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Systematic review

Diagnostic accuracy of point-of-care tests in acute community-acquired lower respiratory tract infections. A systematic review and meta-analysis

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ABSTRACT

Background: Point-of-care tests could be essential in differentiating bacterial and viral acute community-acquired lower respiratory tract infections and driving antibiotic stewardship in the community.
Objectives: To assess diagnostic test accuracy of point-of-care tests in community settings for acute community-acquired lower respiratory tract infections.
Data sources: Multiple databases (MEDLINE, EMBASE, Web of Science, Cochrane Library, Open Gray) from inception to 31 May 2021, without language restrictions.
Study eligibility criteria: Diagnostic test accuracy studies involving patients at primary care, outpatient clinic, emergency department and long-term care facilities with a clinical suspicion of acute community-acquired lower respiratory tract infections. The comparator was any test used as a comparison to the index test. In order not to limit the study inclusion, the comparator was not defined a priori.
Assessment of risk of bias: Four investigators independently extracted data, rated risk of bias, and assessed the quality using QUADAS-2.
Methods of data synthesis: The measures of diagnostic test accuracy were calculated with 95% CI.
Results: A total of 421 studies addressed at least one point-of-care test. The diagnostic performance of molecular tests was higher compared with that of rapid diagnostic tests for all the pathogens studied. The accuracy of stand-alone signs and symptoms or biomarkers was poor. Lung ultrasound showed high sensitivity and specificity (90% for both) for the diagnosis of bacterial pneumonia. Rapid antigen-based diagnostic tests for influenza, respiratory syncytial virus, human metapneumovirus, and *Streptococcus pneumoniae* had sub-optimal sensitivity (range 49%–84%) but high specificity (>80%).
Discussion: Physical examination and host biomarkers are not sufficiently reliable as stand-alone tests to differentiate between bacterial and viral pneumonia. Lung ultrasound shows higher accuracy than chest X-ray for bacterial pneumonia at emergency department. Rapid antigen-based diagnostic tests cannot be

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considered fully reliable because of high false-negative rates. Overall, molecular tests for all the pathogens considered were found to be the most accurate. **Elisa Gentilotti, Clin Microbiol Infect 2022;28:13**

Introduction

Acute respiratory tract infections in community-care settings (including primary care, outpatient clinic, emergency department and long-term care facilities) are the most frequent reasons for medical consultation and for antibiotic prescription [1]. Frequently, the decision to prescribe antibiotics is taken at the point-of-care (POC) without availability of diagnostic tests, so increasing the risk of inappropriate antibiotic treatments and avoidable adverse effects [2]. Most of the time, the clinical presentation of acute community-acquired lower respiratory tract infections (CA-LRTI) is highly non-specific and a reference standard for the diagnostic process has not been clearly defined [3]. The GRACE score proposed a combination of clinical prediction items reaching a receiver operating characteristic curve (ROC) area of 70%, slightly improved by the addition of C-reactive protein (CRP) serum concentration at the optimal cut-off of >30 mg/L [4]. Antigen-based rapid diagnostics tests (RDT-Ag) for CA-LRTIs have shown good to high specificity but modest sensitivity [5–9], whereas rapid nucleic-acid amplification tests (NAAT) demonstrated a similar diagnostic performance with a shorter turn-around time compared with laboratory-based PCR [10,11]. In this already complex scenario, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has added further complexity to the diagnostic process with patients presenting with non-specific respiratory symptoms.

The goal of this systematic review and meta-analysis is therefore to assess the accuracy of point-of-care tests (POCTs) for acute CA-LRTI, to inform clinicians on the appropriate interpretation of POCT results.

Materials and methods

In this systematic review all the diagnostic test accuracy (DTA) studies assessing pathogens that are commonly implicated in acute CA-LRTI pathogenesis have been included, based on a syndromic approach. For DTA assessing RDT-Ag, antibody-based RDT (RDT-Ab) and NAAT, the findings are given, stratified by pathogen. Complete details of the study methods are provided in the online data supplement (Appendix S1, Methods).

Data sources and searches

A combination of Medical Subject Headings (MeSH) and equivalent terms was used in the search strategy. DTA studies were retrieved from PubMed, Web of Science, the Cochrane Library, Embase and Open Gray databases. Systematic reviews and meta-analyses were checked as a source of further studies.

Study selection

All the DTA studies published until 31 May 2021 with no language restrictions and conducted on patients of any age were eligible for inclusion. SARS-CoV-2 studies, which included preprint articles, were assessed in a previous review [12], so were not included in the present systematic review.

Data extraction and quality assessment

Study data extraction for each specific DTA systematic review was performed independently by four reviewers. Each study population was included once, for one test, sample type, or comparator. The methodological quality of the eligible studies was independently assessed by two reviewers using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [13].

Data synthesis and analysis

From the raw data extracted (true positive, true negative, false positive and false negative) the relevant measures of diagnostic accuracy were calculated with 95% CI for each individual index test. We applied the methods recommended for the diagnostic test accuracy meta-analysis by the Cochrane Methods Group [14]: the bivariate random effects model [15,16] for estimating the summary points and the hierarchical summary receiver operating characteristics (HSROC) implemented in the mada [17] R v.351 (R Core Team, 2018) package. The other specialized package meta [18] was used for generating forest plots. To control and limit the heterogeneity and publication bias [19] we carried out an extensive literature search that included grey literature, and thoroughly investigated all possible subgroups: setting, population, index test/comparator, manufacturer, WHO region [20] according to the availability of the information and provided that enough studies for each category were available to run the analysis. In the Supplementary material (Appendix S2–S6) we provide SROC plots outlining sensitivity, specificity, population size, subgroups, in relation to summary points and HSROC curves. For the diagnostic utility of clinical signs, study populations were stratified by age group into adult (>14 years of age), children (0–14 years of age), and paediatric (<5 years of age). Ages were pooled for the diagnostic accuracy of RDTs, NAATs and POCTs. The study protocol was registered on PROSPERO [21].

