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REVIEW ARTICLE

Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies

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We systematically reviewed available evidence from Embase, Medline, and the Cochrane Library on diagnostic accuracy and clinical impact of commercially available rapid (results <3 hours) molecular diagnostics for respiratory viruses as compared to conventional molecular tests. Quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies criteria for diagnostic test accuracy (DTA) studies, and the Cochrane Risk of Bias Assessment and Risk of Bias in Nonrandomized Studies of Interventions criteria for randomized and observational impact studies, respectively. Sixty-three DTA reports (56 studies) were meta-analyzed with a pooled sensitivity of 90.9% (95% confidence interval [CI], 88.7%–93.1%) and specificity of 96.1% (95% CI, 94.2%–97.9%) for the detection of either influenza virus (n = 29), respiratory syncytial virus (RSV) (n = 1), influenza virus and RSV (n = 19), or a viral panel including influenza virus and RSV (n = 14). The 15 included impact studies (5 randomized) were very heterogeneous and results were therefore inconclusive. However, we suggest that implementation of rapid diagnostics in hospital care settings should be considered.

Keywords. rapid test; molecular diagnostics; diagnostic accuracy; impact; review.

Acute respiratory tract infections (RTIs) have a high disease burden and are the third cause of death worldwide [1, 2]. Respiratory viruses predominate as causative pathogens in patients hospitalized with acute RTI, accounting for 50%–66% of microbiological etiologies [3–5]. Rapid identification of viral etiologies may improve effective patient management by influencing decision making on antibiotic treatment, antiviral therapy, hospital admission, length of stay, and implementation of infection-control measures to prevent further transmission [2, 6]. It may also lead to avoidance of unnecessary costs and antimicrobial resistance by reducing unnecessary prescriptions of antibiotics [7–10].

About a decade ago, the transition from conventional techniques as viral cultures and immunoassays to reverse-transcription polymerase chain reaction (RT-PCR) techniques did not result in a reduction in overall antibiotic use in hospitalized patients with lower RTI [6]. Although being faster in comparison to conventional techniques, RT-PCR–based diagnostics still took up to 48 hours from sampling to result [6], whereas nowadays we have access to rapid diagnostics with turnaround times of >1 hour [11].

Whether these rapid methods lead to improved patient outcomes, however, is still under debate. First, there is a wide range of rapid tests available with large differences in diagnostic accuracy. Reviews evaluating accuracy of available rapid tests for respiratory viruses either included a heterogeneous group of tests including both ultrarapid but less sensitive antigen-based tests and more sensitive but slightly slower molecular tests [11–13], compared rapid tests to outdated techniques as viral culture or immunoassays [13], focused on only 1 or 2 viral pathogens, mostly influenza virus [11], or focused on 1 specific assay [14, 15]. To guide physicians and hospitals in their choice for rapid diagnostic tools and how to value and interpret their results, a diagnostic test accuracy (DTA) review of available molecular rapid tests as compared to the best available reference standard—RT-PCR or other molecular methods—is essential. Second, even with tests that demonstrate high accuracy, there are conflicting conclusions on whether implementation of these tests results in better patient outcomes. A review on clinical impact of rapid molecular tests that summarizes and assesses sources of heterogeneity to explain these discrepant results is therefore highly needed.

In this review, we provide an overview of available molecular rapid tests that can provide results for the detection of

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respiratory viruses within 3 hours. We systematically summarize quality and meta-analyze results of DTA studies and systematically review studies evaluating the clinical impact of rapid molecular testing for respiratory viruses.

METHODS

We followed the guidance provided by the Cochrane DTA Working Group [16]. This systematic review was registered in the Prospero database under CRD42017057881. A systematic literature search for both DTA and clinical impact studies was conducted (Supplementary Materials 1*A*). The search was performed in Medline, Embase, and the Cochrane Library on 31 August 2017. Inclusion and exclusion criteria and the screening process are described in Supplementary Materials 1*B* and 1*C*, respectively. Data extraction for both DTA and clinical impact studies was conducted in a systematic manner (Supplementary Materials 1*D* and 1*E*). Methodological quality of the included studies was reviewed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria [17] for DTA studies, the Cochrane Risk of Bias tool [18] for randomized clinical impact studies, and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool [19] for nonrandomized clinical impact studies.

Statistical Analysis

Sensitivity and specificity were calculated using 2 × 2 contingency tables for all index tests from the included DTA studies. Sensitivities and specificities of individual studies with their corresponding 95% confidence intervals (CIs) were presented in paired forest plots. We used the bivariate random-effects model to meta-analyze the logit-transformed sensitivities and specificities to obtain a summary estimate together with a random-effects 95% confidence and prediction interval. This model takes into account the precision by which sensitivities

