Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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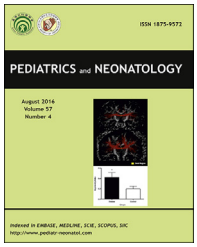

Original Article

Diagnostic accuracy of SARS-CoV-2 antigen test in the pediatric population: A systematic review and meta-analysis

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Background: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused the global coronavirus disease 2019 (COVID-19) pandemic. Rapid identification and isolation of patients infected with SARS-CoV-2 are critical methods for blocking COVID-19 transmission. The advantages of antigen tests, such as their relatively low cost and short turnaround time, can contribute to the prompt identification of infectious individuals. However, the diagnostic accuracy of antigen tests for COVID-19 in children remains inconclusive. This meta-analysis aimed to evaluate the diagnostic performance of antigen tests for SARS-CoV-2 in the pediatric population.

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Methods: We conducted a literature search for relevant studies in the PubMed, Embase, Google Scholar, and Biomed Central databases. Studies evaluating the diagnostic accuracy of antigen tests for SARS-CoV-2 in pediatric patients were included. In addition, we included studies that provided sufficient data to construct a 2 × 2 table on a per-patient basis. The final literature search was performed on October 10, 2021. Days after symptom onset, asymptomatic and symptomatic individuals may have been potential sources of heterogeneity. The overall sensitivity and specificity of the antigen tests were generated using a bivariate random-effects model.

Results: Five studies with 4400 participants were included. The meta-analysis of antigen tests generated a pooled sensitivity of 65.9% (95% CI: 52.8%—77.0%) and pooled specificity of 99.9% (95% CI: 98.9%—100.0%). A subgroup analysis of studies reporting antigen test data for symptomatic patients showed a pooled sensitivity of 64.5% and a pooled specificity of 99.7%. The subgroup analysis of studies that included 881 asymptomatic participants generated a pooled sensitivity of 48.4% and a pooled specificity of 99.5%.

Conclusion: Antigen tests exhibit moderate sensitivity and high specificity for detecting SARS-CoV-2 in children. Antigen tests might have moderate sensitivity for detecting SARS-CoV-2 in symptomatic children, and serial testing might effectively prevent further SARS-CoV-2 transmission.

1. Introduction

The spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused the global coronavirus disease 2019 (COVID-19) pandemic. It is estimated that at least 50% of patients with COVID-19 contracted the virus from asymptomatic people.[1] To break the SARS-CoV-2 transmission chain, testing infected individuals and tracing and quarantining their contacts have been used as a major nonpharmaceutical intervention.[2] Rapid identification and isolation of infectious individuals with SARS-CoV-2 are critical methods to block COVID-19 community transmission. Approximately 40% of infected individuals with high viral loads may be asymptomatic.[3] The World Health Organization and Centers for Disease Control and Prevention have implemented reverse-transcription polymerase chain reaction (RT-PCR) technology as the standard diagnostic assay for SARS-CoV-2 detection. RT-PCR has a high sensitivity for SARS-CoV-2.[4] Despite its high sensitivity, RT-PCR has disadvantages, including the necessity of professional lab expertise, costly reagents, and centralized equipment. Therefore, antigen tests that detect viral proteins of SARS-CoV-2 in respiratory samples have been developed.[5] Antigen tests can identify individuals with COVID-19 who are highly contagious, namely those whose viral load is likely to be high. Antigen tests have received the U.S. Food and Drug Administration Emergency Use Authorization for use in asymptomatic and symptomatic individuals.[6]

