group than in the control group. A study by Vos et al. reported that implementation of the rapid molecular tests led to a reduction in number of hospitalized patients requiring in-hospital isolation facilities (56.4% vs 41.7%).[51]

The impact of rapid sample-to-answer multiplex PCR tests on antibiotic use was uncertain; however, results from one study suggested a possible modest reduction in both the proportion of patients treated with antibiotics and the overall duration of antibiotic use.[50] The diagnosis of a virus does not rule out the presence of concomitant bacterial infection and so physicians often prescribe antibiotics to hospitalized patients even when a respiratory virus has been identified. In a study of point-of-care testing for respiratory viruses, shorter turnaround time (less than 1.6 h) was associated with higher rates of early discontinuation of antibiotics and length of stay compared with longer turnaround time (1.6 h or more).[53] With increased awareness of antibacterial stewardship, faster time to result and point-of-care devices with improved technology, and potential combination interventions with biomarkers, multiplex PCR

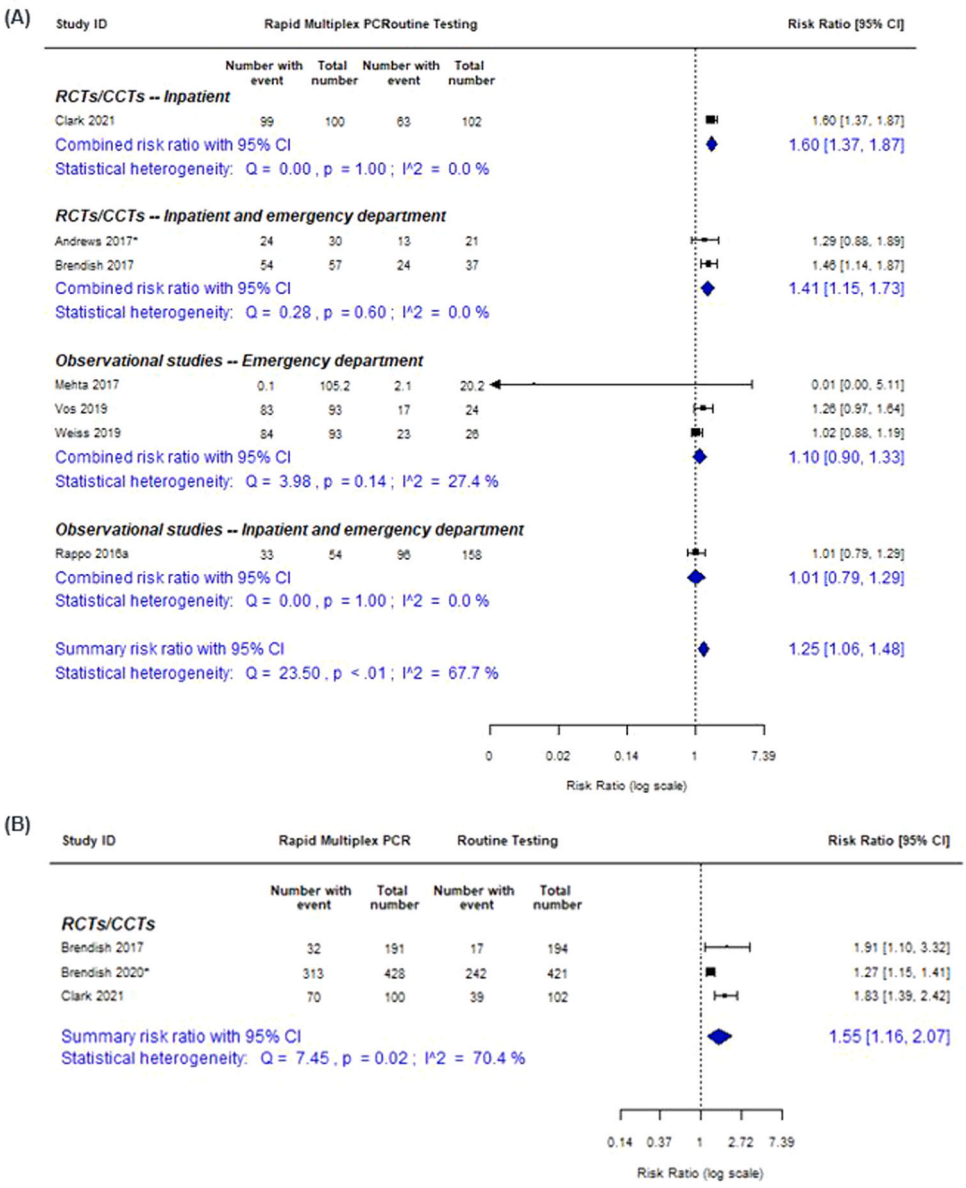

Fig. 4. (A) Forest plot of appropriate NAI use (proportion of influenza-positive patients) with rapid sample-to-answer multiplex PCR versus routine testing. (B) Forest plot of appropriate infection prevention control (proportion of influenza-positive patients) with rapid sample-to-answer multiplex PCR versus routine testing. *denotes CCTs, Abbreviations: RCT, randomized clinical trial; CCT, quasi-randomized controlled clinical trial; CI, confidence interval.

test may more consistently facilitate reductions in antibiotic prescriptions and increased discontinuations. There was little evidence to suggest any impact of rapid sample-to-answer multiplex PCR testing on ED LOS (only three studies reported data) or the rate of hospital admission from ED. In a US-based database study, shorter time to result was associated with shorter ED stays, with a reduction of 0.5 min per 1 min decrease in time to result.