The clinical impact of rapid respiratory virus testing in emergency departments

A systematic review and meta-analysis of randomized trials

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KEY POINTS

Question: Does rapid testing for respiratory viruses impact patient management in the Emergency Department (ED)?

Findings: In this systematic review and meta-analysis of 11 randomized controlled trials, rapid viral testing did not reduce antibiotic use, ED length of stay and the rate of ED return visits or of hospitalization. However, rapid viral testing moderately increased influenza antiviral use (absolute risk difference 1%) and decreased use of chest radiographs and blood tests (absolute risk difference 3-4% each).

Meaning: The benefits of ED rapid viral testing are limited for the general population.

ABSTRACT

Background: Rapid tests for respiratory viruses, including multiplex panels, are increasingly available in Emergency Departments (ED). Their impact on patient outcomes remains unclear.

Objectives: To determine if ED rapid respiratory virus testing in patients with suspected acute respiratory infection (ARI) decreases antibiotic use, ancillary tests, ED length of stay, ED return visits and hospitalization and increases influenza antiviral treatment.

Data sources: We searched Ovid MEDLINE, Embase (Ovid), Scopus, and Web of Science from 1985 to November 14, 2022.

Study selection: We included randomized controlled trials of patients of any age with ARI in an ED. The primary intervention was rapid viral testing.

Extraction, Data and Synthesis: In this systematic review and meta-analysis, PRISMA reporting guidelines were followed. Two independent reviewers extracted data and assessed risk of bias using Cochrane's Risk of Bias 2.0. Estimates were pooled using random-effects models. Quality of evidence was assessed using the GRADE framework.

Main outcomes and measures: Antibiotic use and secondary outcomes were pooled separately as risk ratio (RR) and risk difference estimates with 95% confidence intervals [CI]s.

Results: Of 7157 studies identified, 11 (n=6068 patients) were included in pooled analyses. Routine rapid viral testing did not impact antibiotic use (RR 0.99; 95% CI 0.93-1.05; high certainty) but was associated with higher use of influenza antivirals (RR 1.33; 95% CI 1.02-1.75; moderate certainty) and lower use of chest radiography (0.88; 95% CI 0.79-0.98; moderate certainty) and blood tests (RR 0.81; 95% CI 0.69-0.97; moderate certainty). There was no association with urine testing (RR 0.95; 95% CI 0.77-1.07; low certainty), ED length of stay (0h; 95% CI -0.17h-0.16h; moderate certainty), return visits (RR 0.93; 95% CI 0.79-1.08; moderate certainty) or hospitalization (RR 1.01; 95% CI 0.95-1.08;

high certainty). Adults represented 16% of participants. There was no effect of viral testing on antibiotic use in any prespecified subgroup by age, test method, publication date, number of viral targets, risk of bias, and industry funding.

Conclusions and Relevance: Available evidence shows limited benefits of routine viral testing in EDs for patients with ARI. Further studies in adults, especially those with high-risk conditions, are warranted.

INTRODUCTION

Acute respiratory tract infections (ARI) are the most common cause of medically attended acute illness.[1] Clinically, it is difficult to distinguish bacterial etiologies or influenza – for which specific treatments are available - from ARI caused by other respiratory viruses. This diagnostic uncertainty leads to unnecessary antibiotic treatment and subsequent adverse drug events, increased health care costs, and antibiotic resistance.[2] Accordingly, some antimicrobial stewardship guidelines advocate for rapid viral (RV) testing for respiratory viruses to decrease use of antibiotics.[3]

The SARS-CoV-2 pandemic led to increased availability of RV testing, including multiplex panels, in emergency departments (ED).[4] However, the impact of these tests on patient outcomes is unclear. Previous meta-analyses which included studies until 2017 showed that RV testing in ambulatory care was associated with a reduction of antibiotic prescribing in observational studies, but not in randomised controlled trials (RCTs).[5] Substantial new RCT data investigating the impact of molecular multiplex panels warrants a new assessment.

This systematic review and meta-analysis aims to determine if the use of rapid respiratory viral diagnostic testing in patients of all ages presenting in the ED for ARI decreases ED antibiotic prescribing and impacts other clinically relevant outcomes. These include the use of influenza antivirals, ancillary testing, ED length of stay, ED return visits or hospitalization..

METHODS

The protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement and registered with the international prospective register of systematic reviews (PROSPERO; CRD42018103672). Reporting followed PRISMA guidelines (checklist, Supplementary Materials).

Information sources and Search strategy

We developed an electronic search strategy (Supplementary Materials) in collaboration with a medical librarian and searched Ovid MEDLINE, Embase (Ovid), Scopus, and Web of Science Core Collection for studies published after Jan 1st 1985. To identify additional studies, we screened the reference lists of included studies and relevant reviews. The review was initially planned to include both observational studies and RCTs. A first search was performed on Jun 1st-4th 2018. During full-text screening we identified a sufficient number of RCTs and amended the protocol to limit the analysis to RCTs. The search was updated on Nov 14th 2022.

