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Diagnostic accuracy of rapid point-of-care tests for diagnosis of current SARS-CoV-2 infections in children: a systematic review and meta-analysis

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Abstract

Objective To systematically assess the diagnostic accuracy of rapid point-of-care tests for diagnosis of current SARS-CoV-2 infections in children under real-life conditions.

Design Systematic review and meta-analysis.

Data sources MEDLINE, Embase, Cochrane Database for Systematic Reviews, INAHTA HTA database, preprint servers (via Europe PMC), ClinicalTrials.gov, WHO ICTRP from 1 January 2020 to 7 May 2021; NICE Evidence Search, NICE Guidance, FIND Website from 1 January 2020 to 24 May 2021.

Review methods Diagnostic cross-sectional or cohort studies were eligible for inclusion if they had paediatric study participants and compared rapid point-of care tests for diagnosing current SARS-CoV-2 infections with reverse transcription polymerase chain reaction (RT-PCR) as the reference standard. The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was used to assess the risk of bias and the applicability of the included studies. Bivariate meta-analyses with random effects were performed. Variability was assessed by subgroup analyses.

Results 17 studies with a total of 6355 paediatric study participants were included. All studies compared antigen tests against RT-PCR. Overall, studies evaluated eight antigen tests from six different brands. Only one study was at low risk of bias. The pooled overall diagnostic sensitivity and specificity in paediatric populations was 64.2% (95% CI 57.4% to 70.5%) and 99.1% (95% CI 98.2% to 99.5%), respectively. In symptomatic children, the pooled diagnostic sensitivity was 71.8% (95% CI 63.6% to 78.8%) and the pooled diagnostic specificity was 98.7% (95% CI 96.6% to 99.5%). The pooled diagnostic sensitivity in asymptomatic children was 56.2% (95% CI 47.6% to 64.4%) and the pooled diagnostic specificity was 98.6% (95% CI 97.3% to 99.3%).

Conclusions The performance of current antigen tests in paediatric populations under real-life conditions varies broadly. Relevant data were only identified for very few antigen tests on the market, and the risk of bias was mostly unclear due to poor reporting. Additionally, the most common uses of these tests in children (eg, self-testing in schools or parents testing their toddlers before kindergarten) have not been addressed in clinical performance studies yet. The observed low diagnostic sensitivity may impact the planned purpose of the broad implementation of testing programmes.

PROSPERO registration number CRD42021236313.

Summary box

What is already known on this topic?

⇒ Antigen tests are widely used to detect children with current SARS-CoV-2 infection in schools and kindergarten despite an ongoing debate on potential benefits and harms.

⇒ Sensitivity estimates of antigen tests in adult populations vary broadly and are substantially lower than reported by manufacturers; however, test performance in paediatric populations remained unknown.

What this study adds?

⇒ A systematic literature search and comprehensive author queries allowed the inclusion of 17 studies evaluating the diagnostic accuracy of antigen tests in children.

⇒ Real-life performance of current antigen tests for professional use in paediatric populations is below the minimum performance criteria set by WHO, the United States Food and Drug Administration, or the Medicines and Healthcare products Regulatory Agency (UK).

⇒ Performance of antigen tests for professional use in paediatric populations is simillar to what has been reported previously for adult populations. No evidence on the performance of self-tests in children was identified.

Introduction

Since the beginning of the COVID-19 pandemic caused by SARS-CoV-2, accurate, fast and early detection of people infected with SARS-CoV-2 followed by effective isolation measures of infected individuals has been considered a cornerstone in

Summary box

How might it impact clinical practice in the foreseeable future?

⇒ The observed low diagnostic sensitivity may impact the intended purpose of antigen tests in children.
⇒ Evidence gaps identified in this systematic review demonstrate current research needs to support evidence-based decision making. In particular, evidence is needed on the real-life performance of tests in schools (self-testing performed by children) and kindergarten (sample collection in toddlers by laypersons).

the global fight against the spread of SARS-CoV-2. Laboratory-based reverse transcription polymerase chain reaction (RT-PCR) testing is the standard for diagnosing current infections with SARS-CoV-2. However, limited testing capacities at many laboratories worldwide and limited availability of laboratories in developing countries has shown the urgent need for novel diagnostic tests that are easy to use, less expensive, widely available and suitable for point-of-care use. Today, such tests—and in particular antigen tests—are increasingly used to complement testing with RT-PCR to extend testing capacities or when a short turnaround time is essential.[1] However, the advantages of antigen tests come at the price of lower diagnostic accuracy, most notably a lower diagnostic sensitivity, which increases the risk of missing cases, including those with pre-symptomatic infection who have yet to enter the most infectious period.[2]

Whether a lower sensitivity can be compensated by frequent testing remains a topic of controversial discussions.[3–6] Additionally, the fact that sensitivity and specificity are not inherent test characteristics but are affected by various factors, including population characteristics, sample quality and study design, needs consideration.[7] Data on diagnostic accuracy provided by antigen test manufacturers at market access are often overly optimistic and do not necessarily reflect the test's performance in practice. Sensitivity of antigen tests in adult populations varies considerably across brands,[8] with only a few tests meeting the minimum acceptable sensitivity of 80% or higher as defined by WHO or the United States Food and Drug Administration (US FDA).[9 10]

Because many countries are implementing public health safety measures that involve the use of antigen tests in adults and also in children, such as mass (self-)testing in schools,[11] knowledge about how these tests perform in children is of high importance. However, to our knowledge, systematic reviews analysing the diagnostic test accuracy (DTA) of rapid tests in children are lacking. Therefore, in this systematic review and meta-analysis, we aimed to identify, assess and summarise the best available evidence on the real-life performance of rapid tests for diagnosing current SARS-CoV-2 infections in paediatric populations at the point of care.

Methods

The protocol for this systematic review was registered with PROSPERO (ID: CRD42021236313).[12] The reporting adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses of DTA studies (PRISMA-DTA) guideline[13] and two relevant extensions 'PRISMA-DTA for Abstracts'[14] and 'PRISMA-S for Reporting Literatures Searches in Systematic Reviews'.[15]

Eligibility criteria

We included diagnostic cross-sectional and cohort studies that evaluated the clinical performance of rapid point-of-care tests for detecting current SARS-CoV-2 infections against the reference standard in paediatric or mixed-age populations. Assessing analytical performance parameters such as the analytical sensitivity (limit of detection) or the analytical specificity (cross-reactivity) was not covered by the current review. Diagnostic case-control studies were excluded because they reflect the test's performance under ideal conditions and, therefore, often overestimate the diagnostic accuracy.[16] Moreover, studies evaluating serological tests were excluded because such tests are not suitable for the initial diagnosis of current SARS-CoV-2 infection.[17] We considered a study as eligible if the study population comprised at least 10 paediatric study participants, each identified as positive or negative by the reference standard. In the absence of a true gold standard, laboratory-based RT-PCR alone or in combination with clinical findings or clinical follow-up was defined as the reference standard because it reflects the best available method for diagnosing individuals currently infected with SARS-CoV-2.[7] Furthermore, we required reporting of data that allowed constructing a complete 2×2 contingency table. The full set of eligibility criteria is shown in online supplemental table S1 of Appendix 1. The decision rule for author queries is described in online supplemental appendix 2.

Information sources

We performed a comprehensive search for primary studies and secondary publications (systematic reviews and Health Technology Assessment (HTA) reports) in the following electronic bibliographic databases: MEDLINE (Ovid), Embase (Ovid), the Cochrane Library (Wiley), and preprint servers (Europe PMC) including medRxiv and bioRxiv (see Hamelers and Parkin[18] for a full list of included preprint servers). Here, secondary publications were solely used as sources for potentially relevant studies. In addition, we searched two study registries (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)) for relevant clinical studies. Other information sources comprised the International HTA Database, the Foundation of Innovative Diagnostics (FIND) COVID-19 website, and the Evidence Search and Guidance websites of Britain's National Institute for Health and Care Excellence (NICE).

Search strategy

In accordance with the Cochrane Handbook for DTA Reviews,[19] the search strategy included concepts addressing the index test and the target condition. The development of the search strategy followed an objective approach that involved text-analytic procedures to identify candidate search terms based on the method described by Hausner and colleagues.[20] Further details are available in online supplemental appendix 2. The last search in bibliographical databases and study registries was conducted on 7 May 2021. Other information sources were last searched on 24 May 2021. All search strategies are provided in online supplemental appendix 3.

Study selection

The screening of literature retrieved from bibliographical databases involved a two-step screening procedure and was performed independently by two researchers using the web-based Trial Selection Database (webTSDB).[21] In a first step, potentially eligible primary studies and secondary publications were identified from

screening titles and abstracts of retrieved citations. In a second step, the full texts of these articles were obtained and evaluated. Publications that met the eligibility criteria were included. Any discrepancies were resolved by consensus between the two researchers before finalising each screening step. Reference lists of relevant systematic reviews and HTAs (independent of mentioning paediatric study participants) were manually screened to identify further relevant studies. For the screening of records from study registries, both screening steps were combined. Furthermore, documents identified through searching other information sources were screened for eligibility or information about potentially relevant studies.

Data collection

The individual steps of data collection and data extraction were performed by one researcher. All output was checked by a second researcher to ensure its validity and completeness. Any disagreements were resolved by consensus. See online supplemental appendix 2 for further details.

Quality assessment

We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool[22] to evaluate the methodological quality and applicability of the included studies at the study level. The tool was tailored to our review by adding one signalling question and review-specific guidance was provided to facilitate judgments; see online supplemental appendix 4. The quality assessment of each included study was performed by one researcher. A second researcher verified all judgments. Any disagreements were resolved by consensus. The results were summarised in the text and visualised as a table and figure.

Diagnostic accuracy measures and data synthesis

For each included study, diagnostic sensitivity, diagnostic specificity, positive predictive value (PPV) and negative predictive value (NPV) with corresponding 95% CIs were calculated based on the extracted 2×2 tables. Individual study participants were used as the unit of analysis throughout this work. If a study reported repeat testing of individuals only the initial test was included in our analyses. If a study evaluated more than one test in the same study population, we reported all test evaluations, but only one randomly chosen test was included in the meta-analyses to avoid the necessity to adjust for multiplicity.

The meta-analyses were based on recommendations provided in the methodological guideline 'Meta-analysis of diagnostic test accuracy studies' by the European Network for Health Technology Assessment (EUnetHTA)[23]; see online supplemental appendix 2 for further details.

Results

Study selection

Overall, 3011 records were retrieved from five bibliographical databases. The PRISMA flow diagram is shown in figure 1 and outlines the process of identifying relevant studies from different information sources. References that were excluded at the full-text level can be found in online supplemental appendix 5 with

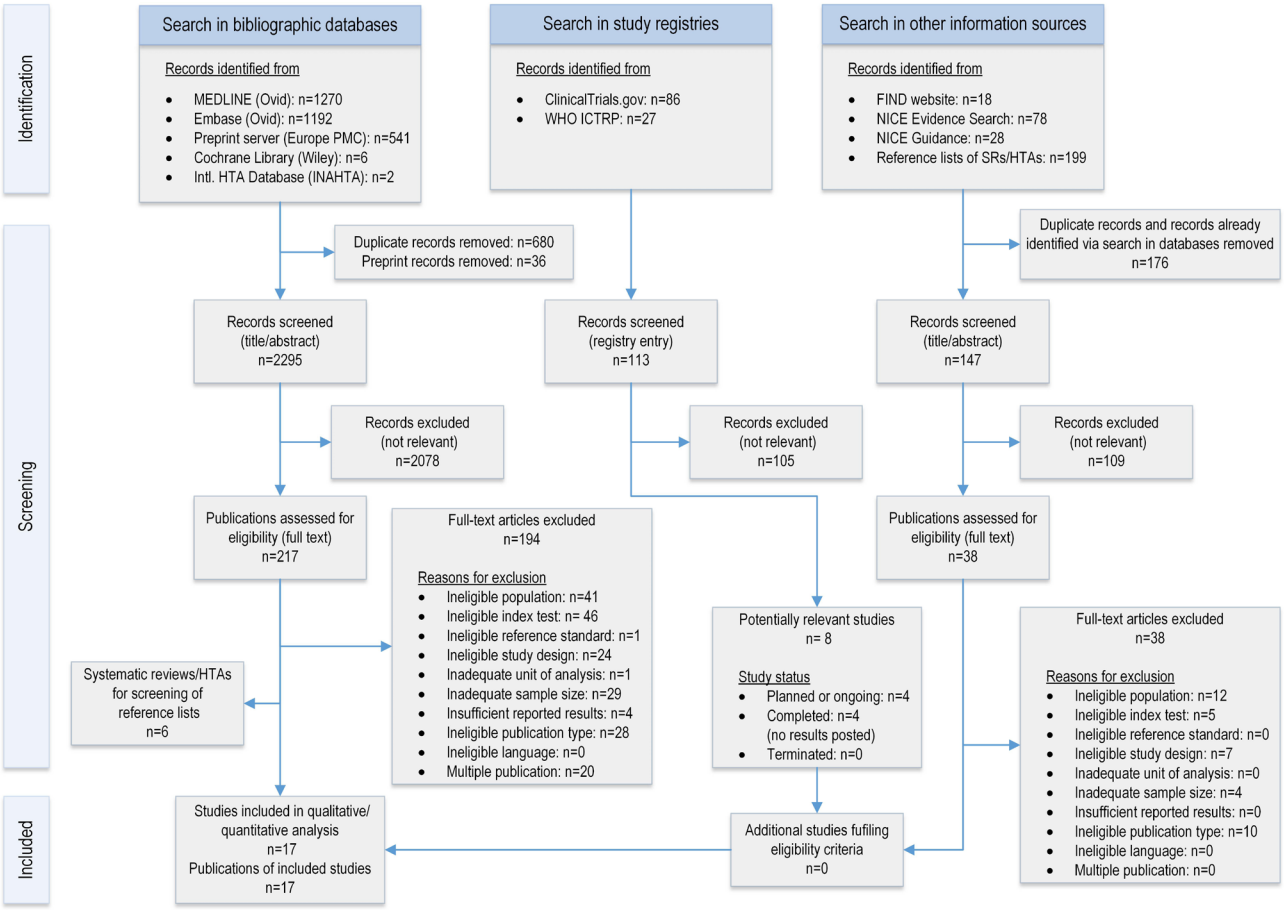

Figure 1 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram showing the selection process of primary studies included in this systematic review and meta-analysis.

the reason for their exclusion. After removing 36 preprint records identified via MEDLINE and 680 duplicate records, 2295 records were screened for eligibility; 2078 records were excluded at the title/abstract level. Full-text publications of 217 records were retrieved for further assessment. Nine studies[24–32] met all eligibility criteria for inclusion. Furthermore, 21 studies[33–53] were identified as eligible for author queries to obtain study data on paediatric subgroups. The authors of nine studies did not respond to our request for data.[33 34 39 40 42 44–46 49] In four cases,[36 47 52 53] the authors reported that the required number of individuals who tested positive or negative by the reference standard was not reached, and in one case[43] no data on age were recorded. Eventually, author queries led to the inclusion of eight further studies,[35 37 38 41 48 50 51 54] resulting in a total of 17 relevant studies for this review (12 peer-reviewed journal articles and five preprints). The full list of included studies is reported in online supplemental table S3 of Appendix 1.

Furthermore, we screened 113 records identified from study registries and 323 records identified from other information sources. The search for studies in study registries allowed us to identify four planned or ongoing and four completed studies with no results posted, see online supplemental table S4 of Appendix 1 for further details. Information retrieval from other information sources included screening 18 records retrieved from the FIND website, 78 records from NICE Evidence Search, 28 records from NICE Guidance, and 23 records from reference lists of six systematic reviews[8 55–59] identified via searching bibliographical databases. As a result, no additional study that met the inclusion criteria was identified.