[57] Thus, future faster time to result and point-of-care devices may be of benefit here as well. The effect of rapid sample-to-answer multiplex PCR tests on mortality outcomes also was inconclusive. The relatively small number of events resulted in imprecise effect estimates; although it is noteworthy that most studies reported fewer inpatient deaths in the rapid sample-to-answer multiplex PCR test group compared with the routine testing.

This systematic review has several notable limitations. Firstly, there was substantial statistical heterogeneity detected across multiple analyses. However, because the direction of effect was consistent across studies, we assessed that it would be unlikely to affect the overall interpretation of results. Heterogeneity across studies was in line with a previous systematic review by Vos et al. which also included studies with considerably heterogeneous design and quality.[58] Secondly, the review included studies that were reported in conference abstracts and provided limited data. However, outcomes reported only qualitatively were in agreement with quantitative outcome data included in meta-analysis and would not likely change the interpretation of the analyses. Third, NAI use and infection control outcomes were infrequently reported across studies and when reported, their definitions varied across studies. Therefore, a comparison was difficult to ascertain for these outcomes and the analyses include only a small proportion of studies identified in the systematic review. Finally, there was uncertainty among some of the included studies as to whether the multiplex PCR testing was conducted at the point of care or was sent to a central laboratory. The large RCTs conducting multiplex PCR testing at the point-of-care may have introduced heterogeneity in outcomes as this would generally to lead to an even faster time to result.