The advantages of antigen tests, such as their relatively low cost and short turnaround time, contribute to the prompt identification of infectious individuals. RT-PCR testing should be considered after negative antigen test results in symptomatic individuals and after positive antigen test results in asymptomatic individuals.[7] The SARS-CoV-2 viral loads are significantly lower in children than in adults. This could influence the lower sensitivity of antigen tests in the pediatric population.[8] Studies that were carried out to evaluate the COVID-19 antigen test in the adult population have reported a sensitivity of approximately 80.4% in the early disease phase. Nevertheless, there is insufficient evidence regarding the diagnostic accuracy of antigen tests in the pediatric population. Moreover, the sensitivity was higher in adults than in pediatric patients.[9] RT-PCR for SARS-CoV-2 is the gold standard for COVID-19 diagnosis. Despite its high sensitivity and specificity, RT-PCR has several disadvantages, including the requirement of professional lab expertise, lengthy time demands, and centralized equipment. Serological testing for SARS-CoV-2 is a diagnostic tool for COVID-19 infection. Serological testing can provide detailed information on the disease prevalence in a population. However, higher levels of antibodies were observed 7—10 days after infection. Hence, serological testing is not suitable for the detection of early SARS-CoV-2 infection.[4]

The diagnostic accuracy of antigen tests for COVID-19 in infants, children, and adolescents remains inconclusive. Therefore, this meta-analysis aimed to evaluate the accuracy of antigen tests for detecting SARS-CoV-2 in the pediatric population.

2. Methods

2.1. Literature search strategy

The study was reported according to "Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement."[10]

We conducted a literature search for relevant studies in the PubMed, Embase, Google Scholar, and Biomed Central

databases. A literature search was conducted using multiple search terms, including (COVID-19 or severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2) AND (Antigen—Antibody Reactions or antigen test or antigen testing or SARS-CoV-2 antigen test) AND (adolescent, child, pediatric, infant, newborn). In addition, a combination of free text and Medical Subject Headings terms was used to identify relevant studies. Our search strategy is detailed in Supplemental Material 1.

2.2. Inclusion and exclusion criteria

Studies evaluating the diagnostic accuracy of antigen tests for SARS-CoV-2 with reference standards in participants with suspected SARS-CoV-2 infection in the pediatric population were included; however, review articles were excluded. Respiratory specimens were collected from both symptomatic and asymptomatic individuals. Studies that defined RT-PCR as the reference standard were included. A literature search was conducted without time restrictions. Studies that provided sufficient data to construct a 2×2 table on a per-patient basis were included. Case reports, case series, proposals, protocols, conference abstracts, in-house tests, and print articles were excluded. Preprint articles need to be evaluated and not used to guide clinical practice. The final literature search was performed on October 10, 2021. One reviewer initially screened the titles and abstracts of potentially eligible studies. After eliminating irrelevant studies, two reviewers independently examined the full-text articles that met the inclusion criteria. Disagreements between reviewers were resolved through discussion.

2.3. Quality assessment

The quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[11] Antigen tests for the SARS-CoV-2 virus were the index tests, and RT-PCR test results for SARS-CoV-2 were the reference standards. QUADAS-2 comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain included questions that allowed for the assessment of the risk of bias. The quality of the diagnostic test comprises the risk of bias and applicability of the study. A study is considered high quality if each domain in the study exhibits low risk of bias.

2.4. Statistical analysis

We extracted data on true positives, true negatives, false positives, and false negatives from each included study to construct 2×2 tables to calculate the pooled sensitivity, specificity, and diagnostic odds ratio (DOR). If 2×2 tables could not be extracted from the main text, we searched for additional information in the Supplementary Material. The sensitivity of a test is defined as the proportion of individuals with the target condition correctly identified as having the condition. In contrast, the specificity of a test is the proportion of individuals without the target condition correctly identified as not having the condition.[12] The DOR is defined as the ratio of the proportion that tests positive among those with the target condition compared to the proportion that tests positive among those without the target condition. It was calculated as sensitivity/(1 − sensitivity) over (1 − specificity)/specificity. DOR has the advantage of being independent of the disease prevalence. A diagnostic test was considered discriminative if its DOR was > 1.[13]

We conducted a meta-analysis using a bivariate random-effects model to generate a summary of the sensitivity, specificity, and DOR on a per-patient basis. We also plotted a summary receiver operating characteristic (SROC) curve to determine the overall diagnostic performance of the index tests. The closer the curve approaches the upper-left corner, the higher the overall performance.[14] A perfect test has an area under the curve (AUC) of 1. The AUC of an excellent test was $\geq$0.97. An AUC of 0.93—0.96 is considered highly satisfactory, and an AUC of 0.75—0.92 is satisfactory.[15] Possible causes of heterogeneity between studies were explored through pre-specified subgroup analysis, which included days after symptom onset, asymptomatic participants, and symptomatic individuals. Summary estimates, including pooled sensitivity, specificity, and DOR, were generated with associated 95% confidence intervals (CIs). All analyses were performed using MetaDiSc version 1.4 and MetaDTA software.[16,17] A p-value of <0.05 was considered statistically significant.