Results

Characteristics of review studies

Of 13 895 screened citations, 421 unique articles addressing at least one of the POCTs or clinical features were included (see Supplementary materials, Appendix S2–S6, tables S1, S5, S6, S7, S8 for list of references included in the meta-analysis). Details of the number of articles screened, assessed for eligibility, extracted and included in the meta-analyses are reported in the PRISMA flow-diagram (Fig. 1; see Supplementary material, Appendix S2–S6, Figs S1, S3, S7, S11, S20). Study characteristics as well as number of studies and individuals overall, stratified by age group, setting and WHO region are reported in the Supplementary material (Appendix S2–S6, Tables S1, S5, S6, S7, S8). The results are summarized in five sections: physical examination (signs and symptoms), host biomarkers (CRP and procalcitonin (PCT)), imaging (chest X-ray, lung ultrasound), pathogen-based tests (RDT-Ab, RDT-Ag) and molecular tests (NAAT, PCR, loop-mediated isothermal amplification (LAMP)). SROC plots are shown in the Supplementary material (Appendix S2–S6, Figs S5, S6, S9, S10, S13–S19, S22–S36),

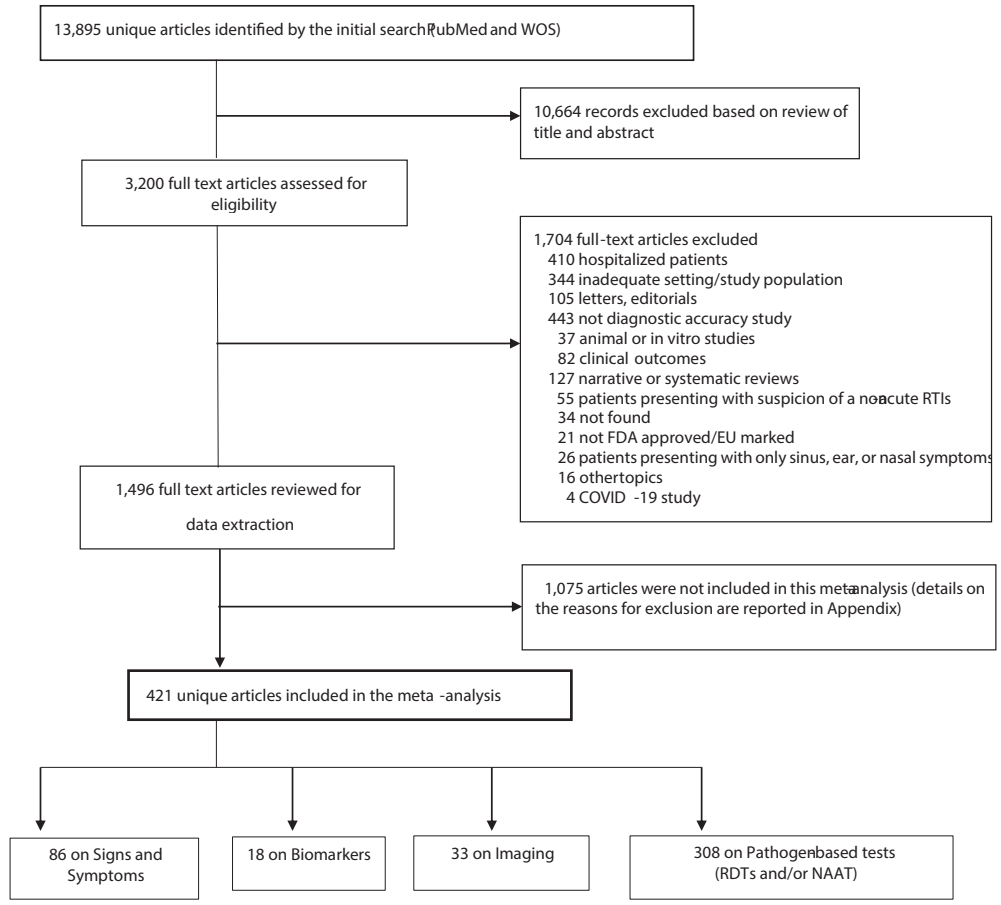


Fig. 1. PRISMA flow-diagram reporting the number of articles screened, assessed for eligibility, extracted and included in the meta-analyses. Only one reason is provided for each excluded study, although many were excluded for multiple reasons.

unless otherwise stated. Quality assessment (QUADAS-2) is reported in the Supplementary material (Appendix S2–S6, Figs S2, S4, S8, S12, S21).

Diagnostic value of signs and symptoms: 86 studies including 88 423 individuals

Seventy-five studies analysed the diagnostic accuracy of 20 different signs and symptoms in adults, 14 in children up to 14 years, and nine in children below 5 years. Overall, the diagnostic accuracy of stand-alone signs and symptoms was poor to distinguish bacterial and viral causes of infection. Acute cough was the symptom with the highest sensitivity for influenza-like syndrome and bacterial pneumonia both in adults and children (flu-like syndrome: 90% (95% CI 83%–94%); bacterial pneumonia, adults: 89% (95% CI 66%–97%); bacterial pneumonia, children: 88% (95% CI 67%–97%)) but with very low specificity, especially for the diagnosis of bacterial pneumonia in adults (flu-like syndrome: 23% (95% CI 13%–39%); bacterial pneumonia, adults: 14% (95% CI 2%–48%); bacterial pneumonia, children: 18% (95% CI 5%–48%)]. Diagnostic values of all extracted signs and symptoms are presented in the Supplementary material (Tables S2–S4; Appendix S2, references S1–S86).

Diagnostic value of host biomarkers

C-reactive protein: ten studies including 5191 individuals

Among 15 studies assessing CRP, ten studies were available for meta-analysis, exploring the following cut-off values: >10 mg/L, >20 mg/L, >50 mg/L, >100 mg/L. The CRP showed a diagnostic accuracy substantially varying by threshold from 52% (95% CI 34%–69%) to 90% (95% CI 67%–98%) in sensitivity and from 42% (95% CI 26%–60%) to 91% (95% CI 82%–96%) in specificity. Selecting a CRP cut-off >50 mg/L (six studies; 4505 patients) the observed sensitivity and specificity were 75% (95% CI 53%–89%) and 75% (95% CI 57%–87%), respectively (see Supplementary material, Appendix S3, references S19, S20, S24, S26, S69, S76, S87–S92).