Study design and participants

We included published original peer-reviewed full reports of RCTs that evaluated the clinical impact of the routine use of respiratory virus testing for physician decision-making in the ED. Our definition of RCT included both full RCTs (using patient level randomization), and quasi-RCTs, i.e., those using a quasi-random method of allocation (such as alternating days). Included studies assessed patients of any age presenting to an ED with ARI. ARI was defined as a new illness with respiratory symptoms suggestive of infection. Studies restricted to populations with specific chronic health conditions were excluded.

The primary intervention was availability of rapid respiratory virus testing (defined as the provision of test results during the patient's ED stay) or the awareness of the treating physician of the rapid test results. Secondary intervention was RV test positivity versus negativity. The primary outcome was the impact on antibiotic prescription during the ED visit. Secondary outcomes were influenza antiviral use, ancillary testing (including chest radiography, blood culture, urinalysis or urine culture, and any blood test), ED length of stay, ED return visits, or hospitalization. When parts of composite outcomes (i.e., urinalysis or urine culture; blood culture or other blood test) were reported individually, the variable with the higher number of events was chosen. Additionally, we determined which social determinants of health were captured using the PROGRESS Plus framework.[6,7]

Study selection

Articles were screened by one reviewer at title and abstract level. Full-text screening, data extraction and quality assessment using Cochrane's Risk-of-Bias tool RoB-2[8] were done independently by 2 reviewers. Discussion or a third reviewer resolved conflicts. Screening and data extraction were performed using DistillerSR (DistillerSR Inc., Ottawa, Canada). Corresponding authors were contacted for missing information.

Statistical analysis

Outcomes for each of the two interventions were analyzed and presented separately. Associations of the intervention with dichotomous outcomes were expressed as risk ratios (RRs) and risk differences (RD) with 95% confidence intervals (CIs), and continuous outcomes were expressed as standardized mean differences with 95% CIs. If ≥2 studies were available, we performed meta-analyses using a random-effects model with the restricted maximum likelihood method. Statistical heterogeneity was

assessed using the I^2 statistic. We conducted meta-analyses within the following prespecified strata: children and adolescents versus adults, antigen detection (enzyme immunoassay [EIA] or immunofluorescence) versus molecular tests, monoplex (influenza) versus multiplex tests, low versus high risk of bias, and industry funding versus no industry funding. Differences in pooled RRs between subgroups were assessed via fixed-effects meta-regression models wherein the subgroup of interest was included as a covariate. All tests were two-sided with a significance level of 0.05. Analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), the metafor package version 4.0-0 and Excel 2016 (Microsoft, Redmond WA, USA). Narrative summaries were presented for results that could not be meta-analyzed.

Certainty of Evidence

Certainty of evidence was assessed by two reviewers for all outcomes of the primary exposure using GRADE.[9,10] We rated certainty of evidence as 'very low', 'low', 'moderate', or 'high' based on risk of bias,[8] imprecision, inconsistency, indirectness, and publication bias. Outcomes where the majority of studies were judged as low risk of bias were considered to be overall of low risk of bias.[9] We chose a minimally-contextualized approach to rate imprecision following the guidance of the GRADE Working Group.[11,12] Minimal important differences (MID) were set at 10% for all outcomes based on previous studies on outpatient antibiotic use and clinical judgement.[13] When the magnitude of pooled estimates were less than ±10%, we rated certainty as little or no effect; otherwise we rated certainty in showing an effect with the MID as a threshold. We rated down for imprecision by two levels when the 95% CI crossed more than one threshold of importance. Publication bias was assessed for meta-analyses by Egger's test and funnel plots for groups with ≥10 studies.[14]

RESULTS

Of 7157 publications identified, 7092 were excluded based on title and abstract screening and the remaining 65 underwent full-text review. After exclusion of 53 studies (details in Supplementary Materials) 12 were included (Figure 1).

Study characteristics

Of the 12 included studies (Table 1), 5 were quasi-RCTs,[15-19] and 7 were full RCTs.[20-26] In the intervention arm, 4 studies tested for influenza only,[17,18,20,23] the other 8 tested for multiple respiratory viruses. Four studies (all published prior to 2010) used EIAs,[17,18,20,23] 1 immunofluorescence[22] and 7 studies (all published since 2017) used molecular testing.[15,16,19,21,24-26] Multiplex tests included influenza and RSV,[15] influenza/RSV/adenovirus/parainfluenza 1-3[22] or a panel of ≥15 respiratory viruses.[16,19,21,24-26] No study evaluated testing for SARS-CoV-2.