3. Results

Five studies with 4400 participants were retrieved.[18—22] Fig. 1 depicts the literature search process, and Table 1 presents the detailed characteristics of the studies. Four studies in the meta-analysis used a prospective study design, and four studies enrolled participants in the hospitals.[18—21] One study evaluated the diagnostic performance of antigen tests with anterior nasal swab specimens,[20] four assessed the accuracy of antigen tests with nasopharyngeal swab specimens,[18,19,21,22] two provided cycle threshold (Ct) values of RT-PCR tests,[19,21] and two reported cut-off values of Ct.[20,21] Our study evaluated the Panbio COVID-19 Ag Rapid Test Device and the BinaxNOW COVID-19 Ag card. Both antigen tests are membrane-based immunoassays (immunochromatography) from Abbott for the detection of the nucleocapsid protein of SARS-CoV-2.[23,24] The meta-analysis of antigen tests generated a pooled sensitivity of 65.9% (95% CI: 52.8%—77.0%) and a pooled specificity of 99.9% (95% CI: 98.9%—100.0%) (Fig. 2). The meta-analysis also presented a pooled DOR for antigen tests of 2097.93 (95% CI: 122.12—36,040.41), showing the discriminative power of the antigen test. The AUC of the SROC curve for antigen tests was 0.99, indicating that antigen tests might be suitable for diagnosing COVID-19. Supplemental Material 2 presents the SROC curve for SARS-CoV-2 antigen tests from the included studies.

3.1. Quality assessment

In our meta-analysis, we applied QUADAS-2, which has four domains to evaluate the quality of the studies. Regarding patient selection, no study enrolled patients randomly or consecutively; all studies avoided a case—control study

design, which might have overestimated diagnostic accuracy. On the basis of the rules for this domain, all studies were judged to have an unclear risk of bias in the patient selection domain. All studies recorded that index tests were interpreted without knowledge of the results of the reference standard. All studies included in the meta-analysis were judged to have a low risk of bias in the index domain. Regarding the reference standard, four studies indicated that the reference standard likely correctly classified the target condition.[18,19,21,22] Regarding the flow and timing domain, four studies demonstrated that all patients received a reference standard.[18,19,21,22] Three studies indicated that all patients were included in the analysis.[19,21,22] Three studies were judged to have a low risk of bias in the flow and timing domain.[19,21,22] Concerning applicability, patient selection, index tests, and reference standards of the studies in our meta-analysis matched our review title.-Fig. 3 shows the overall quality of the studies included in the meta-analysis. Supplemental Material 3 presents the quality of individual studies. Supplemental Material 4 presents the statistical data of the studies included in the meta-analysis.

3.2. Investigation of heterogeneity

Specimen types and duration from symptom onset to specimen collection could represent sources of heterogeneity in the meta-analysis. Subgroup analyses were performed to identify sources of heterogeneity. The I^2 index represents heterogeneity across studies, with values of 25%, 50%, and 75% representing low, moderate, and high levels of heterogeneity, respectively.[25] Four studies with