Study characteristics

All 17 included studies (6355 paediatric study participants) evaluated the performance of antigen tests against the reference standard RT-PCR. The main study characteristics for each individual study are summarised in table 1, further details are reported in table 2 and online supplemental table S5 of Appendix 1. Fourteen studies evaluated the test performance in mixed-age populations (adults and children), including 24 to 928 paediatric study participants. Three studies with a sample size between 440 and 1620 individuals exclusively recruited children. In eight studies, the purpose of testing included diagnostic testing of individuals with symptoms suggestive of SARS-CoV-2 infection. Six studies reported the inclusion of individuals who were asymptomatic but were at increased risk of infection due to previous exposure to SARS-CoV-2. Here, 'asymptomatic' refers to any individual who is healthy, infected but pre-symptomatic or infected but without symptoms at the time of testing. Symptom status definitions were reported in nine of 16 studies that included individuals who were symptomatic. Individuals with at least one symptom (mostly self-reported) were considered symptomatic. Evaluating the performance of antigen tests in a screening setting (eg, community mass testing) was the main objective of six studies. Eight antigen tests (six lateral flow immunochromatographic assays and two fluorescent immunoassays) from six different brands were used in 18 test evaluations, whereas antigen tests by Abbott were most investigated (Panbio COVID-19 Ag Rapid Test n=6, BinaxNOW COVID-19 Ag Card n=5). In more than half of the test evaluations (n=11), nasopharyngeal samples were collected for the index test. Six test evaluations used anterior nasal specimens for the index test. In all studies, the reference standard was RT-PCR performed in a laboratory setting.

Risk of bias and applicability

The results of the quality assessment are summarised in online supplemental table S6 of Appendix 1 and figure 2. Quality among studies varied. Only one study was at low risk of bias in all four domains of the QUADAS-2 tool. For patient selection, more than half of the studies were at high (n=1) or unclear (n=12) risk of bias because inadequate exclusion of participants occurred, or it was not clear whether a consecutive or random sample was enrolled into the study. All but one study was judged as having an unclear risk of bias for the reference standard due to insufficient reporting of blinding. Risk of bias in the flow and timing domain was high in three studies due to more than 5% of missing outcome data.

Overall applicability concerns were high in three studies due to high concerns in either the patient selection or index test domain. Three studies were of low concern and the remaining 11 were rated unclear due to insufficient reporting in at least one domain.

Results of individual studies

RT-PCR positivity rate, diagnostic sensitivity, diagnostic specificity as well as PPV and NPV (and their 95% CIs) of individual studies based on data from 2×2 contingency tables for paediatric populations are reported in online supplemental table S7 and figure 3. The RT-PCR positivity rate, which corresponds to the SARS-CoV-2 prevalence in the sample population, varied between 4.1% and 50%, with a median of 14,5% over n=17 studies. The sensitivity and specificity ranged from 33.3% to 85.7% and 91.7% to 100%, respectively. PPV and NPV ranged from 60.0% to 98.7% and 73.3% to 98.9%, respectively.

For individual studies, separate analyses for subgroups based on symptom status are reported in online supplemental tables S8-S10 of Appendix 1 and figure 4. Here, populations were defined as symptomatic or asymptomatic if at least 80% of paediatric study participants were reported as being symptomatic or asymptomatic at the time of testing, respectively. Mixed populations refer to populations with no predominant symptom status. RT-PCR positivity rates of the primary analysis population and the different subgroups based on symptom status are presented in online supplemental figure S1 of Appendix 1. Two studies[38 41] were performed in high-prevalence populations with RT-PCR positivity rates of 38.7% and 50.0%, respectively. The median RT-PCR positivity rate was 13.2% (n=10 test evaluations) in asymptomatic populations, 13.8% in mixed populations (n=3 test evaluations) and 25.7% in symptomatic populations (n=13 test evaluations). Thus, the median RT-PCR positivity rate in symptomatic study populations was about 12 percentage points higher than in asymptomatic study populations, indicating a slight trend in the RT-PCR positivity rate with respect to the proportion of symptomatic subjects.

Synthesis of results

In our primary meta-analyses, we used data from 17 studies evaluating the diagnostic accuracy of antigen tests in paediatric participants. Estimated pooled sensitivity and specificity were 64.2% (95% CI 57.4% to 70.5%) and 99.1% (95% CI 98.2% to 99.5%), respectively. While the estimates for the sensitivity revealed high heterogeneity and thus justified the application of the bivariate model with random effects, the estimates for the specificity were limited to a small range, as shown in figure 5. Consequently, the estimated summary receiver operating characteristic (SROC) curve cannot be meaningfully interpreted. As prespecified in the protocol, we performed subgroup analysis evaluating the diagnostic accuracy according to symptom status. Estimated pooled sensitivity and specificity in asymptomatic children was 56.2%

Table 1 Characteristics of included studies. All studies aimed to identify individuals currently infected with SARS-CoV-2. The reference standard was RT-PCR performed in the laboratory setting (created by the authors)

Study identifier	Publication status (year)	Study design	Setting	Purpose of testing	Location (recruitment period)	Name of index test	Total number of study participants	Paediatric study participants				Funding/ potential COI
								(n)	Male (%)	Symptomatic (%)	Age (years)	
Akingba*et al*[35]	Preprint (2021)	Cross-sectional	Community testing site (mobile clinic)	D	South Africa (Nov 20)	Panbio COVID-19 Ag Rapid Test	667	41	39.0	100†	Median: 13,‡ IQR: 10–16,‡ range: 3–17‡	None/none
Bianco*et al*[37]	Published (2021)	Cross-sectional	Hospital ED, hospital unit	nr	Italy (Oct–Dec 20)	LumiraDx SARS-CoV-2 Ag Test	907§	165	nr	9.7	Mean: 7.2, range: 0–18	None/none
Dřevinek* *et al*[38]	Preprint (2020)	Cross-sectional	Hospital TC	D, A, S	Czech Republic (Oct 20)	1: Panbio COVID-19 Ag Rapid Test 2: Standard F COVID-19 FIA Ag	591	31	38.7‡	32.3‡	Median: 15,‡ IQR: 13.5–16,‡ range: 11–17‡	Public/none
González-Donapetry *et al*[24]	published (2021)	Cross-sectional	Hospital ED	D	Spain (Sept–Oct 20)	Panbio COVID-19 Ag Rapid Test	440	440	59.1	100†	Median: 3, IQR: 1–7, range:0–15	None/none
Homza* *et al*[41]	Published (2021)	Cross-sectional	Hospital TC	D, A	Czech Republic (nr)	ECOTEST COVID-19 Antigen Rapid Test	494	24	58.3	45.8	Mean: 13.17, SD: 2.79, range: 7–17	Public/none
Kiyasu*†† *et al*[54]	Preprint (2021)	Cohort	Hospital TC	nr	Japan (Oct 20–Jan 21)	QuickNavi COVID-19 Ag	1881	90	68.9	4.4	Median: 12,‡ IRQ: 6–15,‡ range: 0–17‡	Private/yes
L'Huillier *et al*[25]	Preprint (2021)	Cross-sectional	Hospital TC	D, A, S	Switzerland (Nov 20–Mar 21)	Panbio COVID-19 Ag Rapid Test	885	885	50.1	64.8	Median: 11.8, IQR: 9.0–14.3, range: 0–16	Public/none
Möckel *et al*[26]	Published (2021)	Cross-sectional	Hospital ED	D	Germany (Oct–Nov 20)	Roche SARS-CoV-2 Rapid Antigen Test	483	196‡‡	55	87.1	Median: 3, IQR: 1–9	Public/none
Pilarowski *et al*[27]	Published (2020)	Cross-sectional	Community testing site	S	USA (Nov–Dec 20)	BinaxNOW COVID-19 Ag Card	3320	209	nr	nr 30.9¶	≤18 (47%‹13)	Public, private/yes
Pollock *et al* [28]a	Published (2021)	Cross-sectional	Community testing site	S	USA (Oct–Dec 20)	BinaxNOW COVID-19 Ag Card	2482	928	47.0‡	10.7	≤18 (69%‡ ≤ 13)	Public/none
Pollock *et al* [29]b	Preprint (2021)	Cross-sectional	Community testing site	S	USA (Jan 21)	CareStart COVID-19 Antigen test	1603	253	46.2‡	12.6	≤18 (62%‡ ≤ 13)	Public/none
Prince-Guerra *et al*[30]	Published (2021)	Cross-sectional	Community testing site	S	USA (Nov 20)	BinaxNOW COVID-19 Ag Card	3419	236	nr	nr 24.2¶	Range: 10–17	nr/none

Continued

Table 1 Continued

Study identifier	Publication status (year)	Study design	Setting	Purpose of testing	Location (recruitment period)	Name of index test	Total number of study participants	Paediatric study participants				Funding/ potential COI
								(n)	Male (%)	Symptomatic (%)	Age (years)	
Shah* *et al*[48 61]	Published (2021)	Cohort	Community testing site	S	USA (Nov–Dec 20)	BinaxNOW COVID-19 Ag Card	2024	217	nr	53.4‡	Range: 5–17	Public/none
Sood *et al*[31]	Published (2021)	Cross-sectional	Community testing site	S, A	USA (Nov–Dec 20)	BinaxNOW COVID-19 Ag Card	1429	783	49.5	23.5	Range: 5–17, 65%: 5–12, 35%: 13–17	Public, private/yes
Takeuchi*†† *et al*[50]	Published (2021)	Cohort	Hospital TC	D, A	Japan (Oct–Dec 20)	QuickNavi COVID-19 Ag	1208	164	61.6	54.9	Median: 10,‡ IQR: 5-14, ‡ range: 0-17‡	Private/yes
Torres* *et al*[51]	Published (2021)	Cross-sectional	Hospital TC	A	Spain (Oct–Nov 20)	Panbio COVID-19 Ag Rapid Test	634	73	47.9	0**	Median: 13, range: 9–17	None/none
Villaverde *et al*[32]	Published (2021)	Cohort	Hospital ED	D	Spain (Sept–Oct 20)	Panbio COVID-19 Ag Rapid Test	1620	1620	nr	100†	Range: 0–16	Public/none

A: testing of asymptomatic individuals and at increased risk of infection due to previous exposure to SARS-CoV-2; D: diagnostic testing of symptomatic individuals; S: screening of individuals irrespective of symptoms (e.g. mass testing, pretravel testing).

*Study included due to unpublished paediatric study data obtained from author via author queries.

†Not explicitly stated, but as per inclusion criteria only study participants who are symptomatic.

‡Own calculation.

§Analysis population (total number of study participants not reported).

¶Value reported for whole study population.

**Not explicitly stated, but as per inclusion criteria only study participants who are asymptomatic.

††The study reported by Kiyasu *et al*[54] is specified as 'extension study' of a previous study reported by Takeuchi *et al*.[50] Both studies were included in this systematic review and considered as two separate studies due to different but overlapping recruitment periods, substantial differences in the proportion of paediatric study participants who were symptomatic and differences in how discordant RT-PCR test results were re-evaluated.

‡‡The overall paediatric study population as defined by the authors consisted of n=202 individuals and included n=6 adult chaperones.

COI, conflicts of interest; Hospital ED, hospital emergency department; Hospital TC, hospital test centre; nr, not reported; RT-PCR, reverse transcription polymerase chain reaction.

Table 2 Characteristics of the studies' index test and reference standard. (created by the authors)

	Index test				Reference standard			
Study identifier	Name (manufacturer)	Test method*/ readout*	Target analyte*	Specimen type used in study	RT-PCR assay	Viral target	Positivity threshold	Specimen type used in study
Akingba	Panbio COVID-19 Ag Rapid Test (Abbott)	LFA/visual	N protein	NP	Seegene nCoV assay	Three targets (not specified)	At least one target Ct value ‹38; inconclusive: two targets negative and one target positive with Ct value≥38	NP (same swab used for antigen test)
Bianco	LumiraDx SARS-CoV-2 Ag Test (LumiraDx)	Microfluidic FIA/ automated	N protein	Nasal	XpertXpress SARS-CoV-2 assay (Cepheid)†	nr	nr	NP
Dřevinek	1: Panbio COVID-19 Ag Rapid Test (Abbott) 2: Standard F COVID-19 FIA Ag (SD Biosensor)	1: LFA/visual 2: FIA/automated	1: N protein 2: N protein	1: NP 2: NP	Allplex SARS-nCoV-2 (Seegene)	N, E and RdRP/S genes	At least one target with Ct value≤40	NP+OP
González-Donapetry	Panbio COVID-19 Ag Rapid Test (Abbott)	LFA/visual	N protein	NP	Vircell SARS-CoV-2 real-time PCR kit (Vircell)	N and E gene	Both targets with Ct value≤40	NP
Homza	ECOTEST COVID-19 Antigen Rapid Test (Assure Tech)	LFA/visual	N protein	NP (nostril 1)	COVID-19 Multiplex RT-PCR Kit (Diana Biotechnologies)	S gene and gene coding the EndoRNAse	nr	NP (nostril 2)
Kiyasu	QuickNavi COVID-19 Ag (Denka)	LFA/visual	N protein	NP	RT-PCR (National Institute of Infectious Diseases, Japan)‡	nr	nr	NP
L'Huillier	Panbio COVID-19 Ag Rapid Test (Abbott)	LFA/visual	N protein	NP	1: Cobas SARS-CoV-2 assay (Roche) or 2: Nimbus RT-PCR assay	1: nr 2: nr	1: unclear 2: unclear	NP
Möckel	Roche SARS-CoV-2 Rapid Antigen Test (SD Biosensors)	LFA/visual	N protein	ONP	1: Cobas SARS-CoV-2 assay (Roche) or 2: SARS-CoV-2 E-gene assay (TibMolbiol)	1: nr 2: E gene	1: unclear 2: unclear	ONP
Pilarowski	BinaxNOW COVID-19 Ag Card (Abbott)	LFA/visual	N protein	AN (bilateral)	RenegadeXP§ (RenegadeBio)	N gene	'No Ct cut-off', Ct cut-off value=30 and 35	AN (bilateral)
Pollock a	BinaxNOW COVID-19 Ag Card (Abbott)	LFA/visual	N protein	AN (bilateral)	CRSP SARS-CoV-2 Real-time RT-PCR Diagnostic Assay (MIT/Harvard)	N2 gene	Ct cut-off value=40 (in addition: 25, 30, 35)	AN (bilateral)
Pollock b	CareStart COVID-19 Antigen test (Access Bio)	LFA/visual	N protein	AN (bilateral)	CRSP SARS-CoV-2 Real-time RT-PCR Diagnostic Assay (MIT/Harvard)	N2 gene	Ct cut-off value=40 (in addition: 25, 30, 35)	AN (bilateral)
Prince-Guerra	BinaxNOW COVID-19 Ag Card (Abbott)	LFA/visual	N protein	AN (bilateral)	1: CDC 2019-nCoV Real-time RT-PCR Diagnostic Panel or 2: Fosun COVID-19 RT-PCR Detection Kit	1: nr 2: nr	1: nr 2: nr	NP (bilateral)

Continued

Table 2 Continued

Study identifier	Index test				Reference standard			
	Name (manufacturer)	Test method*/ readout*	Target analyte*	Specimen type used in study	RT-PCR assay	Viral target	Positivity threshold	Specimen type used in study
Shah	BinaxNOW COVID-19 Ag Card (Abbott)	LFA/visual	N protein	AN (nostril 1)	TaqPath SARS-CoV-2 Combo Kit (Thermo Fisher Scientific)	S, N and Orf1Ab genes	Ct value≤37 for at least two targets; inconclusive: one target positive	AN (nostril 2)
Sood	BinaxNOW COVID-19 Ag Card (Abbott)	LFA/visual	N protein	AN	Curative SARS-Cov-2 Assay (EUA for testing at KorvaLabs)	nr	Ct value≤40	Oral fluid¶
Takeuchi	QuickNavi COVID-19 Ag (Denka)	LFA/visual	N protein	NP	RT-PCR (National Institute of Infectious Diseases, Japan)**	nr	nr	NP
Torres	Panbio COVID-19 Ag Rapid Test (Abbott)	LFA/visual	N protein	NP (left nostril)	TaqPath SARS-CoV-2 Combo Kit (Thermo Fisher Scientific)	N gene	Ct value≤35 (in addition: ≤30, ≤25, ≤20)	NP (right nostril)
Villaverde	Panbio COVID-19 Ag Rapid Test (Abbott)	LFA/visual	N protein	NP	RT-PCR (not further specified)	E and RdRp genes	nr	NP

*Technical specification taken from FIND Test Directory/manufacturer's instructions for use if not reported in paper.