Comparators varied: the control groups in the influenza-only trials did not test for any viruses,[17,18,23] or the treating physician was unaware of the result.[20] In the rapid multiplex testing studies, the comparator was either multiplex testing in a central laboratory with a longer turnaround time,[15,16] immunofluorescence[19] or routine care which included laboratory-based viral testing at the treating physician's discretion.[21,22,24-26]

The age of participants varied, but pediatric populations were dominant. Eight studies were limited to children and adolescents[17-20,22-24,26] including 4 studies in children ≤6 years old.[17-19,22] Two studies included adults and children.[15,25]

Quality of included studies

All quasi-RCTs were judged at high risk of bias and 7 of the 8 RCTs judged at low risk of bias (Supplementary Figure 1). The RCT by Echavarria et al[19] was at high risk of bias due to deviation from the intended intervention as less than half of patients were randomized as planned. None of the studies were able to blind participants and personnel to testing or test results. No study blinded outcome assessors to test status.

Antibiotic use

Antibiotic prescription during the ED visit was reported in all included studies. The study by Echavarria et al[19] could not be included in meta-analyses as it only reported changes in proportional management without providing absolute numbers. Accordingly, 11 studies were meta-analyzed which showed with high certainty of evidence little or no difference in antibiotic use between RV testing and control (RR 0.99 95% CI, 0.93 to 1.05; I^2 = 0.03%; Table 2; Figure 2A). Funnel plot and Egger's test did not suggest publication bias (Supplementary Figure 2). Overall prevalence of antibiotic use differed substantially between studies ranging from 8.5% to 61.9% (mean 26.3%) in children and 18.9% to 76.7% (mean 46.5%) in adults. There was no effect of viral testing on antibiotic use in any prespecified subgroup analyses: children and adolescents, adults, antigen-based tests (EIA or immunofluorescence), molecular tests (which also correspond to the more recently published studies), monoplex tests, multiplex tests, low risk of bias, high risk of bias, industry funding, no industry funding (Table 3).

Seven studies also evaluated antibiotic use according to the test result (positive versus negative).[15,17,20-23] Overall, patients with a positive viral test in the RV testing group were less likely to receive antibiotics (RR 0.53, 95% 0.37-0.77; I^2= 65.7%, Figure 3B) than those with a negative result. Antibiotic use in the virus-negative RV testing group was correspondingly higher compared to the virus-positive group, and also compared to the corresponding control group without RV testing (52.8% versus 38.5%; p=0.03).

Subgroup analyses demonstrated lower rates of antibiotic use among virus-positive cases for traditional tests, monoplex tests, low risk of bias and high risk of bias, but not for molecular and multiplex tests (Supplementary Table 1).

Antibiotic duration depending on test availability was reported by 2 papers to be comparable in the groups with and without RV testing with a median of 7 versus 7 days[23] and 6.8 versus 6.5 days, respectively.[21] Two studies reported whether patients received antibiotics at follow-up within 7 days, after discharge from the ED. There was no difference in the study by Matilla et al (34.1 versus 34.5%). In contrast, Doan et al reported less antibiotic use at follow-up (5.6 versus 15.5%, RR = 0.36; 95% CI=0.14, 0.95).[22]

Antiviral use

Influenza antiviral use was reported in 7 studies.[15,16,18,20,21,25,26] Meta-analysis showed an increase in antiviral prescribing with RV testing with moderate certainty of evidence (RR 1.33, 95% CI 1.02-1.75; I2 = 0%; absolute RD 1.4%; Table 2, Supplementary Figure 3). This effect was significant in the 2 monoplex studies, which did not offer influenza testing in the control arm (RR 2.12, 95% 1.0-4.51, I^2=0%),[18,20] but not with multiplex testing (RR 1.24, 95% CI 0.93 – 1.66, I^2=0%).[15,16,21,25,26] The impact on antiviral use did not differ significantly (p=0.85) between children (RR 1.25 95% CI 0.70- 2.03) and adults (RR 1.18, 95% CI 0.81-1.72). Six studies reported influenza antiviral use depending on the rapid influenza test result.[15,18,20,21,25,26] Mean influenza antiviral use per study was 28.3% for influenza positive patients and 3.0% for influenza-negative patients (RR 9.8, 95% CI 3.27-30.4, I^2=75.5%).

Ancillary tests

Eight studies reported on chest radiography.[15,17,18,20,22-25] Meta-analysis showed lower chest radiography use among patients with RV testing with moderate certainty (RR 0.88, 95% CI 0.79-0.98, I^2=0%, Supplementary Figure 4), corresponding to an absolute RD of 2.6%. RV testing was associated with decreased blood testing with moderate certainty (RR 0.81, 95% CI 0.69-0.97, I^2=0; absolute RD 3.7%) (Supplementary Figure 5).[15,17,18,22-25] Differentiation of blood testing into blood culture (RR 0.85, 95% CI 0.67-1.07, I^2=0) and other blood tests (RR 0.84, 95% CI 0.70-1.01, I^2=0%) demonstrated possible reductions in testing (very low and low certainty, respectively). In contrast, RV testing appeared to have little or no impact on urine testing (RR 0.95, 95% CI 0.77-1.07, I^2=0%; low certainty; Supplementary Figure 6). Among studies also reporting on the use of ancillary tests depending on RV test results, all examined ancillary tests were performed less frequently among patients with a positive viral test result with RRs between 0.2-0.47 (Supplementary table 2).