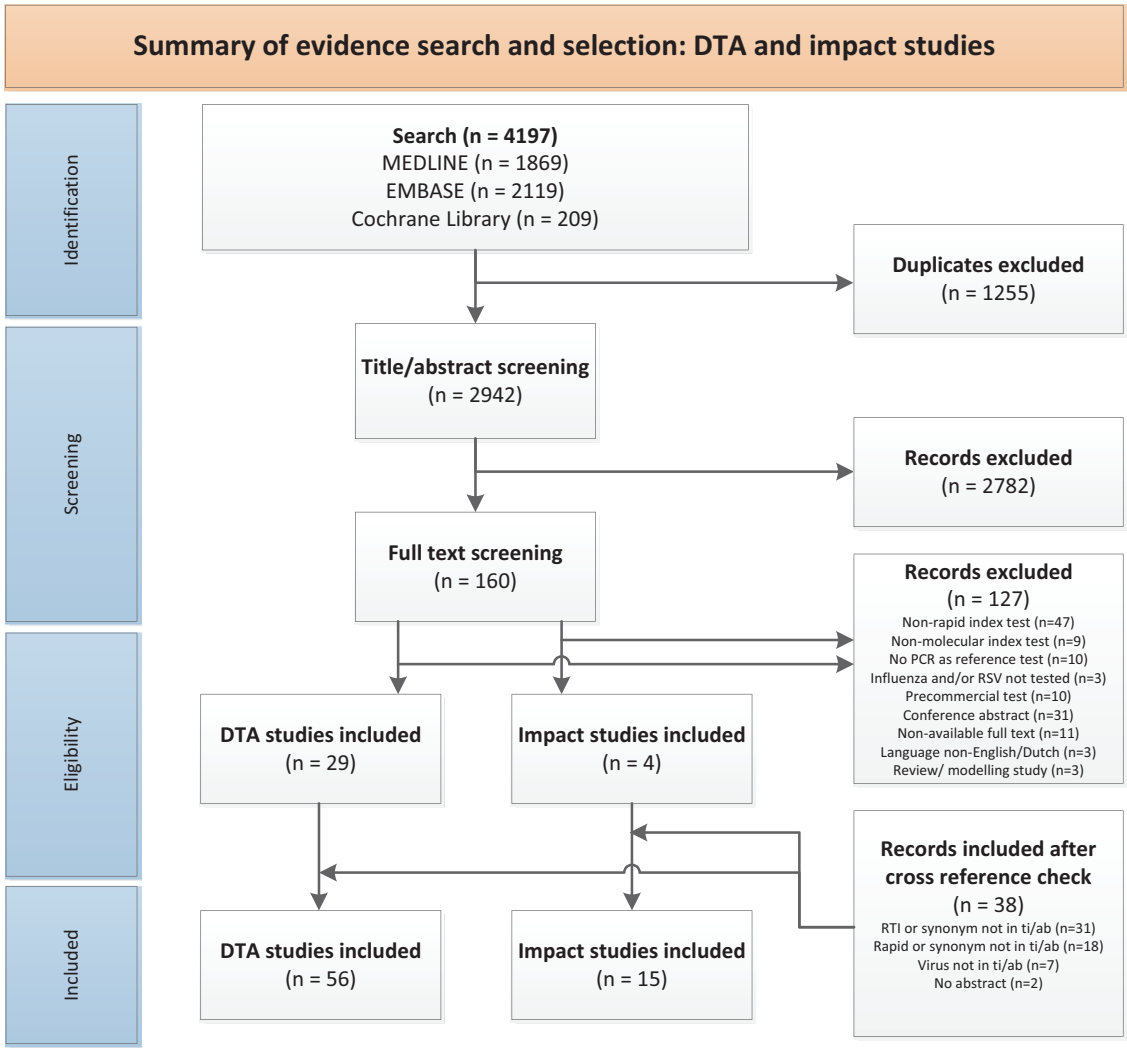

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart. Abbreviations: DTA, diagnostic test accuracy; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; RTI, respiratory tract infection; ti/ab, title/abstract.

and specificities have been estimated in each study using the binomial distribution (ie, weighted average) and incorporates any additional variability beyond chance that exists between studies (ie, random-effects model). Results were plotted in receiver operating characteristic (ROC) space with 95% confidence and 95% prediction intervals. The 95% confidence region reflects the precision of the pooled point estimate, whereas the 95% prediction region represents the region in which the individual results of a new, large study evaluating the diagnostic accuracy of the same rapid assay are to be expected. In these plots, sensitivity and specificity estimates of the most frequently described assays were pooled per assay. Heterogeneity between studies was assessed by subgroup analyses using bivariate random-effects regression for different study populations, different assays, different viruses that were assessed, different study designs, and studies with different quality. For clinical impact studies, a descriptive summary of the quality of included studies was given. Results of clinical impact studies were not pooled quantitatively, but presented per clinical outcome arranged by study quality. All analyses were performed in R Studio, and ROC plots were made using Stata version 11 software.

RESULTS

Diagnostic Accuracy

After screening (Figure 1), 63 separate reports were included in the meta-analysis from 56 individual DTA study publications (Supplementary Materials 2). The main characteristics of the included DTA reports are described in Table 1. The median sample size in these reports was 95 patients (interquartile range [IQR], 49–196). The included reports evaluated 13 commercial molecular rapid diagnostic tests. Of these, the most frequently studied tests were the Alere i Influenza A&B assay (Alere, Scarborough, Maine; 14 reports), Cobas Liat Influenza A/B (Roche Diagnostics, Indianapolis, Indiana; 5 reports), FilmArray (BioFire Diagnostics, Salt Lake City, Utah; 10 reports), Cepheid Xpert Flu Assay (Cepheid, Sunnyvale, California; 9 reports), Simplexa Flu A/B & Respiratory Syncytial Virus (RSV) kit (Focus Diagnostics, Cypress, California; 9 reports), and Verigene Respiratory Virus Plus (Nanosphere, Northbrook, Illinois; 5 reports).

The quality of the included DTA studies (n = 56) was assessed using the QUADAS-2 criteria and is summarized in Supplementary Figure 1. The biggest concern in terms of quality was that a minority (35%) of included studies gave a clear description of their selection criteria and/or used a cohort design for inclusion of patients or specimens. In terms of flow, 17% of studies used samples that were frozen between index and reference testing, used multiple different molecular reference standards, and/or excluded samples that had invalid results on either the index test or reference standard. For the index test, in the majority of studies it was unclear whether

Table 1. Characteristics of the Reports (N = 63) from the 56 Included Diagnostic Test Accuracy Studies

Characteristic	No. (%)
Study design	
Cohort study	28 (44.4)
Case-control study	28 (44.4)
Partially cohort and partially case-control	7 (11.1)
Data collection	
Prospective	25 (39.7)
Retrospective	29 (46.0)
Both prospective and retrospective	9 (14.3)
Virus evaluated	
Influenza A and B[a]	29 (46.0)
Influenza A, B, and RSV[b]	20 (31.7)
Panel of viruses[c]	14 (22.2)
Study population	
Children	8 (12.7)
Adults[d]	7 (11.1)
Children and adults	26 (41.3)
Not reported	22 (34.9)
Patient symptoms	
Patients with ILI or symptoms of an RTI[e]	36 (57.1)
Symptoms not described	27 (42.9)
Tests evaluated	
AdvanSure (LG Life Sciences)[f]	3 (4.8)
Alere i Influenza A&B assay (Alere)	14 (22.2)
Aries Flu A/B & RSV assay (Luminex)[f]	2 (3.2)
Cobas Liat Influenza A/B (Roche Diagnostics)	5 (7.9)
Enigma MiniLab (Enigma Diagnostics Ltd)[f]	1 (1.6)
FilmArray (BioFire Diagnostics)	10 (15.9)
Cepheid Xpert Flu Assay (Cepheid)	9 (14.3)
ePlex RP Panel (GenMark Diagnostics)[f]	1 (1.6)
PLEX-ID Flu Assay (Abbott Molecular)[f]	1 (1.6)
RIDAGENE Flu & RSV kit (R-Biopharm AG)[f]	1 (1.6)
Roche RealTime (Roche Diagnostics)[f]	2 (3.2)
Simplexa Flu A/B & RSV kit (Focus Diagnostics)	9 (14.3)
Verigene Respiratory Virus Plus test (Nanosphere)	5 (7.9)
Reference standard	
In-house or laboratory-developed RT-PCR	22 (34.9)
Commercial RT-PCR[g]	41 (65.1)

See Supplementary Materials 2 for the reference list of studies.