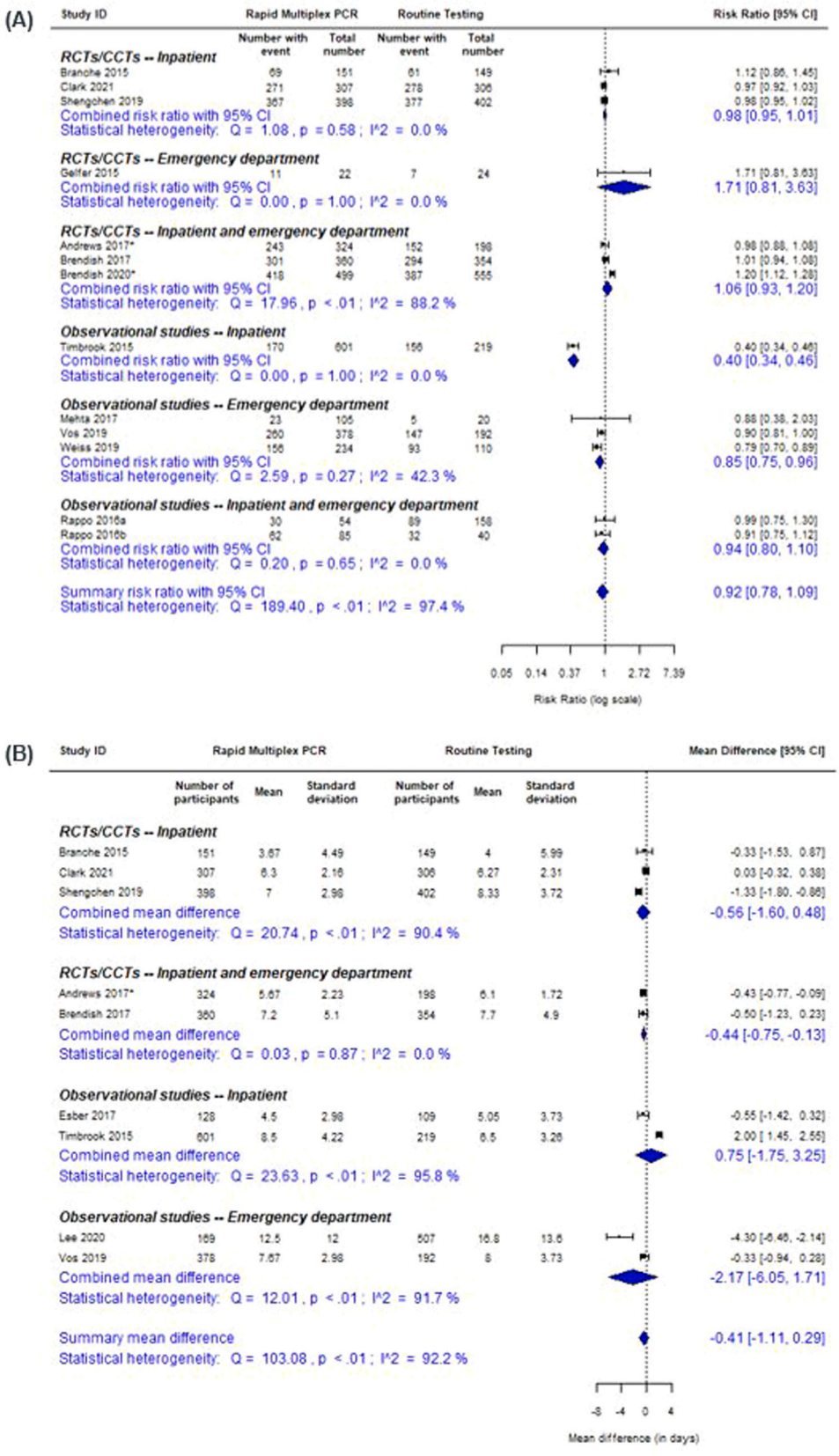

Fig. 5. (A) Forest plot of proportion of patients treated with antibiotics with rapid sample-to-answer multiplex PCR versus routine testing. (B) Forest plot of duration of antibiotic use (in days) with rapid sample-to-answer multiplex PCR versus routine testing. *denotes CCTs, Abbreviations: RCT, randomized clinical trial; CCT, quasi-randomized controlled clinical trial; CI, confidence interval.