Additional outcomes

The impact of RV testing on ED length of stay was available in 6 studies. We could perform a meta-analysis of 4 studies[17,22,24,25] which reported both mean and standard deviation. There was little or no difference between RV testing and control in ED length of stay with moderate certainty (standardized mean difference 0h, 95% CI -0.17h - 0.16h, I^2=67.4%, table 2; Supplementary Figure 7). The follow-up interval for return ED visits varied between 7 and 30 days. Meta-analysis of 6 studies showed no difference in the number of return visits with moderate certainty (RR 0.93, 95% CI 0.79-1.08, I^2=0%, Table 2, Supplementary Figure 8). Nine studies investigated hospitalizations; meta-analysis demonstrated no impact of RV testing with high certainty (RR 1.01; 95% CI 0.95-1.08; I^2=0%; Table 2; Supplementary Figure 9).[16-19,21,23-26]

Two studies assessed total costs of the ED stay which were US$33[17] and US$173[24] higher per patient in the RV test arm. Rao et al was the only study which surveyed the patient perspective:[26] 7% (21/314)

of families stated that the result of ED rapid multiplex testing influenced how they subsequently sought medical care for their child's illness.

Social determinants of health

All studies were from high-income countries. Overall data on social determinants of health were limited. All studies analyzed sex as a variable. Ethnicity was reported in 6 studies,[17,18,20,21,25,26] although 2 of these studies categorized the patients only as Caucasian or 'other'.[17,21] Rao et al[26] was the only study to report data on additional social determinants of health: socioeconomic status, social capital and insurance. Other domains according to the PROGRESS Plus framework,[7] namely place of residence, occupation and religion, were not analyzed in any of the 12 studies.

DISCUSSION

In this meta-analysis of RCTs, availability of RV testing for respiratory viruses in EDs did not impact overall antibiotic use. Fewer patients with a positive RV test were prescribed antibiotics, counterbalanced by more prescribing for patients with a negative result. However, this was only observed in studies using monoplex antigen detection tests for influenza and not molecular or multiplex testing, suggesting that a rapid positive result for influenza is more likely to influence antibiotic prescribing than positive results for other respiratory viruses. RV testing was associated with higher antiviral use and a modest reduction in blood tests and chest radiographs. There was no effect on other outcomes evaluated including overall costs. While study characteristics were heterogeneous, including pediatric and adult populations as well as monoplex and multiplex testing, results were mainly congruent.

Our results align with those from previous systematic reviews. Lee et al. examined the impact of RV testing in ambulatory care among studies published to 2017 and also noted no impact on antibiotic treatment among RCTs, but more antiviral use and fewer chest radiographs and blood tests.[5] This meta-analysis included only traditional antigen detection based rapid tests with limited sensitivity[27,28] and, in most cases, only one viral target. Our analysis included six additional RCTs that used highly sensitive multiplex molecular assays[27,28] and despite recent advances in rapid test technology had similar findings to Lee et al.[5] A 2023 systematic review and meta-analysis by Clark et al focused on the impact of multiplex panels in adults, mainly among hospitalized patients.[29] Among RCTs in inpatients, there was no change in antibiotic prescriptions and a non-significant trend to shorter antibiotic duration. They found improved appropriateness of antiviral treatment and improved infection control practices, but no change in hospital length of stay. Importantly, both systematic reviews included RCTs as well as

observational studies but only found significant reductions in antibiotic use in the latter. Several guidelines on viral testing and antibiotic stewardship refer to these observational studies which are more susceptible to bias than RCTs due to selection and publication biases, confounding by indication, secular trends and other sources of bias. [3,30,31] Accordingly, we believe that future recommendations should focus on the substantial evidence from the expanding number of RCTs.

It is noteworthy that influenza antivirals were only given to 28.3% of influenza positive patients in the RV testing arms and that rapid testing was associated with a pooled absolute RD of 1.4% in antiviral prescribing. Accordingly, the number-needed-to-test for one additional antiviral prescription in these studies was approximately 70 (~50 in adult studies and ~100 in pediatric studies). Perhaps not surprisingly, given that most guidelines, including those of the Infectious Diseases Society of America,[32,33] recommend antiviral treatment only for patients early in the course of infection and for high-risk patients and/or severe or complicated disease, and that the benefits of outpatient antiviral therapy are limited,[34] providers in the included studies only prescribed antivirals to a minority of patients with influenza. Given the absence of benefit of RV testing on overall antibiotic use, these findings suggest that RV testing should not be routine, but rather should be reserved for patients for whom the testing will change management.[33] Current treatment guidelines for COVID-19 also only recommend antiviral treatment for high-risk patients and/or severe or complicated disease.[35] Considering that symptoms of influenza, COVID-19 and other respiratory infections can overlap, targeted multiplex viral testing in these patient populations should have greater clinical impact.