Procalcitonin: seven studies including 4164 individuals

Diagnostic performance of PCT was assessed at the following cut-offs: >0.1 μg/L, >0.25 μg/L, >0.5 μg/L PCT sensitivity ranged from 44% (95% CI 14%–79%) to 74% (95% CI 38%–93) and specificity from 74% (95% CI 36%–94%) to 93% (95% CI 43%–100%). PCT >0.1 μg/L (four studies; 1092 patients) showed a sensitivity of 74% (95% CI 38%–93%) and a specificity of 74% (95% CI 36%–94%) (see Supplementary material, Appendix S3, references S26, S43, S54, S67, S76, S87, S88, S90, S92).

Diagnostic value of imaging

Lung ultrasound: 33 studies including 4901 individuals

Thirty-one studies out of 33 (94%) enrolled patients presenting with signs and symptoms suggestive of community-acquired pneumonia. All the studies were performed at the emergency department. The comparator for lung ultrasound was chest X-ray in 18 studies (54%), computed tomography scan in eight studies (24%), expert consensus in two (6%) and diagnosis at discharge in three (9%). The use of lung ultrasound for the detection of bacterial community-acquired pneumonia demonstrated both high sensitivity and high

specificity (92% (95% CI 88%–95%) and 90% (95% CI 81%–95%), respectively). The diagnostic accuracy for lung ultrasound examinations did not change by operator experience (lung ultrasound performed by highly skilled personnel: sensitivity 92% (95% CI 85%–96%), specificity 89% (95% CI 75%–96%) compared with physicians attending a lung ultrasound short course: sensitivity 89% (95% CI 82%–94%), specificity 88% (95% CI 69%–96%) (Fig. 2). Lung ultrasound subgroup analysis by population showed a slightly better performance in adults (sensitivity: 94% (95% CI 87%–97%); specificity: 90% (95% CI 79%–95%)) compared with children (sensitivity: 89% (95% CI 85%–93%); specificity: 91% (95% CI 80%–96%)) (see Supplementary material, Appendix S4, references S55, S74, S93–S122).

Chest X-ray: 13 studies including 1567 individuals

The comparator for chest X-ray was computed tomography scan in five studies (38%), expert consensus or composite analysis in six (46%) and diagnosis at discharge in the remaining two (15%). Chest X-ray showed a suboptimal diagnostic performance (sensitivity: 75% (95% CI 54%–88%); specificity: 75% (95% CI 42%–92%), respectively). The majority of studies (86%) were performed in adults (78%), emergency departments (92%) and WHO European regions (EURO, 61%), not allowing any subgroup analysis (Fig. 2) (see Supplementary material, Appendix S4, references S93, S95–S97, S101, S102, S106, S111, S113, S117, S120, S122, S123).

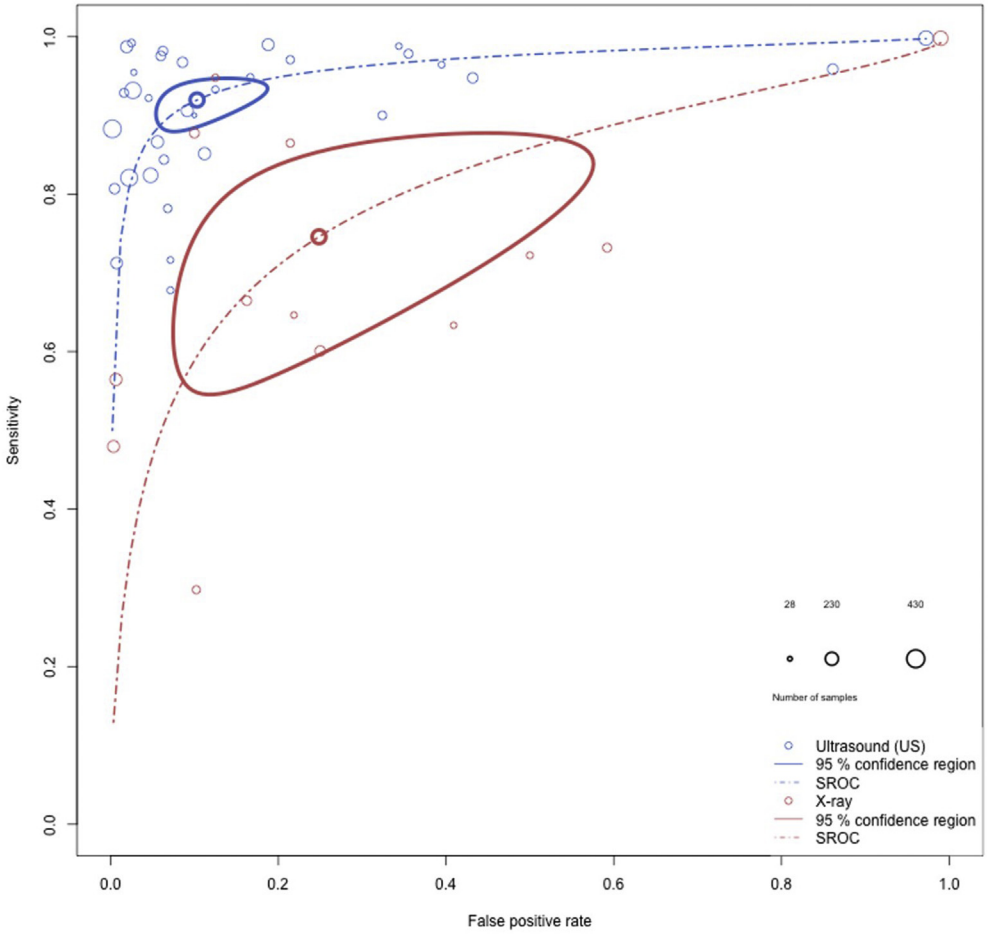
Diagnostic value of pathogen-based tests

Streptococcus pneumoniae—pneumococcal urinary antigen test: 12 studies including 2826 individuals

All studies were performed in a hospital-based setting and 11 evaluated the *Alere* BinaxNOW test, showing an overall sensitivity of 70% (95% CI 60%–79%) and specificity of 83% (95% CI 63%–93%). Subgroup analysis by WHO region revealed better test performance in the EURO region compared to the Western Pacific Region (WPRO) (78% (95% CI 66%–87%) versus 66% (95% CI 51%–78%)) and the opposite trend for specificity (72% (95% CI 42%–90%) versus 92% (95% CI 76%–97%)) (see Supplementary material, Appendix S5, references S124, S126, S127, S129–S135).