†XpertXpress SARS-CoV-2 assay has FDA EUA for both point-of-care and laboratory use (https://www.fda.gov/media/136316/download—accessed online: 20 June 2021). The authors reported that RT-PCR was performed 'at the Microbiology and Virology unit' of the 'University Hospital Citta della Salute e della Scienza di Torino, Turin (Italy)' which is, according to the authors, the 'largest tertiary care facility in Europe',[37] therefore we considered the reference standard as eligible.

‡Classified as 'reference real-time RT-PCR' which was performed at the manufacturer's site. RT-PCR was performed in an in-house microbiology laboratory. In case of discordant RT-PCR test results, a re-evaluation was performed 'with a published for SARS-CoV-2'[54]. The final decision was based on the result of the latter RT-PCR test.

§PCR-positive results were confirmed by the "standard US Centers for Disease Control and Prevention methodology using Qiagen viral RNA purification kits and singleplex RT-PCR detection of the nucleoprotein gene".[27]

¶The FDA's Accelerated Emergency Use Authorisation (EUA) Summary (https://www.fda.gov/media/137089/download—accessed online: 30 May 2021) states that the 'collection of … oral fluid specimens is limited to symptomatic individuals within 14 days of COVID-19 symptom onset … Negative results for SARS-CoV-2 RNA from oral fluid specimens should be confirmed by testing of another specimen type authorised for use with this test if clinically indicated'.

**Classified as 'reference real-time RT-PCR'[50] which was performed at the manufacturer's site. RT-PCR was performed in an in-house microbiology laboratory. In case of discordant PCR test results, a re-evaluation was performed using a BioFire Respiratory Panel 2.1 on the BioFire FilmArray system.

AN, anterior nasal (nares); Ct, cycle threshold; FIA, fluorescent immunoassay; LFA, lateral flow immunochromatographic assay; NP, nasopharyngeal; nr, not reported; ONP, oro-nasopharyngeal; OP, oropharyngeal; RT-PCR, reverse transcription polymerase chain reaction.

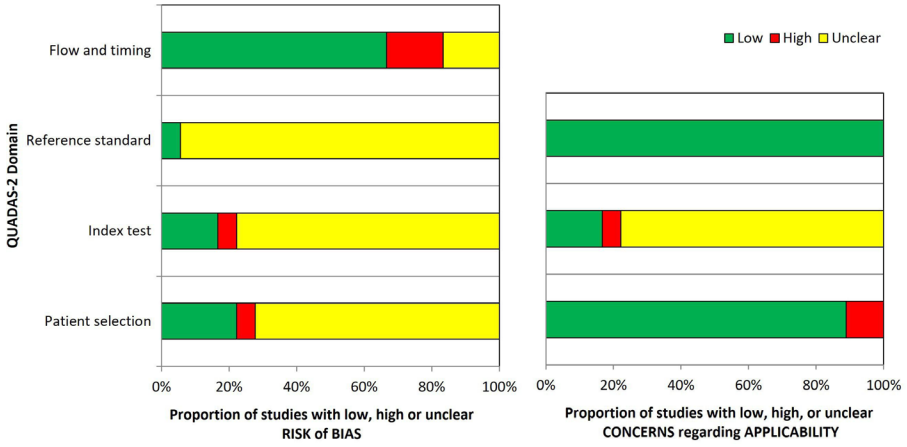

Figure 2 QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) risk of bias and applicability concerns. Graphical summary showing the review authors' judgment about each domain as percentages across 18 test evaluations reported in 17 included studies.

(95% CI 47.6% to 64.4%) and 98.6% (95% CI 97.3% to 99.3%), respectively, based on data from 2439 asymptomatic children in 10 studies. Estimated pooled sensitivity and specificity in symptomatic children was 71.8% (95% CI 63.6% to 78.8%) and 98.7% (95% CI 96.6% to 99.5%), respectively, based on data from 3413 symptomatic children in 13 studies. Estimated pooled sensitivity and specificity in the mixed population of symptomatic and asymptomatic children from three studies including 419 children was 63.4% (95% CI 37.3% to 83.5%) and 98.7% (95% CI 90.8% to 99.8%), respectively. The corresponding SROC curves are shown in online supplemental figure S2 of Appendix 1. The likelihood ratio test (LRT) for differences between the three groups revealed a p-value of p_{LRT}=0.066. Since the bivariate meta-analysis might be influenced by the differences in the prevalence,[60] we performed a bivariate meta-regression taking the prevalences within the studies directly into account. The LRT between the models without and with prevalence revealed a statistically significant p-value of p_{LRT}=0.003. Results for the other subgroup analyses did not show relevant differences in the pooled estimates (setting p_{LRT}=0.400; index test sample type p_{LRT}=0.303; reference standard sample type p_{LRT}=0.723; RT-PCR cycle threshold (Ct) cut-off value p_{LRT}=0.105; publication status p_{LRT}=0.551). The prediction regions of these analyses also showed a higher heterogeneity for sensitivity compared with specificity, see online supplemental figures S3-S6 of Appendix 1. Due to insufficient data, we did not perform subgroup analysis with respect to test type (antigen vs molecular) and end-user (layperson (self-testing) vs trained staff/healthcare worker). Except for one study[48 61] where the testing procedure involved supervised self-collection of samples by study participants, in all other studies, testing was conducted by trained staff and/or healthcare workers (if reported). Univariate meta-analysis with random effects for sensitivity and specificity in cases where only a few studies were included (mixed population of symptomatic and asymptomatic children) did not show remarkable differences to the bivariate analysis. The results of all bivariate meta-analyses are summarised in table 3.

Discussion

To our knowledge, this is the first systematic review that focused on evaluating the diagnostic accuracy of rapid point-of-care tests for current SARS-CoV-2 infections in paediatric populations. Our review comprises 17 studies with 18 evaluations of eight different antigen tests in children, whereas comprehensive author queries allowed us to include eight studies that did not provide sufficient data on paediatric study participants in their original study publication. We did not identify any evaluations of molecular-based tests that met our inclusion criteria confirming the current dominant role of antigen tests for rapid point-of-care usage.

Sensitivity estimates of antigen tests varied broadly among studies and were substantially lower than reported by manufacturers. However, one should note that the intended use of most tests is limited to symptomatic individuals. Thus, performance data reported by manufacturers usually refer to symptomatic individuals only. Less variation and only minor discrepancies to performance claims by manufacturers were observed for specificity estimates across studies. Taking into account test-specific pooled results, no test included in this review fully satisfied the minimum performance requirements as recommended by WHO[9] (minimum sensitivity ≥80% and minimum specificity ≥97%), the US FDA[10] (minimum sensitivity ≥80%, whereas a lower bound

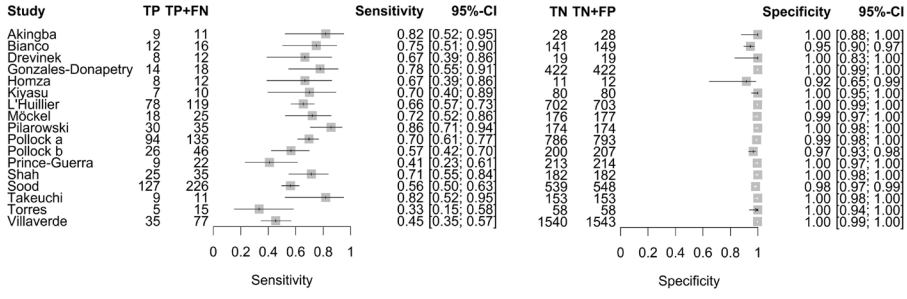

Figure 3 Forest plot of sensitivity and specificity of antigen tests in entire paediatric study populations irrespective of symptoms. The point estimates of sensitivity and specificity from each study (identified by name of first author) are shown as squares; the corresponding 95% CIs are represented as horizontal lines. TP, true positive; FN, false negative; TN, true negative; FP, false positive.

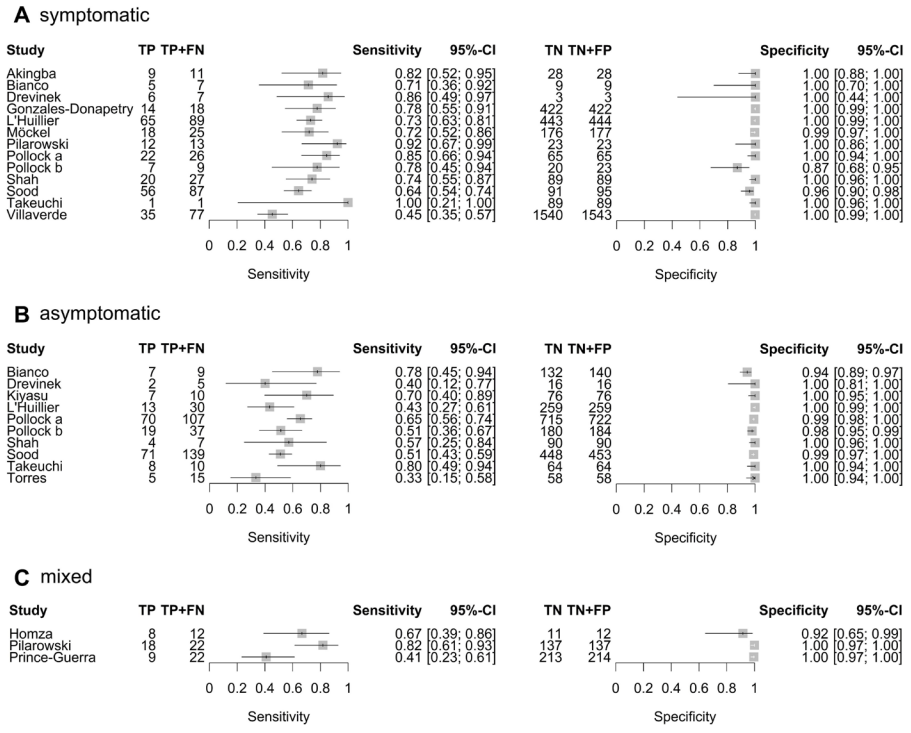

Figure 4 Forest plot of sensitivity and specificity of antigen tests in (A) symptomatic, (B) asymptomatic and (C) mixed paediatric study populations. The point estimates of sensitivity and specificity from each study (identified by name of first author) are shown as squares; the corresponding 95% CIs are represented as horizontal lines. TP, true positive; FN, false negative; TN, true negative; FP, false positive.

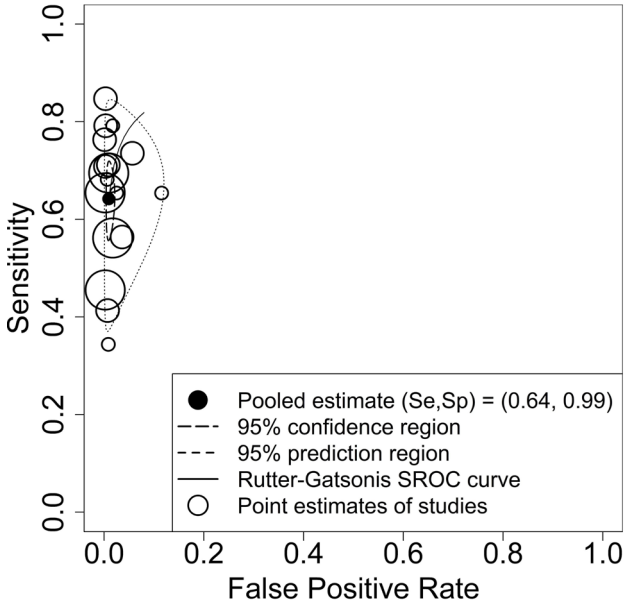

Figure 5 Summary receiver operating characteristic (SROC) plot of sensitivity and specificity of antigen tests for diagnosis of current SARS-CoV-2 infections in entire paediatric study populations irrespective of symptoms. Each circle represents the point estimate of an individual study, whereas the size of the circle correlates with the number of paediatric study participants (small circle: 500 participants). The pooled estimate (black dot) of the pair of sensitivity (Se) and specificity (Sp) is surrounded by its 95% confidence region (closed curve with short dashes) and prediction region (closed curve with long dashes). The estimation of the SROC curve is based on the bivariate approach by Rutter and Gatsonis.[77]

of the two-sided 95% CI above 70% is required for over-the-counter use self-tests[62]) or the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK[63] (minimum acceptable sensitivity ≥80% with two-sided 95% CI entirely above 70% and minimum acceptable specificity of 95% with two-sided 95% CI entirely above 90%). Limited performance was also observed in a recent laboratory-based study that evaluated the sensitivity of 122 of these antigen tests using common SARS-CoV-2 specimens with varying viral concentrations.[64] Even under such ideal conditions, a wide range of sensitivities was observed, whereas 26 tests missed the study's sensitivity criteria of 75% for specimens with high SARS-CoV-2 concentrations of around 106 SARS-CoV-2 RNA/ml and higher corresponding to a Ct value less than 25.

The bivariate meta-regression with respect to prevalence was statistically significant. This result is mirrored in the results of the subgroup analysis with respect to symptom status. While specificities were similarly high in symptomatic (98.7% with 95% CI 96.6% to 99.5%) and asymptomatic (98.6% with 95% CI 97.3% to 99.3%) populations, we observed a drop in sensitivity by about 15 percentage points in asymptomatic populations (56.2% with 95% CI 47.6% to 64.4%) compared with symptomatic populations (71.8% with 95% CI 63.6% to 78.8%). The better performance in symptomatic populations might be explained by changes in the viral load over the course of infection and the timing of the test: most symptomatic individuals were tested within 7 days of symptom onset in contrast to individuals who were asymptomatic at the time of testing with more variable disease onset, including individuals in the early (pre-symptomatic) or late stages of infection when viral loads are relatively low.[65]

As expected, the sensitivity increased when the positivity threshold of the reference standard was set to a lower Ct cut-off value of 30 or 25. However, such analyses should not be over-interpreted

Table 3 Results of the bivariate meta-analyses: pooled sensitivity and specificity with 95% CI (created by the authors)

	Test evaluations included in analysis (n)	Paediatric study participants included in analysis (n)	Sensitivity (95% CI)	Specificity (95% CI)
All studies	17	6287	64.2 (57.4 to 70.5)	99.1 (98.2 to 99.5)
Subgroup analysis				
(a) Symptom status				
- symptomatic population	13	3407	71.8 (63.6 to 78.8)	98.7 (96.6 to 99.5)
- asymptomatic population	10	2431	56.2 (47.6 to 64.4)	98.6 (97.3 to 99.3)
- mixed population	3	419	63.4 (37.3 to 83.5)	98.7 (90.8 to 99.8)
(b) Setting				
- community testing site	8	2680	64.1 (54.7 to 72.6)	98.7 (97.6 to 99.3)
- hospital test centre/emergency department	9	3607	64.1 (53.8 to 73.2)	99.4 (98.2 to 99.8)
(c) Sample type (index test)				
- nasopharyngeal	10	3505	64.3 (54.7 to 73.0)	99.4 (98.5 to 99.8)
- not nasopharyngeal	7	2782	64.6 (54.4 to 73.7)	98.5 (96.7 to 99.3)
(d) Sample type (reference standard)				
- nasopharyngeal	11	3670	65.4 (56.3 to 73.5)	99.1 (97.7 to 99.7)
- not nasopharyngeal	6	2617	64.2 (53.1 to 74.0)	98.9 (97.6 to 99.5)
(e) RT-PCR positivity threshold				
- Ct cut-off value=25	5	2062	92.4 (72.7 to 98.2)	92.7 (85.4 to 96.5)
- Ct cut-off value=30	6	2271	83.3 (63.9 to 93.4)	96.1 (91.8 to 98.2)
(f) Publication status				
- preprint	5	1235	63.2 (55.6 to 70.3)	98.9 (95.9 to 99.7)
- peer reviewed	12	5052	64.3 (54.8 to 72.7)	99.1 (98.1 to 99.6)

Ct, cycle threshold; RT-PCR, reverse transcription-polymerase chain reaction.

because Ct values are not standardised across systems or laboratories, making it difficult to directly compare results between different studies. Furthermore, while the Ct value from RT-PCR is a strong indicator of viral load, there is no specific cut-off viral load which allows distinguishing individuals as being infectious or not. As shown in online supplemental tables S11 and S12 of Appendix 1, an increase in sensitivity comes at the cost of a decrease in specificity as antigen tests also identify some individuals with moderate or low viral loads, who would then be considered as false positives. Despite some methodological differences (such as the stringency of inclusion criteria) and neglecting differences between included studies (eg, settings), the findings of our review are similar to those in the recent Cochrane Review by Dinnes *et al*[8] or the now published living systematic review by Brümmer *et al*.[66] These similarities between paediatric and adult populations might be explained by the findings by Jones *et al*,[67] who only identified minor differences in viral loads across age groups in a comprehensive analysis of more than 25 000 individuals who tested positive for SARS-CoV-2 by RT-PCR.