Abbreviations: ILI, influenza-like illness; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RT-PCR, reverse-transcription polymerase chain reaction.

[a]Among these studies, 1 study (Salez et al, 2013) only validated the Cepheid Xpert Flu Assay for influenza B.

[b]Among these studies, 1 study (Peters et al, 2017) only validated the Alere i Influenza A&B assay for RSV.

[c]FilmArray (15 viral targets): RSV-A, RSV-B, influenza A/H1, influenza A/H3, influenza untypable, influenza B, parainfluenza virus types 1–4, human metapneumovirus (hMPV), adenovirus, enterovirus/rhinovirus, coronavirus NL63, coronavirus HKU1. For some studies, this panel was only partially validated. AdvanSure (14 viral targets): RSV-A, RSV-B, influenza A, influenza B, parainfluenza virus 1–3, hMPV, bocavirus, adenovirus, rhinovirus, and coronaviruses OC43, 229E, and NL63. ePlex RP panel (21 viral targets): RSV-A, RSV-B, RSV untypable, influenza A/H1, influenza 2009 A/H1N1, influenza A/H3, influenza A untypable, influenza B, parainfluenza virus types 1–4, hMPV, bocavirus, adenovirus, enterovirus/rhinovirus, Middle East respiratory syndrome coronavirus, and coronaviruses OC43, 229E, NL63, and HKU1.

[d]Two adult studies only included immunocompromised patients (Steensels et al, 2017 and Hammond et al, 2012).

[e]Among studies that included symptomatic patients, 14 studies included patients with ILI (8 cohort studies, 4 case-control studies, and 2 with both a symptomatic cohort; 21 included patients with symptoms of an upper or lower RTI and 2 that included patients with symptoms that were not further specified.

[f]Full affiliations of index tests not mentioned in text: AdvanSure (LG Life Sciences, Seoul, Korea), Aries Flu A/B & RSV assay (Luminex Corporation, Austin, Texas), Enigma MiniLab Influenza A/B & RSV (Enigma Diagnostics, Salisbury, United Kingdom), ePlex respiratory pathogen panel (GenMark Diagnostics, Carlsbad, California), PLEX-ID Flu assay (Abbott Molecular, Des Plaines, Illinois), RIDAGENE Flu & RSV kit (R-Biopharm AG, Darmstadt, Germany), and Roche RealTime Ready Influenza AH1N1 Detection Set (Roche Diagnostics, Indianapolis, Indiana).

[g]One study used 2 different commercial PCR methods or composite reference with concordance of at least 2 multiplex PCR methods (Popowitch, 2013).

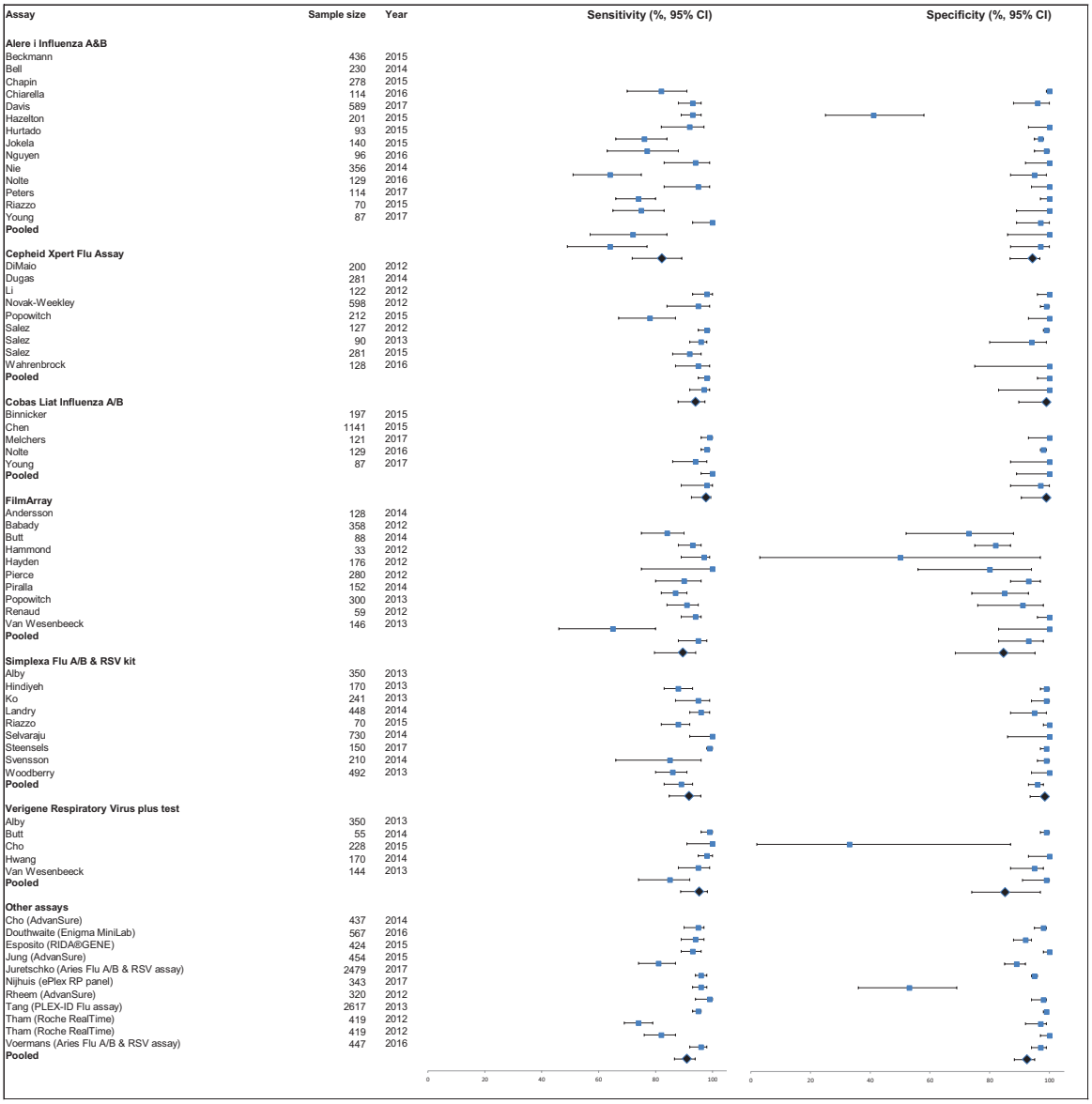

Figure 2. Forest plot for sensitivity (left) and specificity (right) (% with 95% confidence interval) of all study reports (N = 63), stratified and pooled per assay (top to bottom). In one study (Salez 2012), no negative tested samples were included, so specificity could not be calculated for this study and was therefore excluded from the pooled analysis. For specificity, 4 studies had an outstandingly low specificity due to the case-control design with inclusion of a very low number of virus-negative patients: 37 negative patients, of whom 22 tested false positive with the Alere i Influenza A&B assay (Chapin 2015), 2 negative patients, of whom 1 tested false positive with FilmArray (Butt 2014), 3 negative patients, of whom 2 tested false positive with the Verigene Respiratory Virus Plus test (Butt 2014), and 29 negative patients, of whom 10 tested false positive with the ePlex RP panel (Nijhuis 2017). Please see Supplementary Materials 2 for the reference list of studies. Abbreviation: CI, confidence interval.

results were interpreted without knowledge of the results of the reference test.