Streptococcus pneumoniae—NAAT: six studies including 2221 individuals

Sensitivity for *Streptococcus pneumoniae* was 96% (95% CI 93%–98%) whereas specificity was 91% (95% CI 71%–98%) (see Supplementary material, Appendix S6, references S136–S141).



Imaging diagnostic (N. studies, population)	Sen (%)	95% CI	Spc (%)	95% CI
LUS (33, 4901)	91.9	87.9-94.7	89.7	81.3-94.6
Chest X-ray (13, 1567)	74.6	54.5-87.7	75.1	42.4-92.5

Fig. 2. Summary receiving operating characteristic curves and bivariate summary estimates the diagnostic accuracy of lung ultrasound compared with chest X-ray for the detection of bacterial community-acquired pneumonia. Abbreviations: LUS, lung ultrasound; Sen, sensitivity; Spc, specificity.

Mycoplasma pneumoniae—RDT-Ab: seven studies including 1970 individuals

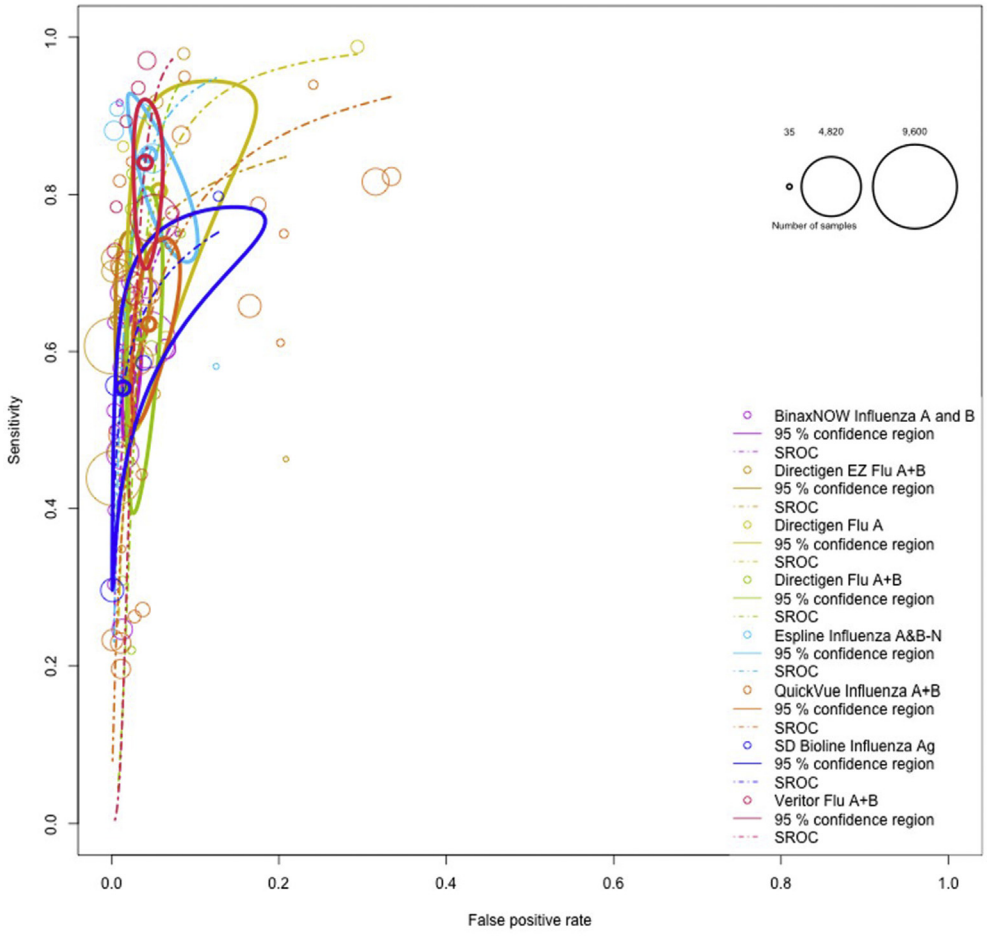
Overall, the reported sensitivity and specificity were 85% (95% CI 63%–95%) and 90% (95% CI 75%–97%), respectively (see Supplementary material, Appendix S5, references S142–S148).

Mycoplasma pneumoniae—NAAT: 25 studies including 9229 individuals

Mycoplasma pneumoniae was evaluated by PCR and by non-PCR assays (LAMP and isothermal amplification technology), reporting a similar sensitivity (87% (95% CI 73%–95%) and 83% (95% CI 60%–94%), respectively) and specificity (98% (95% CI 97%–99%) and 98% (95% CI 95%–99%), respectively) (see Supplementary material, Appendix S6, references S138, S140, S141, S149–S176).

Chlamydophila pneumoniae—NAAT: eight studies including 6177 individuals

NAAT for *C. pneumoniae* showed a sensitivity of 83% (95% CI 58%–94%) and a specificity of 99% (95% CI 96%–100%) (see Supplementary material, Appendix S6, references S138, S150, S151, S158, S163, S165, S177, S178).