It is widely recognised that RT-PCR is an imperfect reference standard for identifying current SARS-CoV-2 infection. However, based on the guidance provided by Reitsma *et al*,[68] we assume that this does not play a pivotal part in the context of DTA studies of SARS-CoV-2 antigen tests because antigen-based testing does not outperform RT-PCR-based molecular testing in terms of diagnostic accuracy.[2] The observed analytical variability between RT-PCR assays that may affect the false-negative rate is considered negligible as the analytical sensitivity (limit of detection) of RT-PCR assays is several magnitudes higher than the analytical sensitivity of antigen tests. Furthermore, RT-PCR-based testing in low prevalence settings confirms the very high specificity of the method in practice. Any pre-analytic issues such as the quality of specimen collection, which may affect the diagnostic accuracy of RT-PCR, also apply to antigen tests.

For the current version of our review, publication bias is not considered relevant due to the novelty of the topic. No study included in our review was published before November 2020. All four completed studies that were identified through searching study registries were completed within the last 9 months. Of note is that for all but one study[26] included in our review no entry in a study registry was reported.

Despite the roll-out of vaccines, testing continues to be a key to pandemic control. Particularly in populations with low vaccination rates or waning immunity, early identification of outbreaks will remain vital for controlling the spread of SARS-CoV-2. Consequently, multi-layered mitigation strategies will continue to involve screening tests of children in schools and kindergarten to avoid further closures. Whether this would still apply in populations with high childhood vaccination rates remains an open point for discussion.

The high specificity of antigen tests and the corresponding PPVs calculated for the paediatric study populations suggest that antigen testing might be a valuable tool to rapidly identify children with SARS-CoV-2 infection in moderate to high prevalence settings. However, at the same time, it is important to raise awareness that antigen tests should not be used to rule out SARS-CoV-2 infection (or infectiousness) because of their limited sensitivity. Whether increasing the frequency of antigen-based testing leads to an improved overall diagnostic accuracy that allows to effectively reduce transmission of SARS-CoV-2 has yet to be demonstrated in practice.[69] The latter two aspects and the urgent need for high-quality screening tests probably led to the recent publication of a new target product profile by the MHRA in the UK,[70] which includes increased performance requirements for self-tests to be used in national testing programmes that aim at detecting current SARS-CoV-2 infections in individuals without symptoms. Here, the minimum acceptable sensitivity for tests to 'rule out' a current infection is at least 97% with two-sided 95% CI entirely above 95%. The minimum acceptable specificity is 99.5% or higher

with two-sided 95%CI entirely above 97%. Furthermore, it is stated that performance claims of repeated testing strategies require adequate clinical evidence rather than evidence from modelling studies only.

Other screening testing methods such as molecular-based pool testing, which involves RT-PCR testing of pooled samples and so-called deconvolution testing of individuals belonging to pools tested positive, are currently under investigation[71–73] and may complement mere antigen testing, in particular in low prevalence settings. Additionally, novel tests, for example, lateral flow tests based on clustered regularly interspaced short palindromic repeat (CRISPR), hold great promise for a highly sensitive direct detection of SARS-CoV-2[74] but have yet to gain market access and demonstrate their value.

Limitations

Because we limited our search to studies published in English or German, it is possible that relevant studies were missed. The chosen implementation of the bivariate approach required a continuity correction for studies with zero cells in 2×2 tables. This approach may introduce bias into the results if multiple small studies with zero cells are included. With regard to bias, one should keep in mind that most studies were at unclear risk of bias in at least three of the four domains of the QUADAS-2 tool because of poor reporting. We acknowledge that infectiousness as a target condition is of higher practical relevance than current SARS-CoV-2 infection, which was chosen as the target condition of this review. While RT-PCR as the corresponding reference standard is a highly sensitive method that is used to detect the presence of viral RNA in a specimen, this does not necessarily indicate that infectious virus is present. Therefore, the actual transmission risk from individuals who tested RT-PCR positive remains unknown. Testing for infectiousness would allow to identify (and isolate) exclusively individuals who could pass the virus to others. However, while there have been attempts to use viral load (estimated from Ct values) or virus viability in cell culture as a proxy to determine individuals who are infectious, up to now, there is no adequate reference standard for infectiousness.[69] We included only eight different antigen tests in our review. Thus, with more than 500 antigen tests for professional use that gained market access in the EU,[75] the performance of most antigen tests under real-life conditions remains unknown. Sample collection in toddlers by laypersons or self-testing in schools performed by children are likely to influence the real-life test performance but were not addressed in any of the studies included in our review. Furthermore, one should keep in mind that diagnostic accuracy is only one factor affecting the effectiveness of testing programmes.[76] We emphasise that all included studies were performed before market authorisation of COVID-19 vaccines for paediatric populations and most individuals identified as RT-PCR positive were likely infected with the wild-type of SARS-CoV-2. Diagnostic accuracy estimates reported in this review may not apply to future variants of SARS-CoV-2 or children who are vaccinated.

Conclusion

The performance of current antigen tests in paediatric populations under real-life conditions varies broadly. Relevant data were only identified for very few antigen tests on the market, and the risk of bias was mostly unclear due to poor reporting. Estimates of sensitivity and specificity and their 95% CIs from the bivariate meta-analyses indicate a subpar real-life performance of current antigen tests in children below the minimum performance criteria set by WHO, the US FDA or the MHRA in the UK. This may affect the planned purpose of the broad implementation of testing programmes. Up to now, the most common uses of these tests in children (eg, self-testing in schools or parents testing their toddlers before kindergarten) have not been addressed in clinical performance studies. Thus, it is of high relevance that these use cases are promptly investigated in independent studies. Moreover, the implementation of routine audits of testing programmes may allow monitoring of test performance in practice outside of studies.

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Diagnostic accuracy of rapid point-of-care tests for diagnosis of current SARS-CoV-2 infections in children: A systematic review and meta-analysis

N. Fujita-Rohwerder, L. Beckmann, Y. Zens, A. Verma

Appendix 1: Supplementary tables and figures

Table of contents

All tables and figures were created by the authors.

Table S1: *Eligibility criteria for primary studies.*

(Sub-)Population	Children (i.e. pediatric study participants <18 years of age) • with symptoms suggestive of COVID-19, or • without symptoms, but at an increased risk of infection (e.g. due to recent exposure to SARS-CoV-2 → contact tracing), or • participating in mass testing (e.g. in schools) regardless of symptoms.
Index test	Any rapid point-of-care test that is designed to detect an active SARS-CoV-2 infection and that meets the following criteria: • performed in a non-laboratory setting at or near the point of care (including non-healthcare settings such as schools or community testing sites) • minimal or no training required for end user • sample condition: fresh • time to result ≤ 60 minutes • commercially available
Reference standard	Any validated laboratory-based reverse transcription-polymerase chain reaction (RT-PCR) assay alone or in combination with clinical findings or clinical follow-up.
Main outcome	Diagnostic test accuracy (DTA)
Target condition	Current SARS-CoV-2 infection
Study design	Diagnostic cross-sectional or cohort studies with prospective sampling.
Unit of analysis	Individual study participants
Sample size	At least 10 (pediatric)[a] study participants each identified as positive or negative by the reference standard
Reported results	Sufficient data that allows constructing a complete 2x2 contingency table for (pediatric)[a] study participants per index test
Publication type	Full-text journal articles (including preprints) and reports (including clinical study reports)
Language	English or German

a: upon availability of pediatric study data

Table S2: *Data extraction items.*

General study characteristics	• First author • Publication date • Publication status • Study design • Type of enrolment • Indication for testing • Inclusion and exclusion criteria • Definition of symptoms suggestive for infection with SARS-CoV-2 • Setting • Location • Country • Total number of study participants • Number of pediatric study participants • Recruitment period • Funding sources • Potential conflicts of interest • Study registry entry
Characteristics of pediatric study population	• Age • Proportion of males • Exposure history • Proportion of symptomatic individuals at the time of testing (if applicable) • Duration of symptoms prior to testing (if applicable)
Index test	• Name • Manufacturer • Regulatory status • Assay target • Test method • Readout • Target analyte • Specimen type used in study • Conduct of test according to manufacturer's instructions for use (as judged and reported by authors)
Reference standard	• Name • Manufacturer • Viral target(s) • (Pre-specified) positivity threshold(s) • Specimen type used in study
Flow and timing	• Specimen for index test collected by • Specimen for reference standard collected by • Time interval between specimen collection for index test and reference standard • Time interval between specimen collection and use of index test

	• Time interval between specimen collection and use of reference standard • Index test performed by • Result of index test interpreted by • Reference standard • Result of reference standard interpreted by • Blinding • Time to result index test • Time to result reference standard • Inconclusive or invalid result(s) of index test • Inconclusive or invalid result(s) of reference standard • Missing data
Reported outcomes for pediatric study population	• True positives (TP) • False negatives (FN) • True negatives (TN) • False positives (FP) (if available: separate outcome data depending on symptom status, symptom onset or positivity threshold of reference standard)

Table S3: *Study pool of the systematic review.*

Study identifier	Data sources	Registry entry
Akingba	Preprint [1], unpublished data provided by author	N/A
Bianco	Journal article [2], unpublished data provided by author	N/A
Drevinek	Preprint [3], unpublished data provided by author	N/A
Gonzalez-Donapetry	Journal article [4]	N/A
Homza	Journal article [5], unpublished data provided by author	N/A
Kiyasu	Preprint [6], unpublished data provided by author	N/A
L'Huillier	Preprint [7]	N/A
Möckel	Journal article [8]	yes[a]
Pilarowski	Journal article [9]	N/A
Pollock a	Journal article [10]	N/A
Pollock b	Preprint [11]	N/A
Prince-Guerra	Journal article [12]	N/A
Sood	Journal article [13]	N/A
Shah	Journal article [14], supplementary file provided by authors (published in [15] after finalization of the study pool)	N/A
Takeuchi	Journal article [16], unpublished data provided by author	N/A
Torres	Journal article [17], unpublished data provided by author	N/A
Villaverde	Journal article [18]	N/A

N/A: not available

a: Study registry identifier: DRKS00019207

Table S4: *Potentially relevant studies identified through searching clinical study registries.*

Study registry identifier	Country	Enrollment	Ages eligible for study	Name of index test	Recruitment status[a] (study completion date)
NCT04513990	USA	1,500	not specified (children included)	unspecified point-of-care test	Recruiting (estimated: Apr 2021)
NCT04557046	USA	400	any	LumiraDx SARS-CoV-2 Ag Test	Recruiting (estimated: Dec 2021)
NCT04583189	France	500	≤18 years	Biosynex Covid-19 Ag BSS Rapid test	Completed (Nov 2020)
NCT04720235	USA	304	14-75 years	Lucira COVID-19 All-In-One Test Kit	Completed (Mar 2021)
NCT04750629	USA	100	≥ 1 year	CoviDx™ Rapid Antigen Test	Not yet recruiting (estimated: Mar 2021)
NCT04808921	USA	151	any	Xiamen Wiz Biotech SARS-CoV-2 Antigen Rapid Test	Completed (Apr 2021)
NCT04859023	France	10,000	≥10 years	unspecified SARS-CoV-2 antigen test	Completed (Feb 2021)
NCT04878068	not reported	300	≥ 12 years	Therma COVID-19 Rapid Antigen Test	Not yet recruiting (estimated: June 2021)

a: Status as of May 24, 2021

Table S5: *Conduct, flow and timing, and interpretation of index test and reference standard.*

Study identifier	Timing of specimen collection for index test and reference standard	Index test					Reference standard			Missing data	Invalid or inconclusive tests
		Specimen collected by	Time to conduct of test after specimen collection	Test performed by / interpreted by	Blinded to reference standard	IFU-conform conduct[a]	Specimen collected by	Time to conduct of test	Blinded to index test		
Akingba	only one swab for both tests (swab used for Ag-test was subsequently used for RT-PCR	n.r.	n.r. (result reported to participants onsite)	n.r. / n.r.	n.r., result determined prior to conduct of RT-PCR	n.r.	n.r.	n.r. (swab previously used for Ag-test)	n.r.	n.r., no participant flow diagram provided	19/677 PCR inconclusive, pediatric subgroup: 2/41 PCR inconclusive
Bianco	"in parallel"	n.r.	n.r.	trained staff / n.r.	n.r.	yes	trained staff	within a few hours	n.r.	n.r., no participant flow diagram provided	n.r.
Drevinek	n.r., but same participant encounter	n.r.	immediately	n.r. / n.r.	n.r.	yes	n.r.	n.r.	n.r.	none, no participant flow diagram provided	0
Gonzalez-Donapetry	paired sample collection	n.r.	n.r.	n.r. / n.r.	n.r.	yes	n.r.	n.r.	n.r.	none, no participant flow diagram provided	0
Homza	paired sample collection	HCW	immediately	n.r. / n.r.	n.r.	yes	HCW	n.r.	n.r.	none, no participant flow diagram provided	0
Kiyasu	"simulta-neously"	n.r.	n.r.	n.r. / n.r.	n.r.	yes	n.r.	n.r.	n.r.	5/1939[b] no symptom data, no participant flow diagram provided	0
L'Huillier	n.r., but same participant encounter	HCW	immediately	n.r. / two members of the study team independently	n.r., result determined prior to RT-PCR	yes	HCW	n.r.	n.r.	58/883 refused Ag-test, 2/825 Ag-test result not reported	1/825 Ag-test result invalid

Study identifier	Timing of specimen collection for index test and reference standard	Index test					Reference standard			Missing data	Invalid or inconclusive tests
		Specimen collected by	Time to conduct of test after specimen collection	Test performed by / interpreted by	Blinded to reference standard	IFU-conform conduct[a]	Specimen collected by	Time to conduct of test	Blinded to index test		
				(consensus required)							
Möckel	n.r., but same participant encounter	HCW	immediately	HCW / two HCW (consensus required)	n.r., result determined prior to RT-PCR	yes	HCW	n.r. (time to result (h): median: 8.2 range:3.8-39)	yes	none	0
Pilarowski	paired sample collection	certified lab assistants	n.r. (1 hour from onsite registration to return of positive test result)	n.r. / certified technician readers	n.r., result determined prior to RT-PCR	n.r. (only specimen collection according to IFU reported)	certified lab assistants	n.r.	n.r.	none, no participant flow diagram provided	0
Pollock a	paired sample collection	trained staff	within 1 hour	laboratorian / two laboratorians independently (1st read = official result)	n.r., result determined prior to RT-PCR	yes	trained staff	n.r.	n.r.	94/2482 samples tested at <53°F, 54/2482 missing data	26/2482 inconclusive RT-PCR
Pollock b	paired sample collection	trained staff	99.7% within 1 hour	laboratorian / two laboratorians independently (1st read = official result)	n.r., result determined prior to RT-PCR	yes	trained staff	n.r.	n.r.	48/1603 invalid or missing RT-PCR result, 57/1603 missing clinical data	invalid missing RT-PCR results, see missing data
Prince-Guerra	paired sample collection	HCW	immediately	n.r. / n.r.	n.r.	yes	HCW	within 24-48 hours	n.r.	n.r., no participant flow diagram provided	n.r.
Shah	same participant encounter	participants (self-collected,	n.r. (participants provided documentation of	trained staff / n.r.	n.r., result determined	yes	participants (self-collected,	n.r. (specimen with inconclu-	n.r.	7/2127 missing RT-PCR result, no participant flow diagram provided	4/2127 indeterminate Ag test result,