Overall, the pooled sensitivity of all rapid molecular tests was 90.9% (95% CI, 88.7%–93.1%) and the pooled specificity was 96.1% (95% CI, 94.2%–97.9%). Forest plots for both sensitivity and specificity of all included studies are shown in Figure 2. ROC plots with sensitivity and specificity of the most frequently assessed assays are depicted in Figure 3. Subgroup analyses were conducted to investigate heterogeneity in sensitivity and specificity (Table 2). The sensitivity of the different index tests ranged from 81.6% (95% CI, 75.4%–87.9%) for the Alere i Influenza A&B assay to 99.0% (95% CI, 98.3%–99.6%) for the Simplexa Flu A/B & RSV kit (P = .000). The specificity of assays detecting a panel of viruses (eg, the FilmArray, AdvanSure, and ePlex RP panel) was significantly lower than the specificity of assays detecting only influenza virus and/or RSV (P = .009). Subgroup analyses based on differences in study design showed increased sensitivity of cohort studies as compared to case-control studies (P = .009). The pooled sensitivity of studies that only included children (n = 8) was 93.0% (95% CI, 91.5%–94.5%) as compared to a pooled sensitivity of 79.8% (95% CI, 70.7%–88.9%) in adults (n = 7) (P = .01), whereas the pooled specificity was

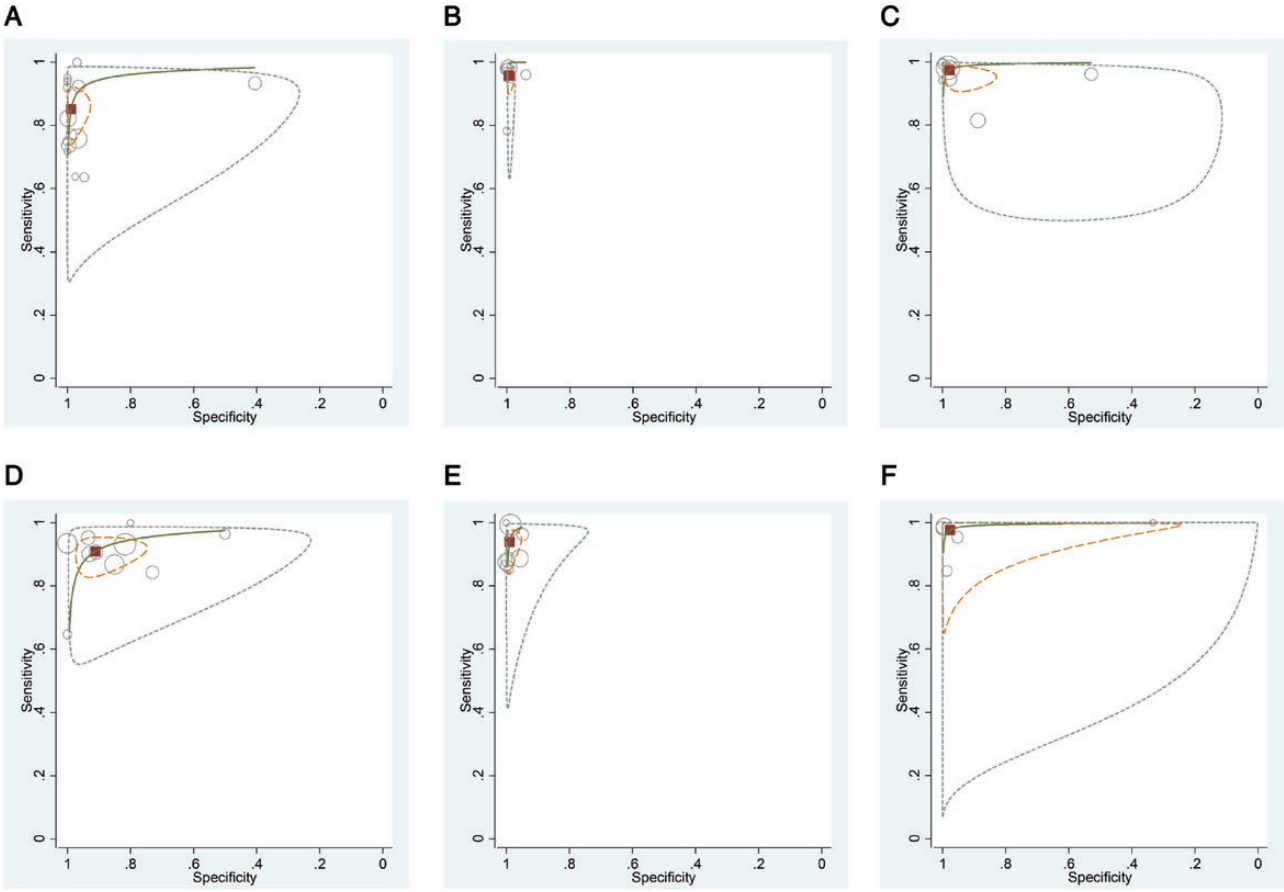

Figure 3. Receiver-operating characteristic (ROC) curve plots of most frequently evaluated rapid molecular diagnostic tests: Alere i Influenza A&B assay (*A*), Cepheid Xpert Flu Assay (*B*), Cobas Liat Influenza A/B (*C*), FilmArray (*D*), Simplexa Flu A/B & Respiratory Syncytial Virus kit (*E*), and Verigene Respiratory Virus Plus test (*F*). The size of the circles indicates the sample size of the individual studies. The pooled summary estimate is represented by the square, the 95% confidence region by the finely dotted lines, the 95% prediction region by the striped lines, and the ROC curve by the continuous line.

higher in adults (98.6% [95% CI, 95.5%–100%]) as compared to child studies (80.8% [95% CI, 73.1%–88.4%]) (P = .001).