Commercial name **(N. studies, population)**	**Sen (%)**	**95% CI**	**Spc (%)**	**95% CI**
Espline Influenza A&B-N (5 , 2224)	85.0	71.4-92.8	95.5	89.7-98.1
Directigen Flu A (6, 810)	84.5	50-94.4	94.3	82.7-98.3
Veritor Flu A+B (8, 5123)	84.0	70.5-92.1	96.0	93.8-97.4
Directigen EZ Flu A+B (13, 12102)	65.7	54.7-75.2	98.5	95.3-99.5
QuickVue Influenza A+B (28, 12372)	63.5	50.9-74.5	95.5	91.8-97.6
Directigen Flu A+B (9, 1484)	62.4	39.4-80.8	96.7	94.0-98.2
BinaxNOW Influenza A and B (19, 11647)	56.7	48.7-64.4	97.9	96.5-98.7
SD Bioline Influenza Ag (4, 1689)	55.3	29.7-78.4	98.6	81.6-99.9

Fig. 3. Summary receiving operating characteristic plot showing the diagnostic accuracy of different commercial immunochromatographic tests for the rapid diagnosis of influenza. Abbreviations: Sen, sensitivity; Spc, specificity.

Table 1
Diagnostic accuracy of host biomarkers, imaging and bacterial lower CA-LRTI pathogen based test

	Overall accuracy		Population		Setting		WHO region		Notes
	Sen, % (95% CI)	Spec, % (95% CI)	Sen, % (95% CI)	Spec, % (95% CI)	Sen, % (95% CI)	Spec, % (95% CI)	Sen, % (95% CI)	Spec, % (95% CI)	
Biomarker, no. of articles (population)									
CRP, 24 (10 5191)									
>10 mg/L 5 (1230)	90 (67–98)	42 (26–60)	**Ad**: 92 (56–99)	**Ad**: 43 (22–66)	—	—	—	—	*See online data supplement for CRP thresholds sROC* (Fig. S5)
>20 mg/L 6 (3817)	82 (68–91)	55 (39–70)	**Ad**: 83 (64–93)	**Ad**: 55 (37–73)	**PC:** 78 (57–90)	**PC:** 58 (36–78)	**EURO:** 82 (68–91)	**EURO:** 55 (39–70)	
>50 mg/L 6 (4505)	75 (53–89)	75 (57–87)	**Ad**: 77 (51–91)	**Ad**: 74 (51–88)	—	—	**EURO:** 75 (53–89)	**EURO:** 75 (57–87)	
>100 mg/L 7 (4704)	52 (34–69)	91 (82–96)	**Ad**: 52 (31–72)	**Ad**: 91 (79–97)	—	—	—	—	
PCT, 7 (4164)									
>0.1 μg/L 4 (1092)	74 (38–93)	74 (36–94)	**Ad**: 74 (38–93)	**Ad**: 74 (36–94)	—	—	—	—	*See online data supplement for PCT thresholds sROC* (Fig. S6)
>0.25 μg/L 5 (4019)	44 (14–79)	89 (50–98)	**Ad**: 44 (14–79)	**Ad**: 89 (50–98)	—	—	**EURO:** 44 (14–79)	**EURO:** 89 (50–98)	
>0.5 μg/L 4 (1195)	44 (19–73)	93 (43–100)	—	—	—	—	—	—	
Imaging, no. of articles (population)									
LUS 33 (4901)	92 (88–95)	90 (81–95)	**Ch:** 89 (85–93) **Ad**: 94 (87–97)	**Ch:** 91 (80–92) **Ad**: 90 (79–95)	**ED:** 89 (84–93)	**ED:** 89 (78–94)	**EURO:** 92 (87–95) **EMRO**: 97 (63–100)	**EURO:** 93 (83–97) **EMRO:** 62 (9–96)	*See* Fig. 2
Chest X-ray 13 (1567)	74 (54–88)	75 (42–92)	—	—	**ED:** 73 (56–84)	**ED:** 64 (42–82)	**EURO:** 69 (48–85)	**EURO:** 81 (57–93)	
Bacterial lower CA-LRTI pathogen based tests, no. of articles (population)									
Streptococcus pneumoniae									
PUAT 12 (2826)	72 (62–80)	83 (65–93)	**Ad:** 74 (60–85)	**Ad:** 76 (45–92)	—	—	**EURO:** 78 (66–87) **WPRO:** 66 (51–78)	**EURO:** 72 (42–90) **WPRO:** 92 (76–97)	*See online data supplement for WHO region sROC* (Fig. S13)
PCR 5 (1276)	96 (93–98)	91 (71–98)	—	—	—	—	—	—	
Mycoplasma pneumoniae									
RDT-Ab 7 (1970)	85 (63–95)	90 (75–97)	—	—	—	—	—	—	
PCR 22 (9687)	87 (73–95)	99 (97–99)	**Ch:** 79 (45–95)	**Ch:** 97 (96–98)	**ED:** 83 (60–94)	**ED:** 98 (96–99)	**EURO:** 88 (72–95) **PAHO:** 92 (81–97) **WPRO:** 92 (58–99)	**EURO:** 99 (97–100) **PAHO:** 99 (96–100) **WPRO:** 97 (95–98)	*See online data supplement for PCR sROC* (Fig. S22) *and subgroup analysis for real time PCR vs other* (Fig. S23)
Non-PCR 12 (3479)	83 (60–94)	98 (96–99)	**Ch:** 85 (45–96)	**Ch:** 98 (94–100)	**ED:** 80 (44–96)	**ED:** 98 (92–99)	**WPRO:** 88 (68–96)	**WPRO:** 99 (93–100)	*See online data supplement for non-PCR sROC* (Fig. S24)
Chlamydophila pneumoniae									
PCR 8 (6177)	83 (58–94)	99 (96–100)	—	—	—	—	**PAHO:** 80 (41–96)	**PAHO:** 99 (78–100)	
Influenza, no. of articles (population)									
RDT-Ag, 131 (63 095)									
ICA 118 (64 199)	69 (64–74)	97 (96–98)	**Ch:** 74 (63–82) **Ad**: 65 (47–79)	**Ch:** 98 (96–99) **Ad**: 96 (92–98)	**ED:** 71 (60–80) **OC:** 66 (55–76) **PC:** 56 (36–74) **LTCF:** 63 (25–90)	**ED:** 98 (96–99) **OC:** 97 (93–99) **PC:** 95 (89–98) **LTCF:** 98 (90–99)	**EURO:** 61 (47–73) **PAHO:** 69 (61–75) **SEARO:** 60 (35–80) **WPRO:** 78 (71–84)	**EURO:** 97 (96–98) **PAHO:** 97 (96–98) **SEARO:** 98 (86–100) **WPRO:** 96 (92–98)	*See online data supplement for type of test sROC* (Fig. S14); *ICA population sROC* (Fig. S15); *ICA setting*