Our analysis of social determinants of health showed that these were generally not sufficiently evaluated and/or underreported. Importantly, all studies were from high-income countries. As antibiotic use is higher among marginalized communities within high-income countries and highest in middle

income countries,[36,37] the impact of viral testing might have been different in other patient populations limiting the generalizability.

Our review has limitations. First, allocation concealment was not possible in any of the studies as effects work through awareness of the test result. Despite this, our main findings are consistent, including among the 7 studies considered to be low risk of bias. Second, information on antibiotic duration is limited. However, the two studies which evaluated antibiotic duration did not show a difference between groups. Third, only 16% of all patients were adults. Additional RCTs in adults, especially those with high-risk conditions, would strengthen the evidence base. Nonetheless, subgroup analysis of adults and children did not differ for our primary outcome. Fourth, there is uncertainty among some of the included studies as to whether the RV result was communicated before prescribing medications or ordering ancillary tests. This could bias results towards the null and underestimate the effect of viral testing. However, this is a clinical reality in the ED where diagnostic testing and treatment decisions are made in parallel rather than sequentially. Finally, none of the studies was conducted since the start of the COVID-19 pandemic and therefore none evaluated testing for SARS-CoV-2. However, as for influenza, testing for SARS-CoV-2 in EDs is increasingly restricted to severe illness or high-risk patients where results would change management.[35]

A strength of our study is the focus on RCTs. We also used GRADE to systematically assess the certainty of evidence. Moreover, while individual studies had insufficient power to show some effects, pooling results from several studies allowed us to reveal these associations. Finally, we included data specific to ED from two studies that had not previously reported their ED data separately.[15,21]

Conclusion

Overall, the benefits of routine RV testing in the ED are limited. Such testing in EDs has no effect on overall antibiotic use, length of ED stay, ED return visits, or hospitalization rates. Testing results in a minority of patients with influenza being prescribed antivirals and in decreases in ordering of some ancillary tests. Patients with positive viral tests received less antibiotics compared to patients with negative tests, possibly improving appropriateness of antibiotic treatment in this subgroup. Evidence suggests that RV testing in the ED should be reserved for patients for whom results will change management. Further RCTs in adults and high-risk populations are warranted.

AUTHOR CONTRIBUTIONS

Drs Schober and Papenburg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Schober, DeLisle, Dendukuri, Doan, Fontela, Gore, Li, McGeer, Robinson, Suarthana, Papenburg

Acquisition, analysis, or interpretation of data: all authors

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DATA SHARING POLICY

Template data collection forms, data extracted from individual studies and analytical code are available upon reasonable request.

CONFLICTS OF INTEREST:

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Table 1. Characteristics of included studies

Study	Study design	Number of patients	Age range	Setting / Country	Target & type of rapid test	Rapid test	Comparator
Bonner, 2003	RCT	391	2 months – 21 years	ED; USA	Influenza; Antigen	FluOIA Biostar	Same test - result unknown
Esposito, 2003	RCT	957	0 – 15 years	ED; Italy	Influenza; Antigen	Sofia Quickvue	No test
Iyer, 2006	Quasi RCT (alternating days)	700	2 – 24 months	ED; USA	Influenza; Antigen	Sofia Quickvue	No test
Poehling, 2006	Quasi RCT (randomized days)	305	<5 years	ED; USA	Influenza; Antigen	Sofia Quickvue	No test
Doan, 2009	RCT	199	3 – 36 months	ED; Canada	Multiple; Immuno-fluorescence[4]	SimulFluor	Routine care
Brendish, 2017	RCT	279	≥18 years	ED & Acute Medical Unit[3]; UK	Multiple; Molecular[5]	BioFire FilmArray	Routine care
Echavarría, 2018[1]	RCT	442	2 months - 6 years	ED; Argentina	Multiple; Molecular[5]	BioFire FilmArray	Immunofluorescence
May, 2019	RCT	191	≥12 months[2]	ED; USA	Multiple; Molecular[5]	BioFire FilmArray	Routine care
Bouzid, 2021	Quasi RCT (alternating weeks)	474	≥18 years	ED; France	Multiple; Molecular[6]	*QIAstat-Dx*	Respiratory panel in centralized laboratory
Rao, 2021	RCT	908	1 month – 18 years	ED; USA	Multiple; Molecular[5]	BioFire FilmArray	Routine care
Bibby, 2022	Quasi RCT (alternating days)	421	All age groups[2]	ED & Inpatients,[3] Canada	Influenza & RSV; Molecular	Xpert Xpress	Respiratory panel in centralized laboratory
Matilla, 2022	RCT	1243	0 – 17 years	ED; Finland	Multiple; Molecular[6]	*QIAstat-Dx*	Routine care