Clinical Impact

After screening (Figure 1), we included 15 clinical impact studies [1, 20–33]. Characteristics of included clinical impact studies are described in Table 3. The implemented diagnostic rapid molecular test was combined with procalcitonin measurements in 2 studies [21, 30]. Two studies implemented guidelines on treatment decisions based on the rapid test results [20, 21], whereas in other studies no changes in treatment recommendations and antibiotic stewardship were made or treatment consequences of rapid testing were not described. Five studies were randomized diagnostic impact trials [1, 20, 21, 24, 25], 6 studies used a nonrandomized before-after design [23, 26–29, 32], and 4 studies were observational noncomparative studies [22, 30, 31, 33]. Only 1 study included patients at >1 center [22]. Three studies [1, 20, 31] placed the rapid test at the point of care, whereas others located the diagnostic test at the microbiological laboratory. Seven studies were sponsored by the manufacturer of the diagnostic test [20, 21, 23–25, 28, 29]. The median number of included patients in the studies was 300 (IQR, 121–630) and most studies (n = 9) included only adult patients [1, 20, 21, 24–26, 28, 30, 34]. The FilmArray was used most frequently (11 of 15 studies) as a diagnostic intervention test [1, 20, 21, 24, 25, 27–31, 33].

The quality assessment of all studies is summarized in Supplementary Figure 2. All nonrandomized studies suffered from potential confounding bias and bias in outcome measurements.

The results of the impact studies were very heterogeneous. Clinical outcomes for each study are categorized and summarized in Table 4, with studies of higher quality at the top. The turnaround time of the rapid molecular tests vs reference molecular techniques was significantly faster in all studies that assessed turnaround time (n = 10) [1, 20, 23–25, 27–29, 31, 32]. Implementation of rapid molecular tests did not decrease the number of antibiotic prescriptions or the duration of antibiotic treatment. Only 1 multivariable adjusted before-after

Table 2. Accuracy Estimates From Subgroup Analyses Using Bivariate Random-effects Regression

Characteristic	No. of Studies	Pooled Sensitivity, % (95% CI)	*P* Value[a]	Pooled Specificity, % (95% CI)	*P* Value[a]
Population age group					
Children	8	93.0 (91.5–94.5)	.010	80.8 (73.1–88.4)	.001
Adults	7	79.8 (70.7–88.9)		98.6 (95.5–100)	
Population symptoms					
Respiratory/ILI	34	90.4 (87.2–93.7)	.655	96.2 (93.6–98.7)	.478
Unclear	29	91.4 (88.6–94.2)		94.8 (91.9–97.7)	
Viruses					
Influenza	29	87.9 (83.7–92.1)	.078[b]	97.4 (94.2–100)	.009[b]
Influenza + RSV	19	94.1 (90.9–97.4)		96.4 (93.6–99.2)	
Panel of viruses	14	91.8 (88.7–95.0)		88.8 (82.7–95.0)	
Index test					
Alere i Influenza A&B	14	81.6 (75.4–87.9)	.000[c]	94.0 (86.0–100)	.623
Cobas Liat Influenza A/B	5	98.1 (90.8–100)		99.7 (88.5–100)	
FilmArray	10	89.2 (86.4–92.0)		96.1 (90.5–100)	
Simplexa Flu A/B & RSV	9	99.0 (98.3–99.6)		98.2 (93.3–100)	
Verigene RV Plus test	5	96.2 (88.0–100)		97.1 (87.6–100)	
Cepheid Xpert Flu	9	94.9 (91.1–98.6)		100 (97.8–100)	
Study design					
Cohort	28	94.7 (92.5–96.8)	.009	96.5 (94.3–98.8)	.147
Case-control	28	88.8 (85.2–92.5)		91.2 (84.5–97.9)	
Prospective or retrospective study					
Prospective	25	91.4 (89.2–93.6)	.461	95.9 (93.4–98.5)	.200
Retrospective	29	89.7 (86.0–93.4)		91.9 (85.7–98.1)	

Abbreviations: CI, confidence interval; ILI, influenza-like illness; RSV, respiratory syncytial virus.

[a] *P* values are calculated comparing sensitivity and specificity of ≥2 groups, using an independent sample *t* test for 2 groups and a 1-way analysis of variance for >2 groups.

[b] Post hoc test using Tukey honestly significant difference (HSD) gives a significant result between influenza and panel of viruses ($P = .008$); between influenza + RSV and panel of viruses ($P = .036$); no significant result between influenza and influenza + RSV.

[c] Post hoc test using Tukey HSD gives significant result between Alere i Influenza A&B and Cobas Liat Influenza A/B ($P = .001$); between Alere i Influenza A&B and Simplexa Flu A/B & RSV ($P = .000$); between Alere i Influenza A&B and Verigene RV Plus ($P = .007$); between Alere i Influenza A&B and Cepheid Xpert Flu ($P = .002$); no significant result between the other groups.

study [23] reported a significantly lower percentage of antibiotic prescriptions in the patients tested with the Simplexa Flu A/B & RSV kit during the second season as compared to patients tested with the laboratory-developed RT-PCR during the first season. One other before-after study [29] reported a significant reduction in duration of antibiotic treatment. Both studies were not adjusted for differences in the proportion of influenza virus–positive patients, which was significantly higher during the second (intervention) season. Oseltamivir prescriptions were more appropriate in influenza virus–positive patients according to 1 randomized study [1] and 1 nonrandomized study [26]. Two other nonrandomized comparative studies showed no effect of rapid testing on oseltamivir prescriptions [23, 28]. The number of hospital admissions was not reduced by rapid molecular testing [1, 22, 26, 28], but 2 studies, among which 1 was a randomized study, showed a decreased length of hospital stay among admitted patients [1, 28]. Length of hospital stay was not reduced in 4 other studies, among which 2 were randomized studies [20, 21, 23, 29] that, however, were smaller and potentially underpowered as compared to the randomized study that showed a significant effect [1]. Safety outcomes as mortality, serious adverse events, and intensive care unit admissions and/or readmissions did not differ between the intervention and control groups [1, 20, 21, 23, 29, 30]. In terms of efficiency, 1 study reported lower costs of therapy with the use of a rapid molecular test [24] and 2 studies reported a reduction in the number of chest radiographs in influenza virus–positive patients [22, 28]. There was no effect on the use of isolation facilities in 2 studies [1, 29] but 1 unadjusted before-after study reported a significant reduction in the mean droplet isolation days, a reduction in isolation days for suspected influenza (0.4 vs 2.7 days; $P < .001$), and an increase in isolation days for confirmed influenza virus infection (1.1 vs 0.9 days; $P = .16$) [32].