Study identifier	Timing of specimen collection for index test and reference standard	Index test					Reference standard			Missing data	Invalid or inconclusive tests
		Specimen collected by	Time to conduct of test after specimen collection	Test performed by / interpreted by	Blinded to reference standard	IFU-conform conduct[a]	Specimen collected by	Time to conduct of test	Blinded to index test		
		super-vised)	the initial test result about 30 minutes after initial sample collection)		prior to RT-PCR		super-vised)	sive results were retested)			6/2127 inconclusive RT-PCR result
Sood	n.r., but same participant encounter	trained staff	n.r.	n.r. / two study staff (no consensus required)	n.r.	yes	participant s (self-collected, super-vised)	n.r.	n.r.	4/783 (pediatric subgroup) reason not reported, no participant flow diagram provided	5/779 (pediatric subgroup) inconclusive result of index test
Takeuchi	”simulta-neously”	n.r.	immediately	n.r. / examiner	n.r.	yes	n.r.	in-house RT-PCR: same day as sample collection, reference RT-PCR: up to 1 week	n.r.	22/1208 not the first participant encounter, 4/1208 missing symptom data, no participant flow diagram provided	0
Torres	paired sample collection	HCW	immediately	n.r. / n.r.	n.r.	n.r.	HCW	within 24 hours of specimen collection	n.r.	none, no participant flow diagram provided	0
Villaverde	“concur-rently”	HCW	n.r.	n.r. / HCW	n.r.	yes	HCW	within 24 hours of specimen collection	n.r.	none, no participant flow diagram provided	0

Abbreviations

HCW: health care worker; IFU: instructions for use; n.r.: not reported; RT-PCR: reverse transcription-polymerase chain reaction

Footnotes

a: as judged and reported by the authors; b: unit of analysis = samples, but unit of analysis for paediatric subgroup = individual study participants

Table S6: *QUADAS-2 risk of bias and applicability concerns summary – review authors' judgment about each domain for 18 test evaluations reported in 17 included studies.*

Study identifier	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Akingba	unclear	unclear	unclear	low	low	unclear	low
Bianco	unclear	unclear	unclear	unclear	low	unclear	low
Drevinek (IT1)	unclear	unclear	unclear	low	low	unclear	low
Drevinek (IT2)	unclear	low	unclear	low	low	unclear	low
Gonzalez-D.	unclear	unclear	unclear	low	high	unclear	low
Homza	low	unclear	unclear	low	low	unclear	low
Kiyasu	unclear	unclear	unclear	low	low	unclear	low
L'Huillier	low	low	unclear	high	low	low	low
Möckel	low	low	low	low	low	unclear	low
Pilarowski	unclear	unclear	unclear	low	low	unclear	low
Pollock a	unclear	unclear	unclear	high	low	unclear	low
Pollock b	unclear	unclear	unclear	high	low	low	low
Prince-G.	unclear	unclear	unclear	unclear	low	low	low
Shah	unclear	unclear	unclear	low	low	unclear	low
Sood	unclear	high	unclear	unclear	low	high	low
Takeuchi	unclear	unclear	unclear	low	low	unclear	low
Torres	low	unclear	unclear	low	low	unclear	low
Villaverde	high	unclear	unclear	low	high	unclear	low

IT1: Index test 1; IT 2: Index test 2

Table S7: *Calculated RT-PCR positivity rate, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for each included study based on the 2x2 contingency tables extracted for the entire paediatric study populations irrespective of symptom status.*

Study identifier	TP	FP	TN	FN	RT-PCR positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Akingba	9	0	28	2	28.2	81.8 (52.3-94.9)	100 (87.9-100)	95.0 (65.6-99.5)	91.9 (77.2-97.5)
Bianco	12	8	141	4	9.7	75.0 (50.5-89.8)	94.6 (89.8-97.3)	60.0 (38.7-78.1)	97.2 (93.1-98.9)
Drevinek (IT1)	8	0	19	4	38.7	66.7 (39.1-86.2)	100 (83.2-100)	94.4 (62.9-99.4)	81.2 (61.8-92.1)
Drevinek (IT2)	8	0	19	4	38.7	66.7 (39.1-86.2)	100 (83.2-100)	94.4 (62.9-99.4)	81.2 (61.8-92.1)
Gonzales-Donapetry	14	0	422	4	4.1	77.8 (54.8-91.0)	100 (99.1-100)	96.7 (74.7-99.7)	98.9 (97.4-99.6)
Homza	8	1	11	4	50.0	66.7 (39.1-86.2)	91.7 (64.6-98.5)	88.9 (56.5-98.0)	73.3 (48.0-89.1)
Kiyasu	7	0	80	3	11.1	70.0 (39.7-89.2)	100 (95.4-100)	93.8 (59.8-99.3)	95.8 (89.2-98.5)
L'Huillier	78	1	702	41	14.5	65.5 (56.6-73.5)	99.9 (99.2-100)	98.7 (93.2-99.8)	94.5 (92.6-95.9)
Möckel	18	1	176	7	12.4	72.0 (52.4-85.7)	99.4 (96.9-99.9)	94.7 (75.4-99.1)	96.2 (92.3-98.1)
Pilarowski	30	0	174	5	16.7	85.7 (70.6-93.7)	100 (97.8-100)	98.4 (86.3-99.8)	96.9 (93.3-98.6)
Pollock a	94	7	786	41	14.5	69.6 (61.4-76.8)	99.1 (98.2-99.6)	93.1 (86.4-96.6)	95.0 (93.3-96.3)
Pollock b	26	7	200	20	18.2	56.5 (42.2-69.8)	96.6 (93.2-98.4)	78.8 (62.3-89.3)	90.9 (86.4-94.0)
Prince-Guerra	9	1	213	13	9.3	40.9 (23.3-61.3)	99.5 (97.4-99.9)	90.0 (59.6-98.2)	94.2 (90.4-96.6)
Shah	25	0	182	10	16.1	71.4 (54.9-83.7)	100 (97.9-100)	98.1 (84.0-99.8)	94.6 (90.4-97.0)
Sood	127	9	539	99	29.2	56.2 (49.7-62.5)	98.4 (96.9-99.1)	93.4 (87.9-96.5)	84.5 (81.5-87.1)
Takeuchi	9	0	153	2	6.7	81.8 (52.3-94.9)	100 (97.6-100)	95.0 (65.6-99.5)	98.4 (95.0-99.5)
Torres	5	0	58	10	20.5	33.3 (15.2-58.3)	100 (93.8-100)	91.7 (51.7-99.1)	84.8 (74.5-91.4)
Villaverde	35	3	1540	42	4.8	45.5 (34.8-56.5)	99.8 (99.4-99.9)	92.1 (79.2-97.3)	97.3 (96.4-98.0)

TP: true positive, FP: false positive, TN: true negative, FN: false negative
RT-PCR: reverse transcription-polymerase chain reaction
IT1: Index test 1; IT2: Index test 2

Table S8: *Calculated RT-PCR positivity rate, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for each included study based on the 2x2 contingency tables extracted for symptomatic paediatric study populations.*

Study identifier	TP	FP	TN	FN	RT-PCR positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Akingba	9	0	28	2	28.2	81.8 (52.3-94.9)	100 (87.9-100)	95.0 (65.6-99.5)	91.9 (77.2-97.5)
Bianco	5	0	9	2	43.8	71.4 (35.9-91.8)	100 (70.1-100)	91.7 (51.7-99.1)	79.2 (50.9-93.3)
Drevinek (IT1)	6	0	3	1	70.0	85.7 (48.7-97.4)	100 (43.9-100)	92.9 (56.1-99.2)	70.0 (29.9-92.7)
Drevinek (IT2)	6	0	3	1	70.0	85.7 (48.7-97.4)	100 (43.9-100)	92.9 (56.1-99.2)	70.0 (29.9-92.7)
Gonzales-Donapetry	14	0	422	4	4.1	77.8 (54.8-91.0)	100 (99.1-100)	96.7 (74.7-99.7)	98.9 (97.4-99.6)
L'Huillier	65	1	443	24	16.7	73.0 (63.0-81.2)	99.8 (98.7-100)	98.5 (91.9-99.7)	94.9 (92.5-96.5)
Möckel	18	1	176	7	12.4	72.0 (52.4-85.7)	99.4 (96.9-99.9)	94.7 (75.4-99.1)	96.2 (92.3-98.1)
Pilarowski	12	0	23	1	36.1	92.3 (66.7-98.6)	100 (85.7-100)	96.2 (71.7-99.6)	94.0 (77.7-98.6)
Pollock a	22	0	65	4	28.6	84.6 (66.5-93.8)	100 (94.4-100)	97.8 (82.2-99.8)	93.6 (85.3-97.3)
Pollock b	7	3	20	2	28.1	77.8 (45.3-93.7)	87 (67.9-95.5)	70.0 (39.7-89.2)	90.9 (72.2-97.5)
Shah	20	0	89	7	23.3	74.1 (55.3-86.8)	100 (95.9-100)	97.6 (80.8-99.8)	92.3 (85.2-96.1)
Sood	56	4	91	31	47.8	64.4 (53.9-73.6)	95.8 (89.7-98.4)	93.3 (84.1-97.4)	74.6 (66.2-81.5)
Takeuchi	1	0	89	0	1.1	100 (20.7-100)	100 (95.9-100)	75.0 (19.8-97.3)	99.4 (94.9-99.9)
Villaverde	35	3	1540	42	4.8	45.5 (34.8-56.5)	99.8 (99.4-99.9)	92.1 (79.2-97.3)	97.3 (96.4-98.0)

TP: true positive, FP: false positive, TN: true negative, FN: false negative
RT-PCR: reverse transcription-polymerase chain reaction
IT1: Index test 1; IT 2: Index test 2

Table S9: *Calculated RT-PCR positivity rate, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for each included study based on the 2x2 contingency tables extracted for asymptomatic paediatric study populations.*

Study identifier	TP	FP	TN	FN	RT-PCR positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Bianco	7	8	132	2	6.0	77.8 (45.3-93.7)	94.3 (89.1-97.1)	46.7 (24.8-69.9)	98.5 (94.7-99.6)
Drevinek (IT1)	2	0	16	3	23.8	40.0 (11.8-76.9)	100 (80.6-100)	83.3 (31.0-98.2)	82.5 (61.1-93.4)
Drevinek (IT2)	2	0	16	3	23.8	40.0 (11.8-76.9)	100 (80.6-100)	83.3 (31.0-98.2)	82.5 (61.1-93.4)
Kiyasu	7	0	76	3	11.6	70.0 (39.7-89.2)	100 (95.2-100)	93.8 (59.8-99.3)	95.6 (88.7-98.4)
L'Huillier	13	0	259	17	10.4	43.3 (27.4-60.8)	100 (98.5-100)	96.4 (73.2-99.6)	93.7 (90.2-96.0)
Pollock a	70	7	715	37	12.9	65.4 (56.0-73.8)	99.0 (98.0-99.5)	90.9 (82.4-95.5)	95.1 (93.3-96.4)
Pollock b	19	4	180	18	16.7	51.4 (35.9-66.6)	97.8 (94.5-99.2)	82.6 (62.9-93.0)	90.9 (86.1-94.2)
Shah	4	0	90	3	7.2	57.1 (25.0-84.2)	100 (95.9-100)	90.0 (46.3-99.0)	96.3 (90.3-98.6)
Sood	71	5	448	68	23.5	51.1 (42.9-59.2)	98.9 (97.4-99.5)	93.4 (85.5-97.2)	86.8 (83.6-89.5)
Takeuchi	8	0	64	2	13.5	80.0 (49.0-94.3)	100 (94.3-100)	94.4 (62.9-99.4)	96.3 (88.7-98.8)
Torres	5	0	58	10	20.5	33.3 (15.2-58.3)	100 (93.8-100)	91.7 (51.7-99.1)	84.8 (74.5-91.4)

TP: true positive, FP: false positive, TN: true negative, FN: false negative
RT-PCR: reverse transcription-polymerase chain reaction
IT1: Index test 1; IT 2: Index test 2

Table S10: *Calculated RT-PCR positivity rate, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for each included study based on the 2x2 contingency tables extracted for mixed paediatric study populations.*

Study identifier	TP	FP	TN	FN	RT-PCR positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Homza	8	1	11	4	50.0	66.7 (39.1-86.2)	91.7 (64.6-98.5)	88.9 (56.5-98.0)	73.3 (48.0-89.1)
Pilarowski	18	0	137	4	13.8	81.8 (61.5-92.7)	100 (97.3-100)	97.4 (79.1-99.7)	96.8 (92.5-98.7)
Prince-Guerra	9	1	213	13	9.3	40.9 (23.3-61.3)	99.5 (97.4-99.9)	90.0 (59.6-98.2)	94.2 (90.4-96.6)

TP: true positive, FP: false positive, TN: true negative, FN: false negative
RT-PCR: reverse transcription-polymerase chain reaction

Table S11: *Calculated RT-PCR positivity rate, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for each included study based on the 2x2 contingency tables extracted for entire paediatric study populations irrespective of symptom status when the RT-PCR cycle threshold cut-off value is set to 30.*

Study identifier	TP	FP	TN	FN	RT-PCR positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Akingba	9	0	30	0	23.1	100 (70.1-100)	100 (88.6-100)	95.0 (65.6-99.5)	98.4 (86.3-99.8)
Pilarowski	24	6	179	0	11.5	100 (86.2-100)	96.8 (93.1-98.5)	79.0 (61.9-89.7)	99.7 (97.4-100)
Pollock a	84	17	818	9	10.0	90.3 (82.6-94.8)	98.0 (96.8-98.7)	83.2 (74.7-89.2)	98.9 (97.9-99.4)
Pollock b	24	9	215	5	11.5	82.8 (65.5-92.4)	96.0 (92.5-97.9)	72.7 (55.8-84.9)	97.7 (94.8-99.0)
Sood	42	91	625	11	6.9	79.2 (66.5-88.0)	87.3 (84.7-89.5)	31.6 (24.3-39.9)	98.3 (96.9-99.0)
Torres	5	0	60	8	17.8	38.5 (17.7-64.5)	100 (94.0-100)	91.7 (51.7-99.1)	87.7 (77.9-93.5)

TP: true positive, FP: false positive, TN: true negative, FN: false negative
RT-PCR: reverse transcription-polymerase chain reaction

Table S12: *Calculated RT-PCR positivity rate, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) for each included study based on the 2x2 contingency tables extracted for entire paediatric study populations irrespective of symptom status when the RT-PCR cycle threshold cut-off value is set to 25.*

Study identifier	TP	FP	TN	FN	RT-PCR positivity rate	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Akingba	4	5	30	0	10.3	100 (51.0-100)	85.7 (70.6-93.7)	45.0 (20.1-72.6)	98.4 (86.3-99.8)
Pollock a	61	40	826	1	6.7	98.4 (91.4-99.7)	95.4 (93.8-96.6)	60.4 (50.6-69.4)	99.9 (99.3-100)
Pollock b	20	13	220	0	7.9	100 (83.9-100)	94.4 (90.7-96.7)	60.3 (43.6-74.9)	99.8 (97.9-100)
Sood	15	118	635	1	2.1	93.8 (71.7-98.9)	84.3 (81.6-86.8)	11.3 (7.0-17.8)	99.8 (99.1-100)
Torres	4	1	65	3	9.6	57.1 (25.0-84.2)	98.5 (91.9-99.7)	80.0 (37.5-96.4)	95.6 (87.8-98.5)

TP: true positive, FP: false positive, TN: true negative, FN: false negative
RT-PCR: reverse transcription-polymerase chain reaction