[1] Not included in any meta-analysis except for the hospitalization outcome
[2] Separate data for children & adults available
[3] Only ED data analyzed for the current systematic review
[4] Includes Adenovirus, Influenza, Parainfluenza 1-3, RSV
[5] Includes Adenovirus, Coronaviruses HKU1, NL63, 229E and OC43, human Metapneumovirus, Influenza, Rhinovirus/Enterovirus, RSV, Parainfluenza 1-4.
[6] Includes Adenovirus, Bocavirus, Coronaviruses HKU1, NL63, 229E and OC43, human Metapneumovirus, Influenza, Rhinovirus/Enterovirus, RSV, Parainfluenza 1-4.

Table 2. Summary of results for rapid viral test availability

Outcome	Studies / References	Number of patients	Relative Effect Estimate	Absolute Effect Estimate		Certainty of Evidence (GRADE)	Plain language summary
				Rapid viral testing	Control		
Antibiotic use	11[15-18,20-26]	6068	0.99; 95% CI 0.93 - 1.05; I^2=0.03%	1111 per 3206; 34.7%	1007 per 2862; 35.2%	High	There is little or no difference between rapid viral test and control in antibiotic use
				Risk difference: -0.01; 95% CI -0.04–0.02; I^2=43.4%			
Influenza antiviral use	7[15,16,18,20,21,25,26]	2969	1.33; 95% CI 1.02 - 1.75; I^2=0%	116 per 1465; 7.9%	85 per 1504; 5.7%	Moderate[b]	Rapid viral testing probably increases influenza antiviral use
				Risk difference: 0.01; 95% CI 0.00–0.03; I^2=0%			
Chest radiography	8[15,17,18,20,22-25]	4408	0.88; 95% CI 0.79 - 0.98; I^2=0%	417 per 2346; 17.8%	444 per 2062; 21.5%	Moderate[b]	Rapid viral testing probably decreases chest radiography use
				Risk difference: -0.03; 95% CI -0.05–0.00; I^2=31.1%			
Blood test (any)	5[17,18,20,22,23]	2552	0.81; 95% CI 0.69 - 0.97; I^2=0%	188 per 1240; 15.2%	246 per 1312; 18.8%	Moderate[b]	Rapid viral testing may decrease blood testing
				Risk difference: -0.04; 95% CI -0.06– -0.01; I^2=0%			
Blood culture	2[17,20]	1091	0.85; 95% CI 0.67- 1.07; I^2=0%	95 per 538; 17.7%	116 per 553; 21.0%	Very low[b,c,d]	It is uncertain whether rapid viral testing decreases blood culture testing
				Risk difference: -0.03; 95% CI -0.07–0.01; I^2=0%			
Blood test (other)	4[17,20,22,23]	2247	0.84; 95% CI 0.70- 1.01; I^2=0%	174 per 1105; 15.7%	215 per 1142; 18.8%	Low[b,c]	Rapid viral testing may decrease other blood testing
				Risk difference: -0.03; 95% CI -0.06–0.00; I^2=0%			
Urine analysis / culture	4[17,18,20,22]	1595	0.95; 95% CI 0.77- 1.07; I^2=0%	130 per 762; 17.1%	153 per 833; 18.4%	Low[b,d]	Rapid viral testing may have little or no impact on urine testing
				Risk difference: -0.02; 95% CI -0.05–0.02; I^2=0%			
ED length of stay	4[17,22,24,25]	2333	1.02; 95% CI 0.96- 1.08; I^2=63.4%[a]	Mean: 3.40; SD: 1.78	Mean: 3.53; SD: 1.96	Moderate[e]	There is probably little or no difference between rapid viral test and control in ED length of stay
				Standardized mean diff: 0.00; 95% CI -0.17-0.16; I^2=67.4%			
ED return visit	7[17,21,22,24-26]	3086	0.93; 95% CI 0.79 - 1.08; ; I^2=0%	282 per 1941; 14.5%	249 per 1579; 15.8%	Moderate[b]	There is probably little or no difference between rapid viral test and control in ED return visit
				Risk difference: -0.01; 95% CI -0.03–0.02; I^2=0%			
Hospitalization	9[16-19,21,23-26]	5489	1.01; 95% CI 0.95 - 1.08; ; I^2=0%	882 per 3029; 29.1%	642 per 2460; 26.1%	High	There is little or no difference between rapid viral test and control in hospitalization rate
				Risk difference: 0.00; 95% CI -0.02–0.02; I^2=0%			