DISCUSSION

In our meta-analysis, DTA studies for molecular rapid tests for respiratory viruses showed that these tests are accurate with a pooled sensitivity of 90.9% (95% CI, 88.7%–93.1%) and a pooled specificity of 96.1% (95% CI, 94.2%–97.9%). In our subgroup analysis, the Cobas Liat Influenza A/B system was most reliable for the detection of influenza virus, with a sensitivity of 98.1%, and the Simplexa Flu A/B & RSV kit was most reliable for detection of influenza virus and RSV with a sensitivity of 99.0%. The FilmArray simultaneously tests for a panel of 15 viruses with a

Table 3. Characteristics of Studies Included in the Review of Clinical Impact Studies (n = 15)

Characteristic	No. (%)
Study design	
Randomized controlled trial	5 (33.3)
Cohort study with before-after design	6 (40.0)
Cohort study without control group	4 (26.7)
Single-center study	14 (93.3)
Study population	
Children	2 (13.3)
Adults	9 (60.0)
Children and adults	2 (13.3)
Not reported	2 (13.3)
Sample size	
Eligible patients, No., median (IQR)[a]	475 (232–945)
Included patients, median (IQR)	300 (121–630)
Intervention group patients, median (IQR)	151 (72–347)
Control group patients, median (IQR)[b]	149 (50–205)
Symptoms of patients	
Patients with ILI or symptoms of RTI	10 (67.7)
(Eventual) symptoms unclear	5 (33.3)
Tests evaluated	
Alere i Influenza A&B assay	1 (6.7)
FilmArray[c]	11 (73.3)
Cepheid Xpert Flu assay	2 (13.3)
Simplexa Flu A/B & RSV kit	1 (6.7)
Reference standard	
In-house or laboratory-developed RT-PCR and/or other routine viral pathogen test	11 (73.3)
No comparison for clinical outcomes	4 (26.7)
Clinical outcomes	
Antibiotics	11 (73.3)
Oseltamivir	5 (33.3)
Hospital admission	4 (26.7)
Length of hospital stay	7 (46.7)
Isolation measurements	3 (20.0)
Safety outcomes	6 (40.0)
No. of radiographs and other investigations	2 (13.3)
Turnaround time	10 (67.7)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ILI, influenza-like illness; IQR, interquartile range; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RT-PCR, reverse-transcription polymerase chain reaction.

[a]In 4 studies, the number of eligible patients was unclear (Chu 2015, Keske 2017, Muller 2016, and Xu 2013).

[b]In 4 studies, no control group was used for comparison (Busson 2017, Keske 2017, Timbrook 2015, and Xu 2013).

[c]In 2 studies, the FilmArray (partially) was a combined diagnostic intervention with procalcitonin measurement (Branche 2015 and Timbrook 2015).

sensitivity of 89.2%. Overall, molecular tests had better sensitivity in children than adults, presumably due to higher viral loads in children [35]. Studies on the clinical impact of rapid molecular testing had large variation in design and quality. Nevertheless, they unanimously found significantly decreased turnaround times. In addition, a reduced length of hospital stay, increased appropriate use of oseltamivir in influenza virus–positive patients, and a potential reduction in costs and additional radiographs as compared to conventional molecular methods were observed in the majority of the (high-quality) studies. No effect was seen on antibiotic prescriptions, duration of antibiotic therapy, use of in-hospital isolation measurements, or the number of hospital admissions.

This is the first systematic review to compare and pool the diagnostic accuracy of multiple rapid molecular assays and to analyze clinical outcomes. Other systematic reviews on this topic have either included nonrapid molecular assays [36, 37], only focused on 1 or 2 particular assays [14, 15, 38], or also included nonmolecular rapid tests with lower sensitivity as compared to molecular assays [11, 12, 39, 40]. Studies have shown superior accuracy of molecular assays compared with rapid antigen tests [11], and pooling the results of assays that use different underlying techniques gives pessimistic estimates of the diagnostic accuracy of molecular tests [41]. Potential practical concerns of molecular tests as compared to antigen tests, such as increased costs, longer turnaround times, and more complicated procedures, have largely been overcome with recent technological innovations [4]. Molecular tests are replacing antigen-based rapid assays. Therefore, further comparisons should be using molecular assays as a gold standard. In this review we included both pathogen-specific singleplex and multiplex assays detecting a range of respiratory viruses, whereas in most reviews and studies there is special focus on assays that detect only 1 or 2 pathogens, mainly influenza virus [11, 38, 40] and sometimes RSV [12]. Viral pathogens other than influenza virus and RSV also have a high burden of disease [42], and their detection may have clinical consequences as antiviral treatment [43] and application of isolation measurements in a hospital setting. Depending on the clinical setting and patient population, assays that are capable of detecting a panel of viruses may therefore be of increased interest when rapid tests are to replace conventional molecular tests.

To determine which rapid test to implement, the overall diagnostic accuracy of a multiplex test may then be more important than its individual pathogen accuracy, whereas in the current diagnostic accuracy reviews, overall sensitivity and specificity are often given per virus instead of per assay [11, 12, 39]. However, it should be noted that judging discrepant viral results similarly for multiplex and singleplex assays will result in poorer diagnostic accuracy, mainly specificity, of multiplex assays. Therefore, when comparing different available rapid molecular assays—for example, Simplexa Flu A/B & RSV and FilmArray—it should always be noted that differences in diagnostic accuracy between these assays can result from testing a different number of viral pathogens while the diagnostic accuracy per individual viral pathogen may be similar.

Former studies assessing the effect of testing with conventional multiplex assays providing results within 24–48 hours showed no effect on antibiotic treatment and hospital length of stay [6, 44]. However, more rapid testing for respiratory viruses

Table 4. Overview of Clinical Outcomes Presented in Included Clinical Impact Studies (n = 15)