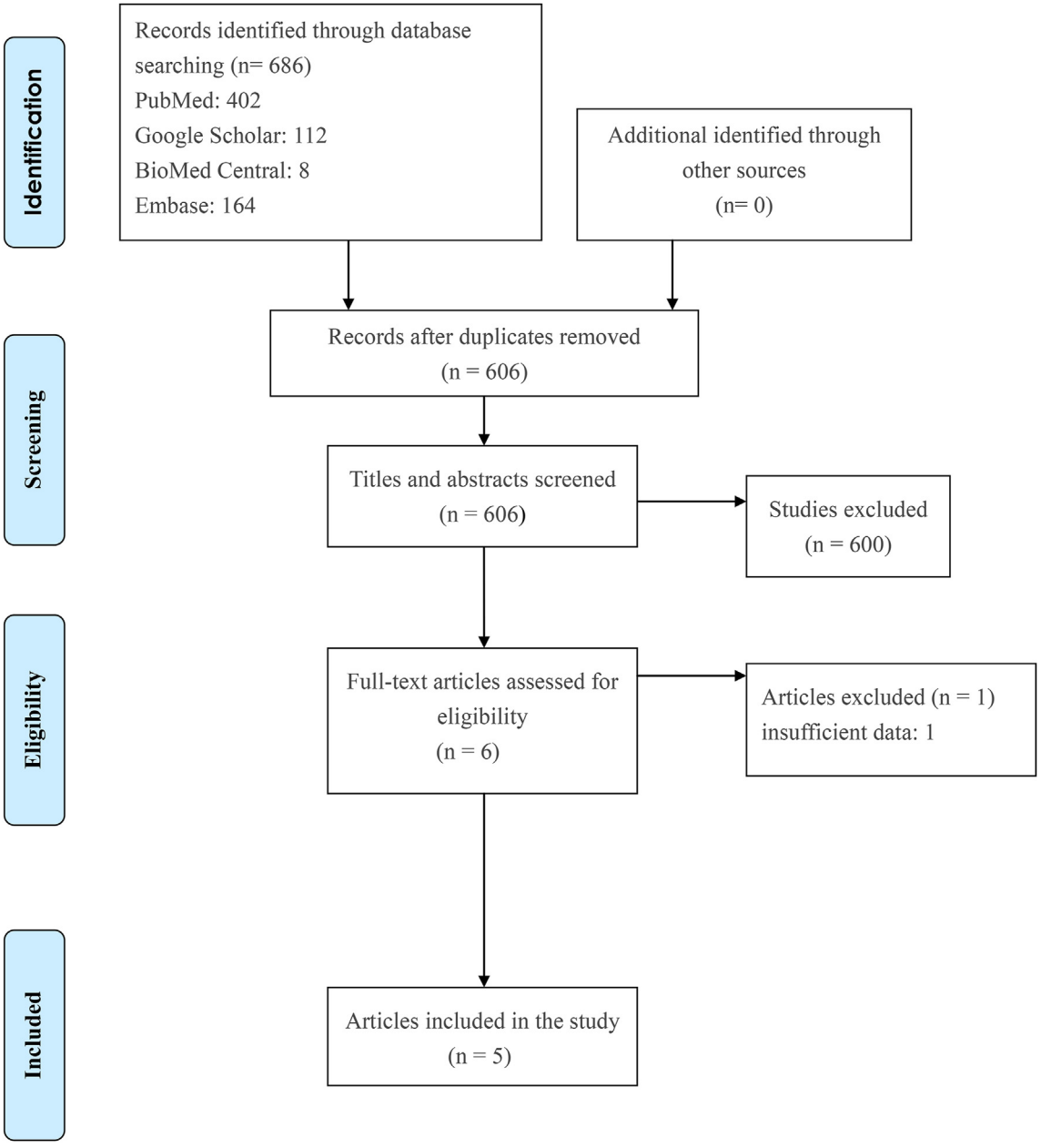

Figure 1 Flowchart of literature search.

Table 1 Characteristics of studies.