[a] Corresponding relative effect estimate log-transformed ratio of means: 1.02; 95% CI 0.96-1.08; I^2=63.4%
[b] Rated down 1 level for imprecision because of the 95% CI crossing the MID decision threshold.
[c] Rated down 1 level for imprecision because of the 95% CI crossing the null effect threshold
[d] Rated down 1 level for bias as ≥half of included studies high risk of bias during randomization process (i.e.quasi RCTs)
[e] Rated down 1 level due to heterogeneity / inconsistency

Table 3. Antibiotic prescribing according to rapid viral test availability in predefined subgroups

Category	Subgroup	Studies / Reference	N of patients	Relative Effect Estimate (Risk Ratio)	Absolute Effect Estimate (Risk Difference)	Subgroup comparison
Age	Children & adolescents[a]	9[15,17,18,20,22-26]	5105	0.97 (95% CI 0.83 - 1.12); I^2=54.5%	-0.01 (95% CI -0.05 - 0.02); I^2=53.3%	p=0.82
	Adults	4[15,16,21,25]	963	0.98 (95% CI 0.89 - 1.09); I^2=0%	-0.01 (95% CI -0.07 - 0.05); I^2=0%	
Test type	Traditional (Antigen & Immuno-fluorescence)[b]	5[17,18,20,22,23]	2552	0.91 (95% CI 0.77 - 1.07); I^2=42.3%	-0.03 (95% CI -0.07 - 0.01); I^2=18.4%	p=0.26
	Molecular[c]	6[15,16,21,24-26]	3516	1.01 (95% CI 0.92 - 1.12); I^2=20.6%	0.01 (95% CI -0.03 - 0.05); I^2=40.7%	
Number of targets	Monoplex (Influenza)	4[17,18,20,23]	2353	0.91 (95% CI 0.76 - 1.09); I^2=53.7%	-0.03 (95% CI -0.08 - 0.02); I^2=35.0%	p=0.32
	Multiplex (≥2)	7[15,16,21,22,24-26]	3715	1.01 (95% CI 0.93 - 1.09); I^2=0.01%	0.005 (95% CI -0.03 - 0.04); I^2=35.5%	
Risk of bias	Low risk of bias	7[20-26]	4168	0.95 (95% CI 0.82 - 1.10); I^2=67.1%	-0.02 (95% CI -0.06 - 0.03); I^2=57.0%	p=0.73
	High risk of bias	4[15-18]	1900	0.99 (95% CI 0.87 - 1.12); I^2=5.5%	0.0005 (95% CI -0.04 - 0.05); I^2=29.8%	
Industry funding	None	7[17,18,20-24]	4074	0.97 (95% CI 0.90 - 1.03); I^2=0%	-0.02 (95% CI -0.05 - 0.00); I^2=0%	p=0.57
	Industry funding	4[15,16,25,26]	1994	1.05 (95% CI 0.79 - 1.39); I^2=70.2%	0.01 (95% CI -0.05 - 0.07); I^2=61.2%	