Outcome per study (author, year, country)	Study design	Sample size (n)	Effect - intervention vs control/ odds ratio (OR)	*P*-value	Conclusion
Antibiotic prescriptions					
Brendish, 2017 (UK)	RCT (1:1)	714	84% vs 83%	.84	No decrease in antibiotic prescriptions
Andrews, 2017 (UK)	RCT (quasi[a])	522[b]	75% vs 77%	.99	
Chu, 2015 (USA)	Before-after, multivariate[c]	350	63% vs 76%	<.001	
Rogers, 2014 (USA)	Before-after, univariate	1136	72% vs 73%	.61	
Rappo, 2016 (USA)	Before-after, univariate	337[d]	66% vs 61%	.35	
Linehan, 2017 (Ireland)	Before-after, univariate	67[e]	33% vs 76%	<.001	
Busson, 2017 (Belgium)	Cohort, no control group	69	In 36.2% of patients antibiotic prescriptions were avoided	-	
Keske, 2017 (Turkey)	Cohort, no control group	359[d]	45% of virus positive patients received antibiotics	-	
Duration of antibiotic therapy					
Branche, 2015 (USA)	RCT (1:1)	300	Median 3 days [IQR 1–7] vs 4 [0–8]	.71	No decrease in duration of antibiotic therapy
Brendish, 2017 (UK)	RCT (1:1)	714	Mean 7.2 days [SD 5.1] vs 7.7 [4.9]	.32	
Andrews, 2017 (UK)	RCT (quasi[a])	522[b]	Median 6 days [IQR 4–7] vs 6 [5–7.3]	.23	
Gilbert, 2016 (USA)	RCT (quasi[f])	127	Mean 1053/1000 patient-days [SD 657] vs 472/1000 [1667]	.07	
Gelfer, 2015 (USA)	RCT (quasi[f])	18[d]	Mean 683/1000 patient-days [SD 317] vs 917/1000 [220]	.052	
Rogers, 2014 (USA)	Before-after, univariate	1136	Mean 2.8 days [SD 1.6] vs 3.2 [SD 1.6]	.003	
Rappo, 2016 (USA)	Before-after, univariate	212[e]	Median 1 vs 2 days	.24	
Keske, 2017 (Turkey)	Cohort, no control group	160[d]	Mean 6.5 days [SD 3.7] in virus positive patients	-	
Oseltamivir prescriptions					
Brendish, 2017 (UK)	RCT (1:1)	714	18% vs 14%	.16	More appropriate oseltamivir use in influenza positive patients
		94[e]	91% vs 65%	.003	
Chu, 2015 (USA)	Before-after, univariate	350	55% vs 45%	.05	
		40[e]	100% vs 100%	1.00	
		136[g]	45% vs 43%	.60	
Rappo, 2016 (USA)	Before-after, univariate	212[e]	61% vs 61%	.96	
Linehan, 2017 (Ireland)	Before-after, univariate	68[e]	95% vs 72%	<.01	
Xu, 2013 (USA)	Cohort, no control group	97[e]	81% of influenza positive patients received oseltamivir	-	
Length of hospital stay					
Branche, 2015 (USA)	RCT (1:1)	300	Median 4 vs 4 days	NS	Reduction in length of hospital stay
Brendish, 2017 (UK)	RCT (1:1)	714	Mean 5.7 days [SD 6.3] vs 6.8 [7.7][h]	.044	
Andrews, 2017 (UK)	RCT (quasi[a])	545	Median 4.1 days [IQR 2.0–9.1] vs 3.3 [1.7–7.9]	.28	
Rappo, 2016 (USA)	Before-after, multivariate[i]	212[e]	Median 1.6 days [IQR 0.3–4.8] vs 2.1 [0.4–5.6]	.040	
Rogers, 2014 (USA)	Before-after, univariate	1136	Mean 3.2 days [SD 1.6] vs 3.4 [1.7]	.16	
Chu, 2015 (USA)	Before-after, univariate	350	Median 4 days [range 1–164] vs 5 [0–117]	.33	
Timbrook, 2015 (USA)	Cohort, no control group	601[d]	Median 1 day [IQR 0–3] in virus positive patients	-	
Hospital admissions					
Brendish, 2017 (UK)	RCT (1:1)	714	92% vs 92%	.94	No reduction in hospital admissions
Rappo, 2016 (USA)	Before-after, univariate	337[d]	76% vs 74%	.60	
Linehan, 2017 (Ireland)	Before-after, univariate	69[e]	45% vs 88%	<.001	

Table 4. Continued

Outcome per study (author, year, country)	Study design	Sample size (n)	Effect - intervention vs control/ odds ratio (OR)	*P*-value	Conclusion
Busson, 2017 (Belgium)	Cohort, no control group	69	5.8% of hospitalizations was avoided	-	
Safety					
Branche, 2015 (USA)	RCT (1:1)	300	No difference in-hospital deaths, SAEs, new pneumonia cases or 90-day post-hospitalization visits	NS	Safety is not affected
Brendish, 2017 (UK)	RCT (1:1)	714	30-day readmission 13% vs 16%	.28	
			30-day mortality 3% vs 5%	.15	
			ICU admission 3% vs 2%	.36	
Andrews, 2017 (UK)	RCT (quasi[a])	545	30-day readmission 19% vs 20%	.70	
			30-day mortality 4% vs 4%	.79	
Rogers, 2014 (USA)	Before-after, univariate	1136	Mortality 0% vs 0%	1.00	
			ICU admission 0% vs 0%	1.00	
Chu, 2015 (USA)	Before-after, univariate	350	Mortality 2% vs 4%	.68	
			ICU admission 31% vs 25%	.19	
Timbrook, 2015 (USA)	Cohort, no control group	601[d]	ICU admission in 8.8% of virus positive patients	-	
(1) Costs; (2a) no. of / (2b) any additional chest radiographs; (3a) use of / (3b) time in isolation facilities					
Gilbert, 2016 (USA)	RCT (quasi[f])	127	(1) $8308/1000 patient-days [SD 10165] vs $11890/1000 [11712]	.02	Potential reduction in costs and additional X-rays
Rappo, 2016 (USA)	Before-after, multivariate[i]	188[e]	(2a) Median 1 [IQR 1-1] vs 1 [1–2]	.005	
Busson, 2017 (Belgium)	Cohort, no control group	28[e]	(2b) 25% reduction of X-rays in influenza positive patients	-	
Brendish, 2017 (UK)	RCT (1:1)	385[j]	(3a) 33% vs 25%	.12	
		50[e]	74% vs 57%	.24	
Rogers, 2014 (USA)	Before-after, univariate	1136	(3b) 2.9 days [SD 1.6] vs 3.0 [1.7]	.27	
Muller, 2016 (Canada)	Before-after, univariate	125	(3b) Droplet isolation: 3.5 days vs 6.0	<.001	
Turnaround time					
Brendish, 2017 (UK)	RCT (1:1)	714	Mean 2.3 hours [SD 1.4] vs 37.1 [21.5]	<.001	Significantly faster
Andrews, 2017 (UK)	RCT (quasi[a])	545	Median 19 hours [IQR 8.1–31.7] vs 39.5 [25.4–57.6][k]	<.001	
Gilbert, 2016 (USA)	RCT (quasi[f])	127	Mean 2.1 hours [SD 0.7] vs 26.5 [15]	<.001	
Gelfer, 2015 (USA)	RCT (quasi[f])	59	Mean 1.8 hours [SD 0.3] vs 26.7 [16]	<.001	
Chu, 2015 (USA)	Before-after, multivariate[c]	350	Median 1.7 hours [range 0.8–11.4] vs 25.2 [2.7–55.9]	<.001	
Rogers, 2014 (USA)	Before-after, univariate	1136	Mean 6.4 hours [SD 4.9] vs 18.7 [8.2][l]	<.001	
Pettit, 2015 (USA)	Before-after, univariate	1102	Mean 3.1 hours vs 46.4	<.001	
Rappo, 2016 (USA)	Before-after, univariate	212[e]	Median 1.7 hours [IQR 1.6–2.2] vs 7.7 [0.8–14]	.015	
Muller, 2016 (Canada)	Before-after, univariate	125	Mean 3.6 hours vs 35.0	-	
Xu, 2013 (USA)	Cohort, no control group	2537	Median 1.4 hours	-	