									sROC (Fig. S16); *ICA WHO region sROC* (Fig. S17)
DIF 19 (7635)	78 (67–86)	95 (90–98)	**Ch:** 81 (48–95)	**Ch:** 93 (68–99)	**ED:** 82 (72–89)	**ED:** 96 (93–97)	**EURO:** 70 (54–82) **PAHO:** 82 (62–92) **WPRO:** 80 (62–91)	**EURO:** 97 (95–99) **PAHO:** 94 (84–98) **WPRO:** 95 (70–99)	
OIA 9 (3910)	68 (51–81)	88 (81–93)	—	—	—	—	**PAHO:** 68 (42–86)	**PAHO:** 87 (75–94)	
MariPOC 5 (1231)	78 (61–89)	99 (97–99)	—	—	—	—	**EURO:** 77 (55–90)	**EURO:** 99 (98–100)	
Chemiluminescent neuraminidase assay 4 (787)	81 (51–94)	82 (65–91)	—	—	—	—	—	—	
NAAT, 71 (34,583)									
PCR 66 (38 899)	94 (90–96)	98 (97–99)	**Ch:** 95 (70–99) **Ad**: 89 (80–95)	**Ch:** 98 (96–99) **Ad**: 99 (98–99)	**ED:** 94 (84–98) **OC:** 95 (84–98)	**ED:** 98 (96–99) **OC:** 96 (90–98)	**EURO:** 91 (86–95) **PAHO:** 94 (92–96) **WPRO:** 95 (79–99)	**EURO:** 97 (94–98) **PAHO:** 98 (96–99) **WPRO:** 98 (87–100)	*See online data supplement for population sROC* (Fig. S25); *setting sROC* (Fig. S26); *multiplex vs stand-alone sROC* (Fig. S27); *real time vs other sROC* (Fig. S28); *type of sample sROC* (Fig. S29); *WHO region sROC* (Fig. S30)
Non-PCR 23 (4863)	92 (88–94)	98 (95–99)	Ch: 92 (86–96)	Ch: 97 (89–99)	**ED:** 91 (87–94)	**ED:** 98 (95–99)	**EURO:** 92 (88–95) **PAHO:** 92 (81–97) **WPRO**: 91 (85–95)	**EURO:** 98 (95–99) **PAHO:** 96 (88–94) **WPRO**: 98 (93–100)	
Respiratory syncytial virus, no. of articles (population)									
RDT-Ag 35 (16 110)	83 (78–86)	97 (94–98)	**Ch**: 83 (77–87)	**Ch:** 97 (95–98)	**ED:** 81 (79–83)	**ED:** 96 (9–99)	**EURO:** 82 (73–89) **PAHO:** 85 (78–89) WPRO: 75 (64–84)	**EURO:** 96 (91–98) **PAHO:** 97 (94–99) WPRO 98 (88–100)	*See online data supplement for commercial name sROC* (Fig. S18) *and WHO region sROC* (Fig. S31)
PCR 38 (18 833)	93 (89–96)	99 (98–99)	**Ch**: 96 (92–98)	**Ch:** 97 (95–98)	·**ED:** 94 (88–97)	**ED:** 99 (97–100)	**EURO:** 90 (74–97) **PAHO:** 94 (89–97)	**EURO:** 98 (97–99) **PAHO:** 99 (98–100)	*See online data supplement for multiplex vs stand-alone sROC* (Fig. S31); *real time vs other sROC* (Fig. S33); *year of study sROC* (Fig. S33); *WHO region sROC* (Fig. S34)
Non-PCR 5 (1086)	94 (71–99)	97 (64–100)	**Ch**: 91 (66–98)	**Ch**: 99 (62–100)	**ED:** 96 (76–100)	**ED:** 99 (83–100)	**WPRO:** 91 (66–98)	**WPRO:** 99 (62–100)	
Human metapneumovirus, no. of articles (population)									
RDT-Ag 5 (1578)	59 (36–78)	99 (95–100)	—	—	—	—	—	—	
PCR 17 (8061)	88 (80–94)	99 (98–100)	—	—	**ED:** 76 (13–98)	**ED:** 99 (84–100)	**EURO:** 84 (62–95) **PAHO:** 87 (73–95)	**EURO:** 98 (95–100) **PAHO:** 100 (98–100)	*See online data supplement for year of study sROC* (Fig. S35); *WHO region sROC* (Fig. S36)

Abbreviations: Ab, antibody; Ad, adults; AFRO, African Region; CA-LRTI, community-acquired acute respiratory tract infection; Ch, children; CI, confidence interval; CRP, C-reactive protein; DIF, direct immunofluorescence; ED, emergency department; EMRO, Eastern Mediterranean Region; EURO, European Region; LUS, lung ultrasound; ICA, immunochromatographic assay; LAMP, loop-mediated isothermal amplification; LTCF, long-term care facilities; NAAT, nucleic acid amplification test; OIA, optical immunoassay; OC, outpatient clinic; PAHO, Region of the Americas; PC, primary care; PCR, polymerase chain reaction; PCT, procalcitonin; PUAT, pneumococcal urinary antigen test; RDT-Ag, rapid antigen detection test; RDT-Ab, rapid antibody detection techniques − RDT-Ab; SEARO, South-East Asia Region; Sen, sensitivity; Spec, specificity; WPRO, Western Pacific Region; −, not available.