[a] cut-off differed between 15-21 years, according to the individual study

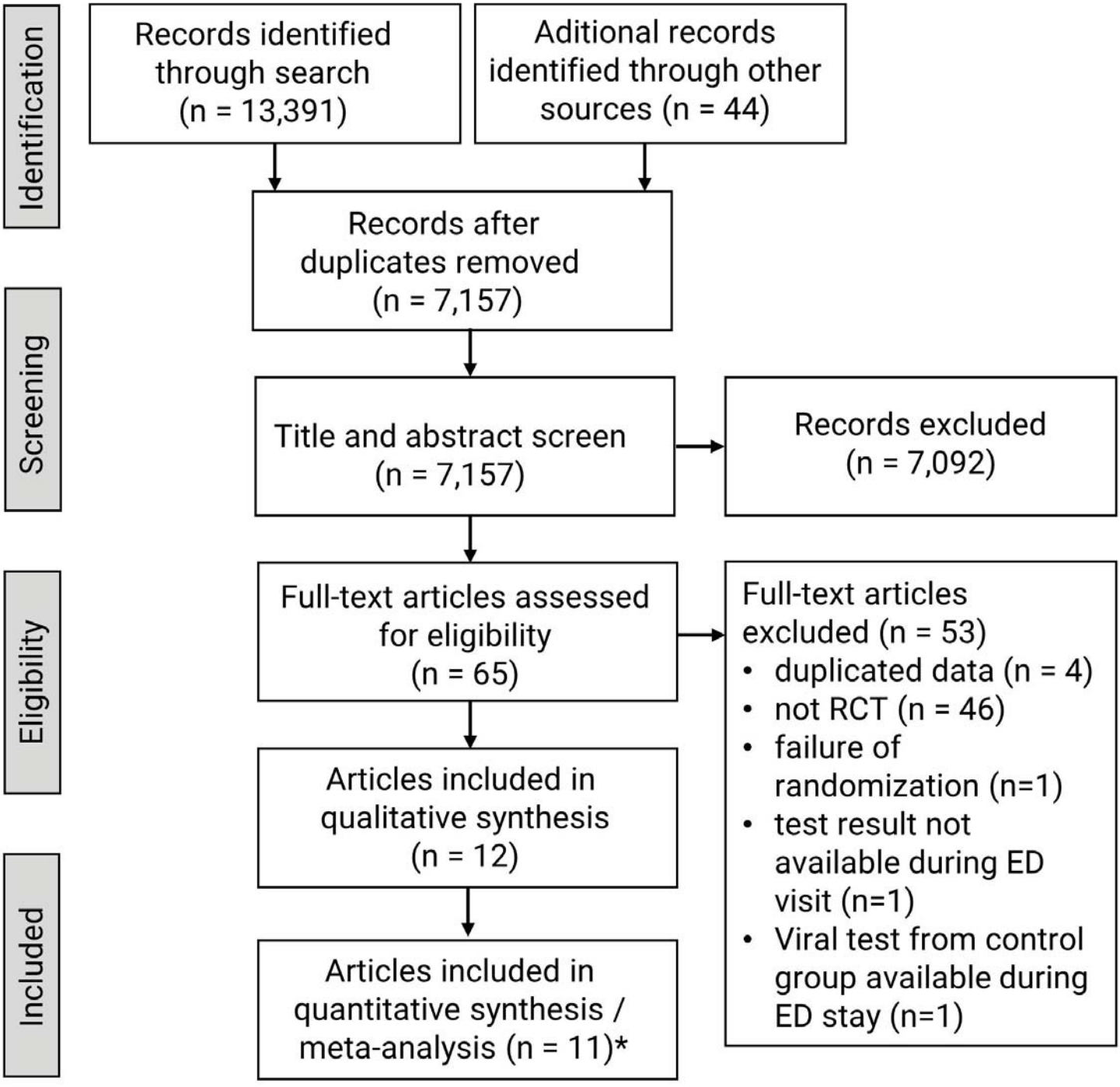
[b] these studies were all published prior to 2010

[c] these studies were all published since 2017

List of captions

Figure 1. PRISMA flow diagram of included and excluded articles

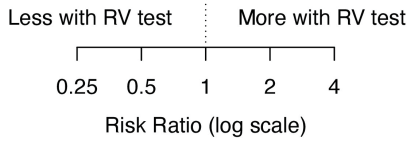
Figure 2. A, Effect of rapid viral testing on antibiotic use **B**, Effect of rapid viral test positive vs negative on antibiotic use



*1 study not included as it only reported changes in proportional management without providing absolute numbers

A

Author and Year	RV Test		Control		Weight, %	Risk Ratio [95% CI]
	Antibiotic	Total	Antibiotic	Total		
Bonner, 2003	34	193	53	198	2.38	0.66 [0.45, 0.96]
Esposito, 2003	296	478	296	479	35.12	1.00 [0.91, 1.11]
Iyer, 2006	77	345	97	355	5.15	0.82 [0.63, 1.06]
Poehling, 2006	43	135	49	170	2.98	1.11 [0.79, 1.56]
Doan, 2009	16	89	23	110	1.06	0.86 [0.48, 1.53]
Brendish, 2017	101	133	113	146	20.66	0.98 [0.86, 1.12]
May, 2019	20	93	33	98	1.53	0.64 [0.40, 1.03]
Bouzid, 2021	160	275	115	199	14.41	1.01 [0.86, 1.18]
Rao, 2021	115	452	88	456	5.79	1.32 [1.03, 1.68]
Bibby, 2022	23	184	22	237	1.14	1.35 [0.78, 2.34]
Mattila, 2022	226	829	118	414	9.76	0.96 [0.79, 1.16]
Random effects model (I^2 = 0.03%, τ^2 = 0.00)						0.99 [0.93, 1.05]



B

Author and Year	Positive RV Test		Negative RV test		Weight, %	Risk Ratio [95% CI]
	Antibiotic	Total	Antibiotic	Total		
Bonner, 2003	7	96	27	97	11.66	0.26 [0.12, 0.57]
Esposito, 2003	14	43	282	435	18.65	0.50 [0.32, 0.78]
Iyer, 2006	15	105	73	240	17.04	0.47 [0.28, 0.78]
Poehling, 2006	4	28	39	107	9.38	0.39 [0.15, 1.00]
Doan, 2009	8	56	8	33	10.18	0.59 [0.24, 1.42]
Brendish, 2017	41	55	60	78	23.75	0.97 [0.80, 1.18]
Bibby, 2022	5	67	18	117	9.34	0.49 [0.19, 1.25]
Random effects model (I^2 = 65.69%, τ^2 = 0.13)						0.53 [0.37, 0.77]