Abbreviations: ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NS, not significant; PCR, polymerase chain reaction; RCT, randomized controlled trial; SAE, serious adverse event; SD, standard deviation.

[a]Quasi randomized randomization process with rapid viral molecular testing on even days of the month and reference laboratory PCR testing on odd days.

[b]Analysis for antibiotic prescription performed in 522/545 patients due to missing data on antibiotic prescriptions for 13 patients in control arm and ten in intervention arm.

[c]Multivariate analysis adjusting for confounders age, location of sample collection, receipt of influenza vaccine, immunosuppressed status and pregnancy.

[d]Subgroup analysis in virus positive patients. In the study of Gelfer (2015) among these virus positive patients only the patients who received antimicrobials were included. In the study of Keske (2017) these virus positive patients included only inpatients, and for the duration of antibiotic therapy only patients with inappropriate antibiotic use were included.

[e]Subgroup analysis in influenza positive patients. In the study of Busson (2017) among these influenza positive patients only the patients who were tested with rapid molecular tests during working hours and who were still in the ED during the test result were included. In the study of Rappo (2016) among these influenza positive patients only the patients who received a chest radiograph were included in the multivariate analysis for the number of chest radiographs.

[f]Quasi randomized randomization process with rapid viral molecular testing during one-week and reference laboratory PCR testing during the following week and so on.

[g]Subgroup analysis in influenza negative patients.

[h]Adjusted for in-hospital mortality.

[i]Multivariate analysis adjusting for confounders age, immunosuppressed status, asthma and admission to ICU.

[j]Analysis for isolation facility use were only available from patients included during the second season of inclusion.

[k]In the study of Andrews (2017) patients were admitted to an Acute Medical Unit of Medical Assessment Centre before inclusion in the study. The turnaround time was calculated as the time from admission to result and therefore also covers the time from admission until the swab was actually taken (during which time the assessment of eligibility for inclusion and informed consent procedure were performed).

[l]In the study of Rogers (2014) patients were included at the Emergency Department, but also after admission, leading to a longer time to result.

might improve the impact on clinical outcomes as results are available before any initial treatment or management is established by the treating physician. To our knowledge, this is the first review to specifically assess the clinical impact of rapid molecular tests, and not rapid antigen tests, without a restriction in the detection of influenza virus and RSV [45, 46]. The included studies, even the high-quality randomized studies [1, 20, 21, 24, 25], show heterogeneous results. The location of the rapid test, which was at the point of care in only 3 studies, may affect turnaround times and thereby clinical outcomes. Apart from other differences in design, and in analysis and power, differences in the implementation strategy might partially explain these discrepancies. First, education and training of personnel and physicians on the implemented rapid test, its diagnostic accuracy, and its potential effects on clinical outcomes may contribute to its effect on clinical outcomes [33]. Second, a combination of a rapid test and a result-based guideline on subsequent clinical management options might have more impact than a stand-alone diagnostic test, even though the 2 studies describing the implementation of a diagnostic bundle did not show any significant effects of their implementation, which might be partially explained by limited adherence to these guidelines [20, 21]. A complicating factor therein is that identification of a viral pathogen from a respiratory tract sample may not necessarily attribute causation [2]. Third, a combination of a rapid test and another diagnostic as procalcitonin [21, 30] or other biomarker-based assays [47] may increase the persuasiveness of the rapid viral test on whether there is a bacterial or viral causative pathogen. However, current evidence for the effect of the combination of respiratory viral testing and procalcitonin on clinical outcomes is disappointing [21].

Strengths of our systematic review and meta-analysis of DTA studies are that we followed a standardized protocol for the inclusion of studies, quality assessment, data extraction, and statistical analysis. To be as complete as possible, we did not exclude studies with a less optimal study design (eg, case-control studies). We evaluated heterogeneity using subgroup analyses. Furthermore, we assessed the clinical impact of rapid molecular testing for respiratory viruses. Since quantitative pooling of clinical impact results was not feasible due to heterogeneity in study design and quality, we made overall conclusions for clinical endpoints that were assessed by at least 2 studies based on majority votes of studies with highest quality and power. Also, an overview of available clinical impact studies may have important implications for the design of future clinical impact studies. Our review also has some limitations. First, due to poor reporting in DTA studies, we had missing information for our subgroup analyses. Second, there was substantial residual heterogeneity between DTA studies that could not be explained by our subgroup analyses. Residual heterogeneity and thereby differences in diagnostic accuracy might have been caused by differences in sampling types [48] and duration of clinical symptoms and associated viral loads of included patients, for example, which were factors that were poorly reported. Furthermore, with an assay level comparison of diagnostic accuracy, the multiplex assays are disadvantaged. The more viruses that an assay tests for, the bigger the chance of any discrepant results with the reference test. Therefore, as mentioned before, when interpreting the results of a head-to-head comparison of the accuracy of different assays, the number of tested pathogens should also be taken into account and results should be interpreted carefully.

In conclusion, rapid molecular tests for viral pathogen detection provide accurate results. Even though results on clinical impact of rapid diagnostic tests are conflicting, there is high-quality evidence that rapid testing might decrease the length of hospital stay and might increase appropriate use of oseltamivir in influenza virus–positive patients, without leading to adverse results. We therefore suggest considering implementation of rapid molecular tests within hospital settings and recommend performance of high-quality randomized studies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. L. M. V. contributed to the design, search, screening, data extraction, data analysis, data interpretation, production of the figures, and writing of the report. A. H. L. B. contributed to the search, screening, data interpretation, and writing of the report. J. B. R., R. S., A. R.-B., and A. I. M. H. contributed to data interpretation and writing of the report. J. J. O. contributed to design, data interpretation, and writing of the report.

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