Influenza—RDT-Ag: 143 studies including 69 699 individuals

Overall, 118 studies reported on immunochromatographic assays for influenza A/B, showing a sensitivity and specificity of 69% (95% CI 64%–74%) and 97% (95% CI 96%–98%), respectively. Subgroup analysis suggested a better performance in children compared with adults (sensitivity: 74% (95% CI 63%–82%) and 65% (95% CI 47%–79%), respectively; specificity: 98% (95% CI 96%–99%) and 96% (95% CI 92%–98%), respectively). Espline Influenza A&B–N (Fujirebio, Tokyo, Japan) and Veritor Flu A+B (BD Becton Dickinson, Franklin Lakes, NJ, USA), provided the best sensitivities (85% (95% CI 71%–93%) and 84% (95% CI 70%–92%), respectively) with similar specificity (Fig. 3). In subgroup analyses, setting and WHO region did not show significant heterogeneity (see Supplementary material, Appendix S5, references S83, S179–S318).

Influenza—NAAT: 89 studies including 43 762 individuals

The pooled sensitivity of PCR for influenza A/B was 94% (95% CI 90%–96%) and specificity was 98% (95% CI 97%–99%). The most frequently reported commercial tests were different *Cepheid* tests and *Biofire*. Other non-PCR based NAATs (23 studies, 4863 patients) included mainly isothermal nicking enzyme amplification-ID NOW (formerly *Alere i)*, isothermal nucleic acid amplification, RT LAMP, and rod-shaped gold nanoparticles. Their pooled sensitivity and specificity values were 92% (95% CI 88%–94%) and 98% (95% CI 95%–99%), respectively. The covariates analysed for heterogeneity through subgroup analysis did not significantly affect the diagnostic accuracy (see Supplementary material, Appendix S6, references S150, S151, S163, S169, S180, S183, S208, S229, S231, S267, S319–S388).

Respiratory syncytial virus (RSV)—RDT-Ag: 35 studies including 16 110 individuals

Twenty-two (63%) studies were conducted in children showing a sensitivity of 83% (95% CI 77%–87%) and a specificity of 97% (95% CI 95%–98%) (Table 1). Sofia® RSV FIA and BinaxNOW RSV showed the best performance in the brand subgroup analysis (sensitivity: 84% (95% CI 77%–89%) and 84% (95% CI 71%–91%) respectively; specificity: 96% (95% CI 88%–99%) and 96% (95% CI 86%–99%) respectively]. Subgroup analysis was only possible for WHO region and did not highlight a significant impact on diagnostic accuracy (see Supplementary material, Appendix S5, references S189, S190, S192, S209, S222, S235, S238, S241, S250, S257, S270, S277, S288, S304, S305, S389–S407).

Respiratory syncytial virus—NAAT: 43 studies including 19 919 individuals

PCR for the diagnosis of RSV was evaluated in 38 studies (18 833 individuals) with a sensitivity of 93% (95% CI 89%–96%) and a specificity of 99% (95% CI 98%–99%). Five studies assessed non-PCR methods (1086 individuals) with a pooled sensitivity of 94% (95% CI 71%–99%) and a specificity of 97% (95% CI 64%–100%). Specificity was high in all subgroups, but sensitivity was higher in studies evaluating RSV PCR as a stand-alone test (97%, 95% CI 93%–99%) and with real-time PCR (97%, 95% CI 95%–98%) (see Supplementary material, Appendix S6, references S150, S151, S163, S169, S319, S321, S324, S330, S334, S339, S340, S342, S345, S348, S349, S351, S352, S357, S363, S365, S366, S371, S374, S375, S377, S379, S380, S384–S386, S388, S408–S418).

Human-metapneumovirus (hMPV)—RDT-Ag: five studies including 1578 individuals

In pooled analysis of RDTs that detected hMPV in five studies, overall sensitivity and specificity were 59% (95% CI 36%–78%) and 99% (95% CI 95%–100%), respectively (see Supplementary material, Appendix S5, references S189, S238, S390, S419, S420).

Human-metapneumovirus—NAAT: 17 studies involving 8061 individuals

Overall, diagnostic accuracy of PCR for hMPV was 88% (95% CI 80%–94%) for sensitivity, with specificity of 99% (95% CI 98%–100%) (Table 1). Subgroup analysis showed a possible source of heterogeneity depending on the year of study, with sensitivity reported by studies performed after 2011 better compared with previous studies 96% (95% CI 90%–98%) versus 83% (95% CI 71%–91%) (see Supplementary material, Appendix S6, references S150, S151, S163, S169, S324, S330, S348, S349, S352, S363, S365, S366, S368, S369, S371, S375, S421).

Multiplex versus single-plex PCR

In 46 studies (see Supplementary material, Appendix S6, references S136, S139, S140, S141, S150–S152, S158, S163, S169, S181, S267, S319, S324, S326, S327, S330, S332–S334, S337, S339, S340, S345, S349, S351, S352, S354, S357, S361, S363, S365, S367–S371, S375, S381, S383, S385, S386, S388, S410, S411, S415) the sensitivity of multiplex PCR for the diagnosis of influenza was lower compared with that of stand-alone PCR (90% (95% CI 82%–95%) versus 94% (95% CI 88%–97%), with a similar specificity of 99%. For *M. pneumoniae*, multiplex exhibit a better sensitivity of 89% (95% CI 68%–97%) versus 87% (95% CI 62%–96%) with a higher specificity for the multiplex (99% (95% CI 98%–100%) versus 97% (95% CI 96%–98%). The sensitivity of multiplex PCR for the diagnosis of *C. pneumoniae* was lower compared with that of single-plex PCR (78% (95% CI 32%–96%) versus 91% (95% CI 72%–98%)), but with higher specificity (100% (95% CI 98%–100%) versus 97% (95% CI 75%–100%)]. For RSV, the sensitivity of stand-alone PCR was higher compared with that of multiplex (97% (95% CI 93%–99%) versus 91% (95% CI 85%–95%)), whereas the specificity was similar (98% (95% CI 95%–99%) versus 99% (95% CI 98%–99%)). A comparison for *S. pneumoniae* and hMPV was not possible. Meta-analysis of multiplex assays by brand was not possible because of the limited number of studies. A forest plot reporting the accuracy of multiplex PCR assay sensitivity and specificity is shown in the Supplementary material (Fig. S37).