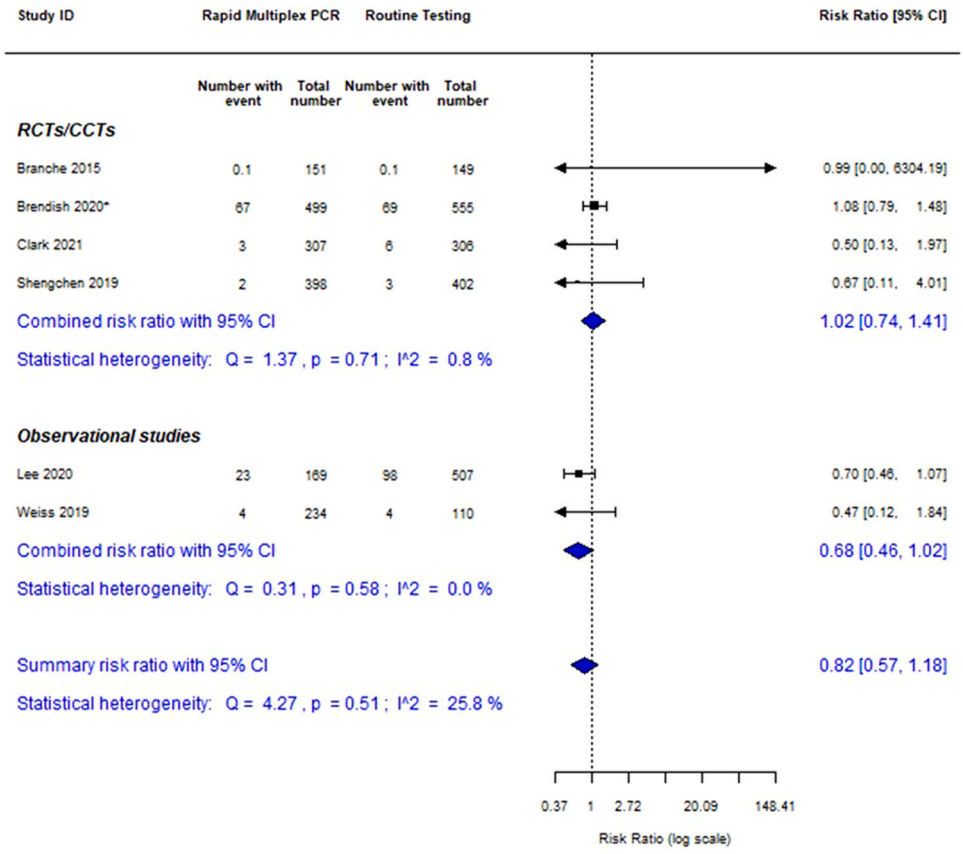

Fig. 6. Forest plot of in-patient mortality (proportion of patients) with rapid sample-to-answer multiplex PCR versus routine testing. *denotes CCTs, Abbreviations: RCT, randomized clinical trial; CCT, quasi-randomized controlled clinical trial; CI, confidence interval.

Conclusions

This study shows that the use of rapid sample-to-answer multiplex PCR for detection of respiratory viruses in adults with acute respiratory illness was associated with a large reduction in time to results and a reduction in length of hospital stay compared with routine laboratory-based PCR testing. In addition, among influenza-positive patients, the appropriate use of NAIs and infection control facilities was increased with rapid sample-to-answer multiplex PCR testing compared with routine testing. This evidence supports the routine use of rapid sample-to-answer multiplex PCR testing in hospital settings for patients with possible acute respiratory tract infections. Consideration should be given to supporting the routine use of rapid multiplex PCR tests for patients with suspected respiratory infections in international guidelines.

Authorship contributions

TWC – Assisted with the design of the study, participated in the interpretation of data, drafted and co-wrote the manuscript, KL - Assisted with the design of the study, participated in the acquisition of data, analysis, and interpretation of data, drafted and co-wrote the manuscript, TBW - Assisted with the design of the study, participated in the interpretation of data, drafted, and co-wrote the manuscript, AB - Assisted with the design of the study, participated in the acquisition of data, analysis, and interpretation of data, drafted, and co-wrote the manuscript, RBH - Assisted with the design of the study, participated in the interpretation of data, drafted, and co-wrote the manuscript, JU - Assisted with the design of the study, participated in the acquisition of data, analysis, and interpretation of data, reviewed and edited the manuscript, TTT – Assisted with the design of the study, participated in the interpretation of data, drafted and co-wrote the manuscript, All authors approved the final version of the manuscript.

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BioMerieux sponsored and funded this study and manufacturers a rapid multiplex PCR test for respiratory tract infections; however, the SLR included eligible tests by type and not by any specific manufacturer.

Declaration of Competing Interest

TWC has received speaker fees, honoraria, consultancy fees, travel reimbursement, and equipment and consumables free of charge for the purposes of research outside of this submitted study, from BioFire diagnostics and BioMerieux. He has received speaker fees and discounted equipment and consumables from QIAGEN. He has received consultancy fees from, Shionogi, Synairgen research, Roche and Janssen. He has been a member of advisory boards for Roche, Janssen, Cepheid, Shionogi, Sanofi and Seqirus. He is a member of an independent data monitoring committees for a trial sponsored by Roche. He has acted as the UK chief investigator for a trial sponsored by Janssen. TBW, RBH, and TTT are employees of bioMerieux, the sponsor of this study. KL, AB, and JU are employees of IQVIA, which received funding from bioMerieux to conduct this study.

Acknowledgments

None.

Data sharing

Following publication of major outputs all anonymized data will be made available on request to the corresponding author for appropriate, ethically approved research.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.03.005.

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