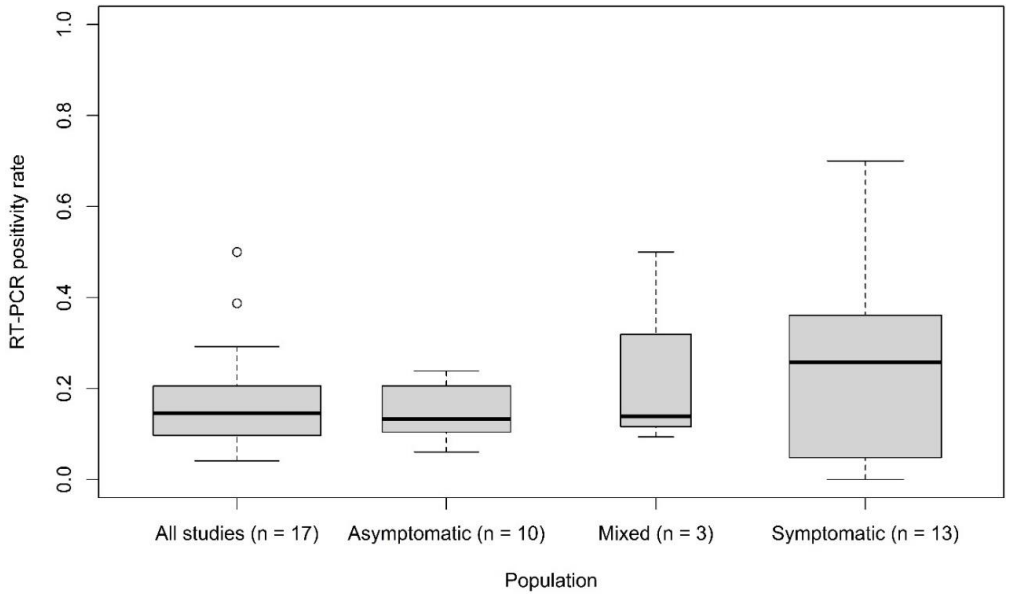

Figure S1: *Box and whisker plots of the RT-PCR positivity rates in entire paediatric study populations irrespective of symptoms and in asymptomatic, mixed, and symptomatic paediatric study populations. The box is drawn from the first to the third quartile, defined via hinges. The bold horizontal line in the box denotes the median. The whiskers extend out of the box by 1.5 times the difference between the hinges. Outliers are plotted as small circle. The width of the box corresponds to the number of considered studies.*

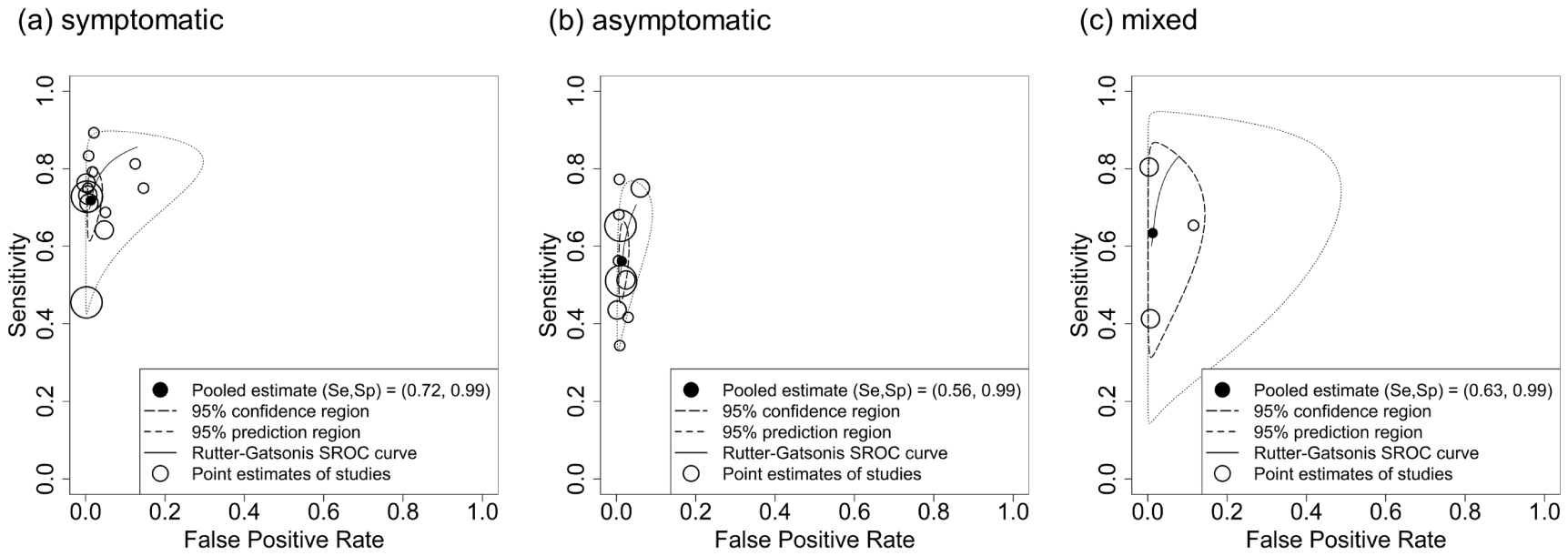

Figure S2: *Summary receiver operating characteristic (SROC) plot of sensitivity and specificity of antigen tests for diagnosis of current SARS-CoV-2 infections in (a) symptomatic, (b) asymptomatic, and (c) mixed symptomatic and asymptomatic paediatric study populations. Each circle represents the point estimate of an individual study, whereas the size of the circle correlates with the number of paediatric study participants (small circle: <100 participants, medium circle: between 100 and 500 participants, large circle: >500 participants). The pooled estimate (black dot) of the pair of sensitivity (Se) and specificity (Sp) is surrounded by its 95% confidence region (closed curve with short dashes) and prediction region (closed curve with long dashes). The estimation of the SROC curve is based on the bivariate approach by Rutter and Gatsonis* [19].

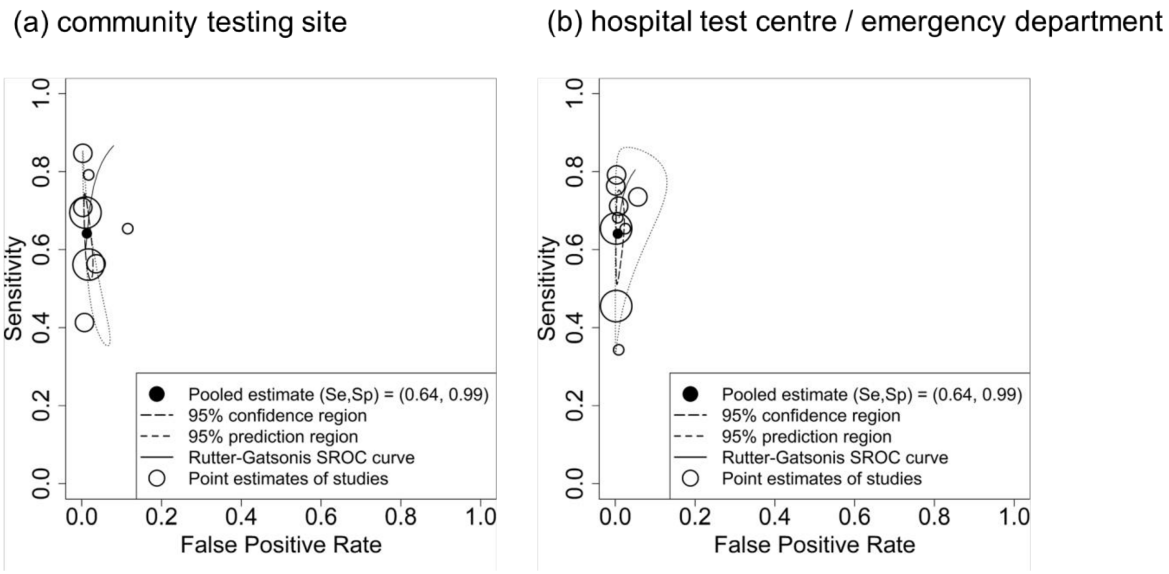

Figure S3: *Summary receiver operating characteristic (SROC) plot of sensitivity and specificity of antigen tests for diagnosis of current SARS-CoV-2 infections with respect to the setting.* (a) community testing site, (b) hospital test centre / emergency department. *Each circle represents the point estimate of an individual study, whereas the size of the circle correlates with the number of paediatric study participants (small circle: <100 participants, medium circle: between 100 and 500 participants, large circle: >500 participants). The pooled estimate (black dot) of the pair of sensitivity (Se) and specificity (Sp) is surrounded by its 95% confidence region (closed curve with short dashes) and prediction region (closed curve with long dashes). The estimation of the SROC curve is based on the bivariate approach by Rutter and Gatsonis* [19].

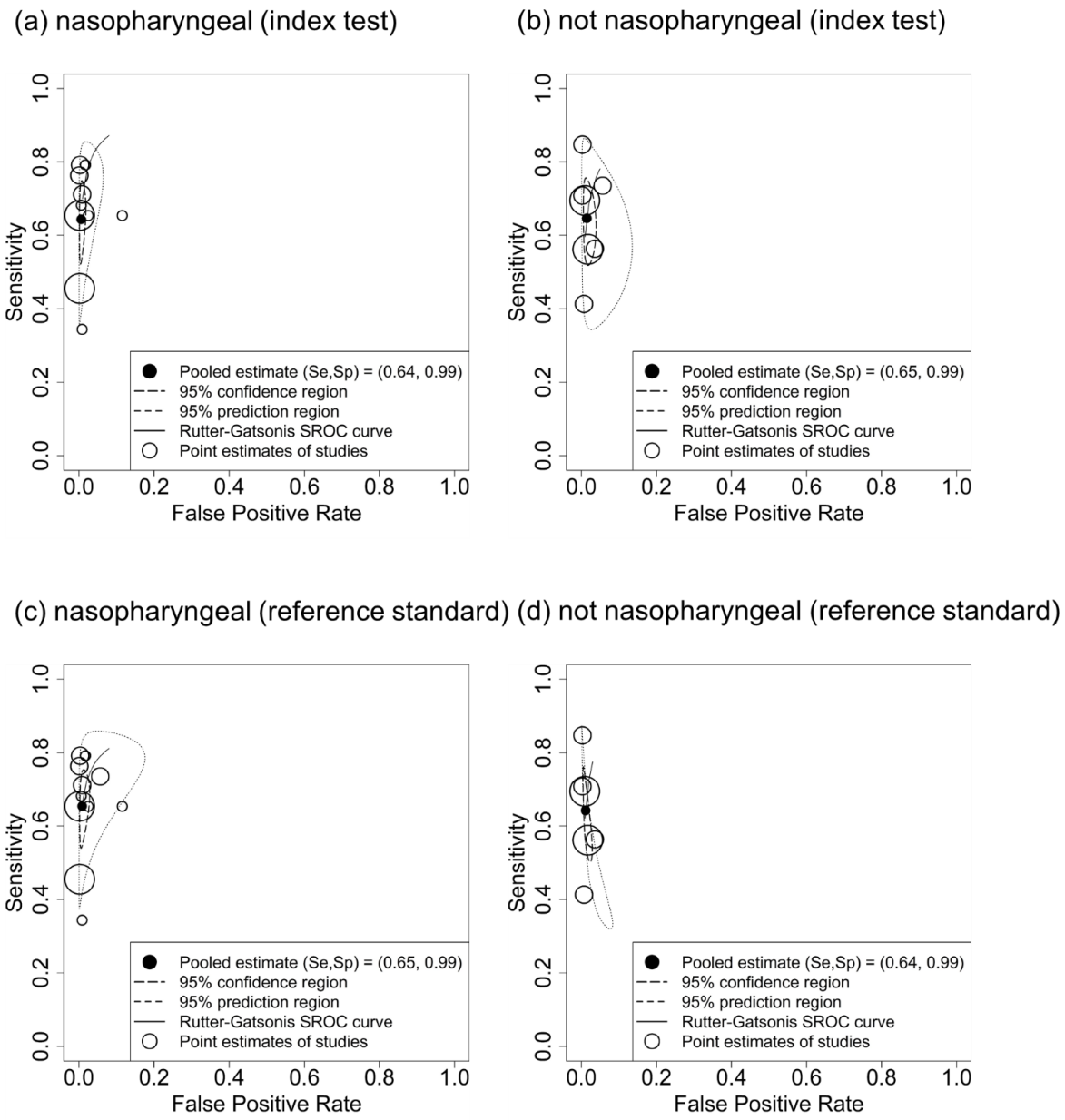

Figure S4: *Summary receiver operating characteristic (SROC) plot of sensitivity and specificity of antigen tests for diagnosis of current SARS-CoV-2 infections with respect to the sample type of index test (Ag test) and reference standard (RT-PCR). (a) nasopharyngeal (index test), (b) not nasopharyngeal (index test), (c) nasopharyngeal (reference standard), (d) not nasopharyngeal (reference standard). Each circle represents the point estimate of an individual study, whereas the size of the circle correlates with the number of paediatric study participants (small circle: <100 participants, medium circle: between 100 and 500 participants, large circle: >500 participants). The pooled estimate (black dot) of the pair of sensitivity (Se) and specificity (Sp) is surrounded by its 95% confidence region (closed curve with short dashes) and prediction region (closed curve with long dashes). The estimation of the SROC curve is based on the bivariate approach by Rutter and Gatsonis* [19].

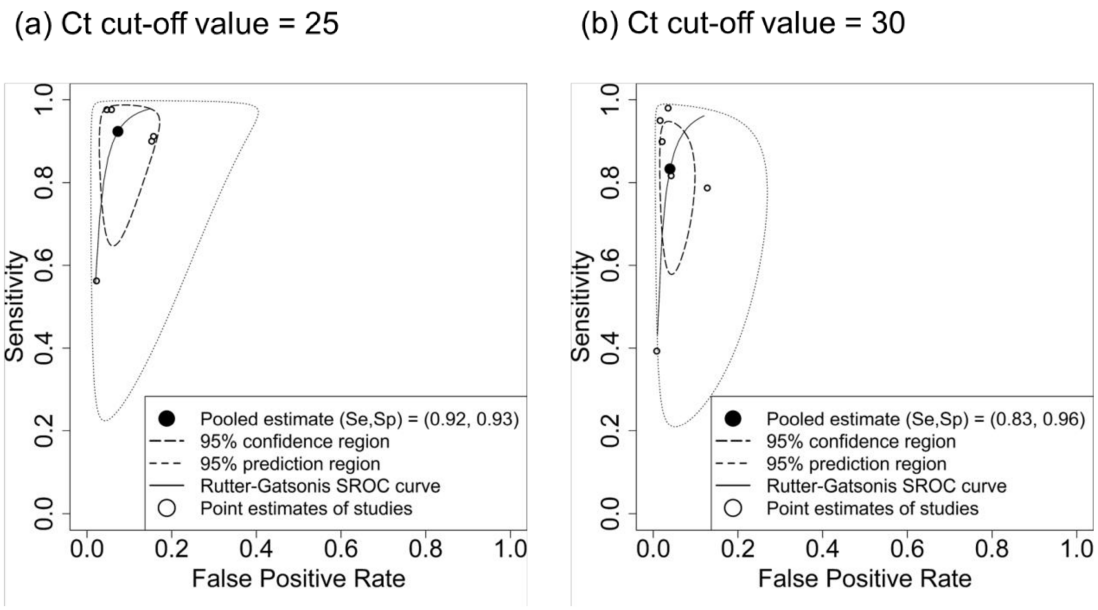

Figure S5: *Summary receiver operating characteristic (SROC) plot of sensitivity and specificity of antigen tests for diagnosis of current SARS-CoV-2 infections with respect to the chosen RT-PCR positivity threshold.* (a) Ct cut-off value = 25, (b) Ct cut-off value = 30. *Each circle represents the point estimate of an individual study, whereas the size of the circle correlates with the number of paediatric study participants (small circle: <100 participants, medium circle: between 100 and 500 participants, large circle: >500 participants). The pooled estimate (black dot) of the pair of sensitivity (Se) and specificity (Sp) is surrounded by its 95% confidence region (closed curve with short dashes) and prediction region (closed curve with long dashes). The estimation of the SROC curve is based on the bivariate approach by Rutter and Gatsonis* [19].