Discussion

The results of this comprehensive protocol-driven systematic review confirm that accuracy of clinical signs and symptoms and biomarkers, is poor while lung ultrasound shows high sensitivity and specificity compared with chest X-ray, even when performed by personnel with limited training. Among POCTs, RDT-Ag for influenza, RSV, hMPV and *S. pneumoniae* have poor-to-suboptimal sensitivity, with high specificity overall, whereas the diagnostic performance of molecular tests is consistently better for all the studied pathogens.

Clinical signs and symptoms, CRP and PCT are not sufficiently reliable as stand-alone tests to differentiate bacterial versus viral pneumonia [22,23]. The main challenge to be addressed for biomarkers is consensus on a diagnostic threshold. With regards to CRP, one of the largest diagnostic European studies conducted in adults, identified a threshold of 30 mg/L as the best cut-off to be combined with signs and symptoms for ruling out severe bacterial infection and to avoid the misuse of antibiotics [4,24]. Previous systematic reviews found that CRP >20 mg/L is of value in diagnosing bacterial pneumonia [24–27]. In our meta-analysis CRP >10 mg/L described the best performance in terms of sensitivity (90%) in contrast with specificity (42%). The diagnostic performance of PCT >0.1 μg/L was overall acceptable (with sensitivity and specificity of 74%). Based on the available evidence, the discriminatory

power of biomarkers has added diagnostic value only if incorporated into multicomponent clinical prediction models.

Lung ultrasound had a better accuracy compared with chest X-ray in children and adults [28–32]. Interestingly the learning curve seems relatively fast [33,34] with accuracy not changing significantly if the lung ultrasound is performed by highly skilled sonographers compared with non-experienced personnel. This result raises questions as to why chest X-ray remains the reference standard for CA-LRTI diagnosis [35–37]. More methodologically rigorous studies conducted at different community settings and in LMICs may contribute to better define lung ultrasound's potential at POC. Molecular tests were confirmed as the most accurate pathogen-based diagnostic tests currently available, with considerably higher accuracy compared with the other pathogen-based tests, despite several factors that could have been negatively affecting the results, such as the timing of sampling—both since the infection and the onset of symptoms—and the location of the sampling [38]. Nonetheless, the applicability of molecular tests at POC is limited by the need for laboratory infrastructure, expensive equipment, skilled personnel and prolonged turn-around times. The accuracy of rapid NAAT, including isothermal nucleic acid amplification, shows promise for introduction at POC with only slightly inferior sensitivity and specificity compared with PCR [39].

Overall, our results are consistent with previously published meta-analyses on rapid antigen detection tests for influenza and RSV [5,6,9] and highlight that, especially for influenza, sensitivity varies considerably. Currently, few RDT-Ag are capable of detecting multiple pathogens. The mariPOC® test allows automated detection of antigens from eight different respiratory viruses. For influenza, this assay has a better sensitivity compared with immunochromatographic assays (78% versus 69%) and an excellent specificity (99%). However, only five studies were included in the antigen detection-based, mariPOC® meta-analysis, thus limiting the strength of the evidence. Immunochromatographic assays and direct immunofluorescence assays for influenza have a similar accuracy in terms of specificity (97% and 95%, respectively), with immunochromatographic assays performing better in children compared with adults. Among immunochromatographic assays, Veritor Flu A+B (BD) and Espline Influenza A&B–N (Fujirebio) showed the best accuracy with sensitivities of 84% and 85%, respectively. Hence, RDT-Ag can be recommended to rule in the diagnosis of influenza with an acceptable level of confidence. A negative result should be not considered fully reliable [40].

As for influenza, RDT-Ag for hMPV allows confirmation of the diagnosis of hMPV infection but cannot rule it out with the same accuracy. All but one studies included in the pneumococcal urinary antigen test meta-analysis (excluding *Sofia S. pneumoniae FIA*) investigated the accuracy of *Alere BinaxNOW*, showing a pooled specificity higher than sensitivity.

This meta-analysis has some limitations. In the biomarker review, a subgroup analysis for every threshold was not available. Few studies were conducted in low- and middle-income countries, therefore reducing the transferability of our results. In several studies, the choice of comparator was considered suboptimal, and the sample size limitations restricted subgroup analyses for many of the tests. The effect of several factors (i.e. specimen type and duration of symptoms) on diagnostic accuracy of pathogen-based tests was often unknown. The prevalence of CA-LRTI was not systematically reported by each study. Most of the studies that were included in our meta-analysis were conducted in primary care or emergency department settings, with very limited representation from long-term care facilities and outpatient clinics.

Our findings suggest that while molecular tests are well recognized as valid and accurate diagnostic tools, their use at POC needs to be explored through further studies especially focusing on LAMP NAAT. By contrast, RDT-Ag applicability at POC and high specificity suggest that they can be used to rule in the diagnosis, but negative results cannot be considered reliable. Cost-effectiveness of implementation of these tests in diagnostic algorithms needs to be explored in different economic settings and by type of population—mostly primary care At the time of the SARS-CoV-2 pandemic, when evidence-based algorithms for CA-LRTI in the emergency department and in primary care need to be re-assessed—also in terms of infection control—the results of this meta-analysis may play a pivotal role, providing an updated summary of the diagnostic accuracy of all POCT available in the community setting.

Supporting information

Additional Supporting Information may be found in the online version of this article (see Supplementary material).

Author contributions

EG, PDN and EC performed the systematic review of the literature and wrote the first draft of the manuscript. MP, MMH and IP performed the systematic review of NAAT. FM contributed to the systematic review protocol and data extraction. AG performed the automated NCBI search, statistical analysis and visualization with input from ML. ET contributed to the protocol development, provided advice on the statistical analysis and reviewed all the drafts of the manuscript. JV and HG reviewed the protocol and final manuscript. All the authors read and approved the final version of the manuscript.

Transparency declaration

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Appendix A. Supplementary data

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