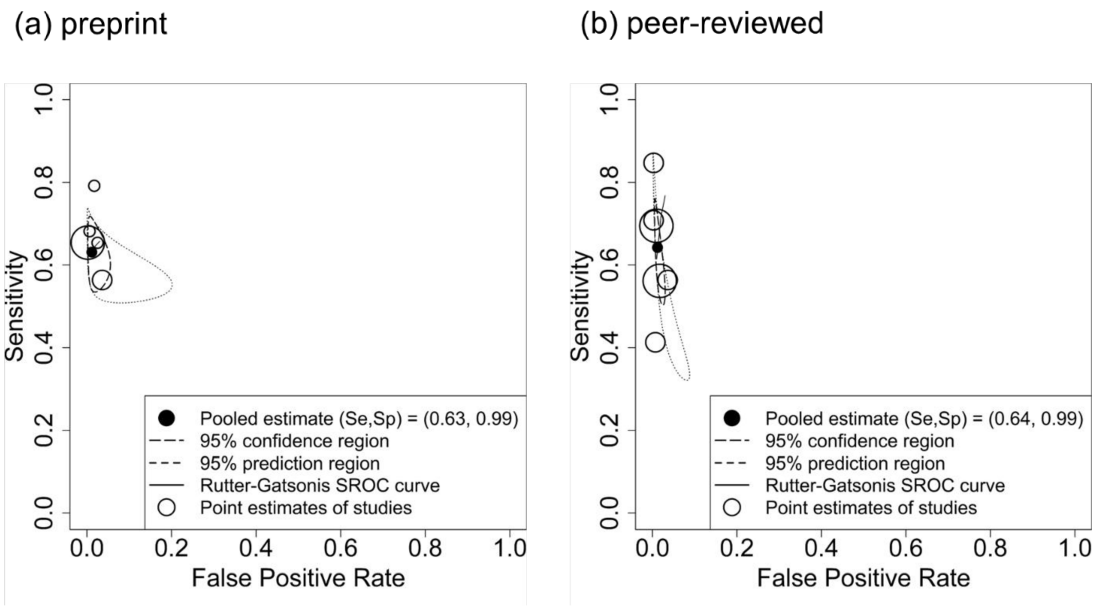

Figure S6: *Summary receiver operating characteristic (SROC) plot of sensitivity and specificity of antigen tests for diagnosis of current SARS-CoV-2 infections with respect to the publication status.* (a) preprint, (b) peer-reviewed. *Each circle represents the point estimate of an individual study, whereas the size of the circle correlates with the number of paediatric study participants (small circle: <100 participants, medium circle: between 100 and 500 participants, large circle: >500 participants). The pooled estimate (black dot) of the pair of sensitivity (Se) and specificity (Sp) is surrounded by its 95% confidence region (closed curve with short dashes) and prediction region (closed curve with long dashes). The estimation of the SROC curve is based on the bivariate approach by Rutter and Gatsonis* [19].

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Diagnostic accuracy of rapid point-of-care tests for diagnosis of current SARS-CoV-2 infections in children: A systematic review and meta-analysis

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Appendix 2: Supplementary methods

Author queries

For studies that did not fully meet the inclusion criteria for the population, index test and/or reference standard, we required that at least 80% of the paediatric (sub-)population matched the population we defined for this systematic review. Studies were excluded if the index test and the reference standard were performed in less than 80% of the paediatric study population. Besides journal articles, reports (including clinical study reports) that adhered to reporting standards such as STARD (Standards for Reporting of Diagnostic Accuracy Studies) [1] or recommendations given by government agencies [2,3] were considered eligible for inclusion. Studies that mentioned the inclusion of paediatric study participants without reporting any corresponding outcome data but otherwise met the eligibility criteria were initially included, and study authors were contacted and asked to provide such data. Further, if the study population's baseline characteristics included information on age, we estimated the proportion of paediatric study participants assuming ages of study participants following a normal distribution and the proportion of PCR-positive paediatric assuming no changes in the PCR positivity rate among age groups. We contacted authors if we estimated at least 10 PCR-positive paediatric study participants in the study population.

Details on the search strategy development and information retrieval process

One researcher performed analyses of simple word frequencies and keywords-in-contexts in R using the "quanteda" package [4]. Because of substantial differences between types of tests, separate test sets were used to identify candidate search terms for antigen tests and molecular tests, respectively. Test sets included 27 potentially relevant studies (irrespective of paediatric study participants) from the Cochrane Review by Dinnes et al. [5] and from a frequently updated website that lists DTA studies on antigen tests [6]. Due to a limited number of potentially relevant references addressing rapid molecular tests for point-of-care usage, the draft search strategy was supplemented by search terms derived from a conceptual approach. Furthermore, brand names of tests included in the Cochrane Review were added to increase sensitivity. The final search strategy achieved 100% completeness against the validation sets with ten studies and relevant references of five studies that

included paediatric participants identified via exploratory searches beforehand. Prior to execution, the search strategy was peer-reviewed by a senior information specialist following the Peer Review of Electronic Search Strategies (PRESS) Guideline statement [7].

We only searched for publications published after December 2019, as we were only interested in literature published after the emergence of SARS-CoV-2. Further, we limited our search to publications written in English or German. Since Embase and MEDLINE provided comprehensive search filters for SARS-CoV-2 related literature via Ovid, our concept addressing the target condition was not used in these two searches.

To acknowledge the unprecedented role of preprints in the rapid dissemination of SARS-CoV-2 related research, we also searched for relevant preprints. Due to the direct availability of full texts of preprints and to increase the efficiency of the information retrieval, a further concept addressing the target population was defined and used in addition to the standard search strategy for identifying potentially relevant preprints directly at the full-text level. We assumed that this approach allowed to increase the precision of the overall search without a relevant reduction of its comprehensiveness.

Endnote X9.3 was used for citation management. Due to the more specific separate search for preprints at full-text level, any preprint records identified from MEDLINE were removed. Duplicates were initially eliminated via Ovid's deduplication feature. After exporting all identified references from Ovid, duplicates were identified in R by comparing digital object identifiers (DOIs) of references from MEDLINE and Embase, and the Embase records of duplicates were removed. Remaining duplicates were manually removed in EndNote X9.3 and by using Endnote's "find duplicates" function. Further, records from ClinicalTrials.gov that were retrieved from the WHO's ICTRP website were removed since directly accessing ClinicalTrials.gov's registry data allows for a more comprehensive search for relevant studies.

Data extraction

At first, a standardized Excel spreadsheet was developed for data extraction. The spreadsheet was piloted before data extraction commenced. Extracted data included information on the general study characteristics, study participant characteristics, index test, reference standard, flow and timing, and reported outcomes. A complete list of data extraction items is presented in Table S2 of Appendix 1.

Meta-analyses

Summary estimates for sensitivity and specificity were derived as follows: if sufficient data was available and the level of heterogeneity allowed meaningful statistical pooling, bivariate meta-analysis with random effects following the approach by Reitsma et al [8–10] was performed. Otherwise, separate univariate meta-analysis was performed. The bivariate approach required a continuity correction to handle zero cells in 2x2 tables. Thus, in studies where zero events were observed in one of the four cells, a continuity correction was applied by adding 0.5 to all four cells.

Depending on the availability of suitable data, subgroup analyses were performed to assess variables that could have an impact on a test's diagnostic accuracy, such as the study participants' presence of symptoms prior to testing and the duration of symptoms prior to testing. The influence of the publication status (preprint vs. peer-reviewed article) was evaluated as well as subgroup analyses with respect to the type of test (antigen vs. molecular; most commonly used antigen tests), setting (community vs. hospital-based), sample type ((oro-) nasopharyngeal vs. anterior nasal for index test and reference standard, respectively), end-user (layperson (self-testing) vs. trained staff/health care worker), and RT-PCR cycle threshold (Ct) value (cut-off values of 25 and 30). Differences between subgroups were assessed within the bivariate model and tested for statistical significance using the likelihood ratio test between the standard model and the model, which includes the corresponding variable. In the case of few studies in a subgroup analysis, univariate analysis for sensitivity and specificity were performed as sensitivity analysis and results were reported if remarkable differences between bivariate and univariate analysis were observed.

All statistical analyses were performed using the statistical platform R version 4.1.0 [11]. Bivariate meta-analysis was performed, along with the construction of the corresponding figures, with the package "mada" [12], while univariate meta-analysis was performed with the package "meta" [13] and "PropCIs" [14]. 95% CIs were computed using the approach proposed by Wilson [15].

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Appendix 3: Search strategies

1) Bibliographic databases

MEDLINE

- Search interface: Ovid
- Segment: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 06, 2021>
- COVID-19 Ovid Filter for MEDLINE: https://ospguides.ovid.com/OSPguides/medline.htm
- Last search: 07/05/2021

#	Search
1	Point-of-Care Testing/
2	((molecular or antigen*) adj5 (test* or detect* or diagnos* or assay*)).ti,ab.
3	(nucleic acid or isothermal or crispr).mp. and (test* or detect* or diagnos* or assay*).ti,ab.
4	2 or 3
5	(rapid or fast or short* or quick*).ti,ab. or point of care.mp.
6	(id now or accula or xpert xpress or covid nudge or samba ii or binaxnow or covid-viro or panbio or veritor or nowcheck or biosynex or respi-strip or dart or espline or innova or strongstep or sofia or biocredit or standard q or standard f or bioeasy).mp.
7	1 or (4 and 5) or 6
8	7 and (english or german).lg.
9	limit 8 to yr="2020 -Current"
10	9 not (exp Animals/ not exp Humans/)
11	limit 10 to covid-19
12	remove duplicates from 11

Fujita-Rohwerder N, *et al. BMJ EBM* 2022;0:1–14. doi: 10.1136/bmjebm-2021-111828

Embase

- Search interface: Ovid
- Segment: Embase <1974 to 2021 May 06>
- COVID-19 Ovid Filter for Embase: https://ospguides.ovid.com/OSPguides/embase.htm
- Last search: 07/05/2021

#	Search
1	rapid test/
2	((molecular or antigen*) adj5 (test* or detect* or diagnos* or assay*)).ti,ab.
3	(nucleic acid or isothermal or crispr).mp. and (test* or detect* or diagnos* or assay*).ti,ab.
4	2 or 3
5	(rapid or fast or short* or quick*).ti,ab. or point of care.mp.
6	(id now or accula or xpert xpress or covid nudge or samba ii or binaxnow or covid-viro or panbio or veritor or nowcheck or biosynex or respi-strip or dart or espline or innova or strongstep or sofia or biocredit or standard q or standard f or bioeasy).mp.
7	1 or (4 and 5) or 6
8	7 and (english or german).lg.
9	limit 8 to yr="2020 -Current"
10	9 not (exp animal/ not exp human/)
11	limit 10 to covid-19
12	remove duplicates from 11
13	12 not medline.cr.
14	13 not (Conference Abstract or Conference Review or Editorial).pt.

Cochrane Library

- Search interface: Wiley
- Database segment: Cochrane Database of Systematic Reviews, Issue 5 of 12, May 2021
- Last Search: 07/05/2021

ID	Search
#1	[mh ^"Point-of-Care Testing"]
#2	((molecular or antigen*) NEAR/5 (test* or detect* or diagnos* or assay*)):ti,ab
#3	("nucleic acid" or isothermal or crispr) and (test* or detect* or diagnos* or assay*):ti,ab
#4	#2 or #3
#5	(rapid or fast or short* or quick*):ti,ab or "point of care"
#6	("id now" or accula or "xpert xpress" or "covid nudge" or "samba ii" or binaxnow or covid-viro or panbio or veritor or nowcheck or biosynex or respi-strip or dart or espline or innova or strongstep or sofia or biocredit or "standard q" or "standard f" or bioeasy):ti,ab,kw
#7	#1 or (#4 and #5) or #6
#8	[mh COVID-19]
#9	("COVID-19" or "SARS-CoV-2" or "SARS-2" or "SARS2" or "coronavir*" or "corona vir*" or "ncov19" or "ncov-19" or "2019-ncov"):ti,ab
#10	#8 or #9
#11	#7 and #10 with Cochrane Library publication date Between Jan 2020 and Jun 2021, in Cochrane Reviews

#12	#11 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))

International HTA Database

- Provided by the International Network of Agencies for Health Technology Assessment (INAHTA)
- https://database.inahta.org
- Search interface: Advanced Search
- Filter: Year 2020 to 2021
- Last Search 07/05/2021

Search
(("Point-of-Care Testing"[mh]) OR ((antigen* OR "nucleic acid" OR molecular OR isothermal OR crispr*) AND (diagnos* OR test* OR detect* OR assay*) AND (rapid OR fast OR short* OR quick* OR "point of care"))) AND (("SARS Virus"[mh]) OR ("Coronavirus Infections"[mh]) OR ("COVID-19" OR "SARS-CoV-2" OR "SARS-2" OR "SARS2" OR "coronavir*" OR "corona vir*" OR "ncov19" OR "ncov-19" OR "2019-ncov"))

2) Preprints

Europe PMC

- Search interface: https://europepmc.org
- Filter: Preprints
- Last search: 07/05/2021

Search
("COVID-19" OR "SARS-CoV-2" OR "SARS-2" OR "SARS2" OR "coronavir*" OR "corona vir*" OR "ncov19" OR "ncov-19" OR "2019-ncov") AND (TITLE:(((antigen* OR molecular OR "nucleic acid" OR crispr OR isothermal) AND (test* OR diagnos* OR detect* OR assay*) AND (rapid OR fast OR quick* OR short* OR "point of care")) OR ("id now" OR accula OR "xpert xpress" OR "covid nudge" OR "samba ii" OR binaxnow OR covid-viro OR panbio OR veritor OR nowcheck OR biosynex OR respi-strip OR dart OR espline OR innova OR strongstep OR sofia OR biocredit OR "standard q" OR "standard f" OR bioeasy)) OR ABSTRACT:(((antigen* OR molecular OR "nucleic acid" OR crispr OR isothermal) AND (test* OR diagnos* OR detect* OR assay*) AND (rapid OR fast OR quick* OR short* OR "point of care")) OR ("id now" OR accula OR "xpert xpress" OR "covid nudge" OR "samba ii" OR binaxnow OR covid-viro OR panbio OR veritor OR nowcheck OR biosynex OR respi-strip OR dart OR espline OR innova OR strongstep OR sofia OR biocredit OR "standard q" OR "standard f" OR bioeasy))

) AND (HAS_FT:n OR BODY:(child* OR pediatric OR paediatric)) AND SRC:PPR

3) Study registries

ClinicalTrials.gov

- Provided by the U.S. National Library of Medicine (NLM)
- Search interface: ClinicalTrials.gov Expert Search
- Filter: Eligibility Criteria: Age Group: Child (birth-17)
- Last Search 07/05/2021

Search
(antigen OR antigenic OR molecular OR nucleic acid OR isothermal OR crispr) AND (test OR diagnose OR detect OR assay) AND AREA[ConditionSearch] COVID-19 AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"

International Clinical Trials Registry Platform (ICTRP)

- Provided by the World Health Organisation (WHO)
- Due to access issues, download of COVID-19 trials repository from https://www.who.int/clinical-trials-registry-platform (accessed online 07/05/2021)

Use R (tidyverse package) to search for entries in column “Public title” or “Scientific title” which include:

> (antigen* OR molecular OR nucleic acid OR isothermal OR crispr) AND (test* OR diagnos* OR detect* OR assay*)

4) Further information sources

NICE Evidence Search

- Provided by the National Institute for Health and Care Excellence (NICE)
- https://www.evidence.nhs.uk/
- Filter: Evidence Type: Policy and Strategy; Date: From 01/01/2020 to 24/05/2021
- Last search: 24/05/2021

Search
COVID-19 rapid test

NICE Guidance

- Provided by the National Institute for Health and Care Excellence (NICE)
- Guidance and advice list
- Filter: Area of interest: Covid-19; Status: Published
- Last search: 24/05/2021

Foundation for Innovative New Diagnostics (FIND) Website

- https://www.finddx.org/test-directory/
    - Filter: Laboratory/Point-of-care = Point-of-care; FIND evaluation = Yes
- https://www.finddx.org/sarscov2-eval-antigen/
    - Table 1: Antigen(Ag)-detection RDTs undergoing evaluation
- Last search: 24/05/2021

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Appendix 4: Quality Assessment – Review-specific guidance to signaling questions of QUADAS-2 tool

DOMAIN 1: Patient selection

A: Risk of Bias

1) Was a consecutive or random sample of individuals enrolled?

Yes	If it is clear that all eligible individuals were asked to participate in the study within a certain recruitment period or if it is stated that the study enrolled a consecutive or random sample of eligible individuals.
No	If a different enrolment method (e.g. via convenience sampling) is described.
Unclear	If the enrolment is not described adequately.

2) Was a case-control design avoided?

Yes	If the study employed a cross-sectional or cohort study design.
No	Not applicable, as "No" would lead to an exclusion of the study.
Unclear	If the design of the study is not described clearly enough, so that a definite judgment cannot be made.

3) Did the study avoid inappropriate exclusions?

Yes	If most (≥90%) eligible individuals were included without unreasonable selection (see applicability).
No	If inappropriate exclusions (>10%) were made that cannot be justified by the test's instructions for use (IFU) (see applicability)
Unclear	If it is not clear whether inappropriate exclusions were made.

Could the selection of individuals have introduced bias?

Low	If all questions are answered "Yes".
High	If ≥ 1 question is answered "No".
Unclear	Either if all questions are answered "Unclear" or if ≥ 1 question is answered "Unclear", and ≥ 1 question is answered "Yes".

B. Concerns regarding applicability

Is there concern that the included individuals do not match the review question?

Low	If at least 80% of the included paediatric study participants are below the age of 18 and match the review question and no exclusions are made to adhere to intended use in IFU (e.g. due to symptom onset > 7 days)
High	If paediatric study participants are selected in accordance with the described intended use in the instructions for use (IFU), for example symptom onset ≤ 7 days. The presence of exclusions based on IFU does not increase the risk of bias but may affect applicability.
Unclear	If no sufficient information is provided to make a judgment.

DOMAIN 2: Index test

A: Risk of Bias

1) Were the index test results interpreted without knowledge of the results of the reference standard?

Yes	If blinding is explicitly stated or if it is clear that index test was carried out first and the result was read and reported prior to the availability of the result of the reference standard and the process of the read out was described.
No	If no blinding was implemented.
Unclear	If no sufficient information is provided to make a judgment.

2) If a threshold was used, was it pre-specified?

Yes	If a pre-specified threshold was reported in the methods section or if is stated that the test was performed according to the test's IFU.
No	If no pre-specified threshold was used.
Unclear	If no sufficient information is provided to make a judgment.

Could the conduct or interpretation of the index test have introduced bias?

Low	If all questions are answered "Yes".
High	If ≥ 1 question is answered "No".
Unclear	Either if all questions are answered "Unclear" or if ≥ 1 question is answered "Unclear", and ≥ 1 question is answered "Yes".

B. Concerns regarding applicability

Is there concern that the index test, its conduct, or interpretation differ from the review question?

Low	If the test kit was used and if the test was performed according to the IFU.
High	If the test kit was not used (different swab) or if deviations from the IFU occurred (e.g. usage outside defined temperature range or specimen handling not in accordance with IFU)
Unclear	If no sufficient information is provided to make a judgment.

DOMAIN 3: Reference Standard

A: Risk of Bias

1) Is the reference standard likely to correctly classify the target condition?

Yes	If a validated laboratory-based RT-PCR was used.
No	Not applicable, as "No" would lead to an exclusion of the study.
Unclear	If no sufficient information is provided to make a judgment.

2) Was the general threshold and any additional thresholds that were used pre-specified?

Yes	If all thresholds that were used are reported in the methods section or if is stated that the test was performed according to the laboratory's protocol or the manufacturer's IFU.
No	If no pre-specified threshold(s) was/were used.
Unclear	If no sufficient information is provided to make a judgment.

3) Were the reference standard results interpreted without knowledge of the results of the index test?

Yes	If blinding is explicitly stated.
No	If no blinding was implemented.
Unclear	If no sufficient information is provided to make a judgment.

Could the reference standard, its conduct, or its interpretation have introduced bias?

Low	If all questions are answered "Yes".
High	If ≥ 1 question is answered "No".
Unclear	Either if all questions are answered "Unclear" or if ≥ 1 question is answered "Unclear", and ≥ 1 question is answered "Yes".

B. Concerns regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Low	If a SARS-CoV-2 RT-PCR assay was used.
High	Not applicable.
Unclear	If it is not clear, whether a SARS-CoV-2 RT-PCR assay was used.

DOMAIN 4: Flow and timing

A: Risk of Bias

1) Was there an appropriate interval between index test(s) and reference standard?

Yes	If both samples are taken at the same time (concurrently or consecutively) or if it is clear that specimen collection occurred during the same participant encounter in an ambulatory setting.

No	If it is clear that both samples are not taken at the same time (time interval > 12 hours) or during one ambulatory visit.
Unclear	If no sufficient information is provided to make a judgment.

2) Did all study participants receive a reference standard?

Yes	If it is clear that all participants received a reference standard.
No	If it is clear that not all participants received a reference standard.
Unclear	If no sufficient information is provided to make a judgment.

3) Did study participants receive the same reference standard?

Yes	If all participants were tested with a RT-PCR assay.
No	Not applicable, as there is only one reference standard defined.
Unclear	If no sufficient information is provided to make a judgment.

4) Were all *study participants* included in the analysis?

Yes	If the number of enrolled participants matches the total number of included participants reported in the 2x2 table (for cohort studies with repeat testing over time: only initial test is included in the analysis)
No	If number of enrolled participants does not match total number in 2x2 table. "No" does not increase the risk of bias, if difference is ≤ 5 % and reasons for exclusion are reported such as missing data on symptom onset, missing clinical data, missing symptom data, inconclusive/missing index test/reference standard.
Unclear	If it is not possible to determine whether all participants were included in the analysis

Could the patient flow have introduced bias?

Low	If all questions are answered "Yes".
High	If ≥ 1 question is answered "No".
Unclear	Either if all questions are answered "Unclear" or if ≥ 1 question is answered "Unclear", and ≥ 1 question is answered "Yes".

FUNDING / CONFLICTS OF INTEREST (COI)

Independent evaluation?

Yes	If authors declare no COI and no financial support was provided from industry or other private sources.
No	If authors declare relevant COI and/or financial support was provided from industry or other private sources.
Unclear	If statement about funding and/or COI is missing.

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Appendix 5: List of excluded studies and reasons for exclusion

Ineligible Population

Basso D, Aita A, Padoan A, Cosma C, Navaglia F, Moz S, et al. Salivary SARS-CoV-2 antigen rapid detection: A prospective cohort study. Clin Chim Acta 2021;517:54–9. https://doi.org/10.1016/j.cca.2021.02.014.

Blairon L, Wilmet A, Beukinga I, Tré-Hardy M. Implementation of rapid SARS-CoV-2 antigenic testing in a laboratory without access to molecular methods: Experiences of a general hospital. J Clin Virol 2020;129:104472. https://doi.org/10.1016/j.jcv.2020.104472.

Bokelmann L, Nickel O, Maricic T, Pääbo S, Meyer M, Borte S, et al. Rapid, reliable, and cheap point-of-care bulk testing for SARS-CoV-2 by combining hybridization capture with improved colorimetric LAMP (Cap-iLAMP). MedRxiv 2020:2020.08.04.20168617. https://doi.org/10.1101/2020.08.04.20168617.

Bruzzone B, De Pace V, Caligiuri P, Ricucci V, Guarona G, Pennati BM, et al. Comparative diagnostic performance of rapid antigen detection tests for COVID-19 in a hospital setting. Int J Infect Dis 2021;107:215–8. https://doi.org/10.1016/j.ijid.2021.04.072.

Caruana G, Croxatto A, Kampouri E, Kritikos A, Opota O, Foerster M, et al. Implementing SARS-CoV-2 Rapid Antigen Testing in the Emergency Ward of a Swiss University Hospital: The INCREASE Study. Microorganisms 2021;9. https://doi.org/10.3390/microorganisms9040798.

Cheah PK, Ongkili DF, Zaharuddin FS, Hashim MI, Ho CV, Lee HG, et al. Discrepancy in Screening Performances of Different Rapid Test Kits for SARS-CoV-2; a Letter to Editor. Arch Acad Emerg Med 2021;9:e9.

Ciotti M, Nicolai E, Marcuccilli F, Bernardini S. Use of a rapid point-of-care molecular test in the triage of suspected COVID-19 cases. J Med Virol 2021;93:4088–9. https://doi.org/10.1002/jmv.26944.

Donato LJ, Trivedi VA, Stransky AM, Misra A, Pritt BS, Binnicker MJ, et al. Evaluation of the Cue Health point-of-care COVID-19 (SARS-CoV-2 nucleic acid amplification) test at a community drive through collection center. Diagn Microbiol Infect Dis 2021;100:115307. https://doi.org/10.1016/j.diagmicrobio.2020.115307.

Fenollar F, Bouam A, Ballouche M, Fuster L, Prudent E, Colson P, et al. Evaluation of the Panbio COVID-19 Rapid Antigen Detection Test Device for the Screening of Patients with COVID-19. J Clin Microbiol 2021;59. https://doi.org/10.1128/JCM.02589-20.

FIND Evaluation of Coris BioConcept COVID-19 Ag Respi-Strip, External Report, Version 1.2. 2020.

FIND Evaluation of Shenzhen Bioeasy Biotechnology Co. Ltd. 2019-nCoV Ag Rapid Test Kit (Fluorescence), External Report, Version 1.0. 2021.

FIND Evaluation of Abbott Panbio COVID-19 Ag Rapid Test Device (NASAL) External Report, Version 1.0. 2021.

FIND Evaluation of Fujirebio Inc. Espline SARS-CoV-2, External Report, Version 1.0. 2021.

FIND Evaluation of Bionote, Inc. NowCheck COVID-19 Ag Test, nasal swab, External Report, Version 1.0. 2021.

FIND Evaluation of SD Biosensor, Inc. STANDARD Q COVID-19 Ag Test, nasal swab, External Report, Version 2.0. 2021.

FIND Evaluation of Mologic Ltd, COVID 19 RAPID ANTIGEN TEST, External Report, Version 1.0. 2021.

FIND Evaluation of Edinburgh Genetics ActivXpress+ COVID-19 Antigen Complete Testing Kit, External Report, Version 1.0. 2021.

FIND Evaluation of Premier Medical Corporation Private Limited. Sure Status COVID-19 Card Test, External Report, Version 1.0. 2021.

García-Fiñana M, Hughes DM, Cheyne CP, Burnside G, Stockbridge M, Fowler TA, et al. Performance of the Innova SARS-CoV-2 Antigen Rapid Lateral Flow Test in the Liverpool Asymptomatic Testing Pilot. Rochester, NY: Social Science Research Network; 2021. https://doi.org/10.2139/ssrn.3798558.

Gupta A, Khurana S, Das R, Srigyan D, Singh A, Mittal A, et al. Rapid chromatographic immunoassay-based evaluation of COVID-19: A cross-sectional, diagnostic test accuracy study & its implications for COVID-19 management in India. Indian J Med Res 2021;153:126–31. https://doi.org/10.4103/ijmr.IJMR_3305_20.

Igloi Z, Velzing J, van Beek J, van de Vijver D, Aron G, Ensing R, et al. Clinical Evaluation of Roche SD Biosensor Rapid Antigen Test for SARS-CoV-2 in Municipal Health Service Testing Site, the Netherlands. Emerg Infect Dis 2021;27:1323–9. https://doi.org/10.3201/eid2705.204688.

Klein JAF, Krüger LJ, Tobian F, Gaeddert M, Lainati F, Schnitzler P, et al. Head-to-head performance comparison of self-collected nasal versus professional-collected nasopharyngeal swab for a WHO-listed SARS-CoV-2 antigen-detecting rapid diagnostic test. MedRxiv 2021:2021.03.17.21253076. https://doi.org/10.1101/2021.03.17.21253076.

Kohmer N, Toptan T, Pallas C, Karaca O, Pfeiffer A, Westhaus S, et al. The Comparative Clinical Performance of Four SARS-CoV-2 Rapid Antigen Tests and Their Correlation to Infectivity In Vitro. J Clin Med 2021;10. https://doi.org/10.3390/jcm10020328.

Krüger LJ, Gaeddert M, Tobian F, Lainati F, Gottschalk C, Klein J a. F, et al. Evaluation of the accuracy and ease-of-use of Abbott PanBio - A WHO emergency use listed, rapid, antigen-detecting point-of-care diagnostic test for SARS-CoV-2. MedRxiv 2020:2020.11.27.20239699. https://doi.org/10.1101/2020.11.27.20239699.

Krüger LJ, Gaeddert M, Tobian F, Lainati F, Gottschalk C, Klein JAF, et al. The Abbott PanBio WHO emergency use listed, rapid, antigen-detecting point-of-care diagnostic test for SARS-CoV-2—

Evaluation of the accuracy and ease-of-use. PLOS ONE 2021;16:e0247918. https://doi.org/10.1371/journal.pone.0247918.

Li J, Hu X, Wang X, Yang J, Zhang L, Deng Q, et al. A novel One-pot rapid diagnostic technology for COVID-19. Anal Chim Acta 2021;1154:338310. https://doi.org/10.1016/j.aca.2021.338310.

Lindner AK, Nikolai O, Kausch F, Wintel M, Hommes F, Gertler M, et al. Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected nasal swab versus professional-collected nasopharyngeal swab. Eur Respir J 2021;57:2003961. https://doi.org/10.1183/13993003.03961-2020.

Lindner AK, Nikolai O, Rohardt C, Burock S, Hülso C, Bölke A, et al. Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with professional-collected nasal versus nasopharyngeal swab. Eur Respir J 2021;57. https://doi.org/10.1183/13993003.04430-2020.

Mahmoud SA, Ibrahim E, Ganesan S, Thakre B, Teddy JG, Raheja P, et al. Evaluation of seven different rapid methods for nucleic acid detection of SARS-COV-2 virus. MedRxiv 2021:2021.04.15.21255533. https://doi.org/10.1101/2021.04.15.21255533.

Moran A, Beavis KG, Matushek SM, Ciaglia C, Francois N, Tesic V, et al. Detection of SARS-CoV-2 by Use of the Cepheid Xpert Xpress SARS-CoV-2 and Roche cobas SARS-CoV-2 Assays. J Clin Microbiol 2020;58. https://doi.org/10.1128/JCM.00772-20.

Nalumansi A, Lutalo T, Kayiwa J, Watera C, Balinandi S, Kiconco J, et al. Field evaluation of the performance of a SARS-CoV-2 antigen rapid diagnostic test in Uganda using nasopharyngeal samples. Int J Infect Dis 2021;104:282–6. https://doi.org/10.1016/j.ijid.2020.10.073.

Oh SM, Jeong H, Chang E, Choe PG, Kang CK, Park WB, et al. Clinical Application of the Standard Q COVID-19 Ag Test for the Detection of SARS-CoV-2 Infection. J Korean Med Sci 2021;36:e101. https://doi.org/10.3346/jkms.2021.36.e101.

Osmanodja B, Budde K, Zickler D, Naik MG, Hofmann J, Gertler M, et al. Diagnostic accuracy of a novel SARS-CoV-2 antigen-detecting rapid diagnostic test from standardized self-collected anterior nasal swabs. MedRxiv 2021:2021.04.20.21255797. https://doi.org/10.1101/2021.04.20.21255797.

Pekosz A, Parvu V, Li M, Andrews JC, Manabe YC, Kodsi S, et al. Antigen-Based Testing but Not Real-Time Polymerase Chain Reaction Correlates With Severe Acute Respiratory Syndrome Coronavirus 2 Viral Culture. Clin Infect Dis 2021. https://doi.org/10.1093/cid/ciaa1706.

Plebani M, Aita A, Cattelan AM, Bonfante F, Padoan A, Giaquinto C, et al. Frequent testing regimen based on salivary samples for an effective COVID-19 containment strategy. MedRxiv 2020:2020.10.13.20210013. https://doi.org/10.1101/2020.10.13.20210013.

Prado JAN del, Reyes AQ, Torre JBL, Loli RG, Olejua AP, Chirinos ERC, et al. Clinical validation of RCSMS: a rapid and sensitive CRISPR-Cas12a test for the molecular detection of SARS-CoV-2 from saliva. MedRxiv 2021:2021.04.26.21256081. https://doi.org/10.1101/2021.04.26.21256081.

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