Study	Study design	Testing Site	Patient population	Prevalence (%)	Participants (total/data extraction)	Age median (range)	Days post symptom onset median (range)	Specimen type	Index test	Reference standard	Ct value median (range)	RT-PCR threshold value (Ct)
L'Huillier AG 2021	prospective	pediatric testing center in a hospital	asymptomatic and symptomatic	NA	(885/822)[a] symptomatic: 533 asymptomatic: 289	11.8 (9.0—14.3, ±IQR)[c]	2 (1.0—3.0, ±IQR)[c]	nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device	RT-PCR	NA	NA
Eleftheriou I 2021	prospective	a hospital	hospitalized children	6.86	(744/744)	7.7 (1.4—13.2)	2 (0.5—8)	nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device	RT-PCR	20.1 (patients with positive antigen test results)	NA
Sood N 2021	prospective	walk-up testing site	asymptomatic and symptomatic	NA	(783/774)[b] symptomatic: 182 asymptomatic: 592	5—17	NA	anterior nasal swab	BinaxNOW COVID-19 Ag card	RT-PCR	NA	40
González-Donapetry P 2021	prospective	pediatric emergency department of a hospital	symptomatic	4.1	(440/440)	3 (1—7, ±IQR)[c]	1 (1—3, ±IQR)[c] (0—7, range)	nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device	RT-PCR (nucleocapsid and envelope genes)	<34 (patients with positive antigen test results)	40
Villaverde S 2021	retrospective	emergency departments of 7 centers	symptomatic	5	(1620/1620)	0—16	≦5	nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device	RT-PCR (E and RdRp genes)	NA	NA

COVID-19 = coronavirus disease 2019; CT = cycle threshold; IQR: interquartile range; NA = not available; RT-PCR = reverse transcription polymerase chain reaction.

[a] Study participants were excluded owing to refused RT-PCR, refused antigen test, invalid antigen test, unreported antigen test, and patient screening error.

[b] Study participants were excluded owing to refused antigen test and inconclusive results.

[c] The numbers indicate IQR.

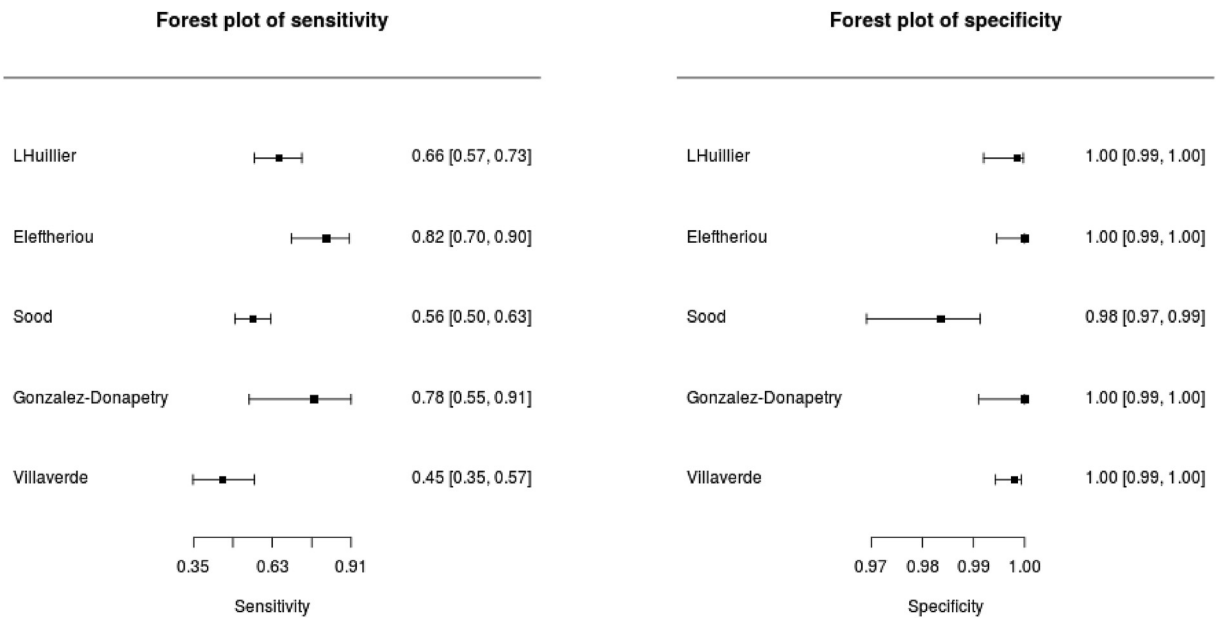

Figure 2 The meta-analysis for antigen tests generated a pooled sensitivity of 65.9% (95% CI: 52.8%—77.0%) and pooled specificity of 99.9% (95% CI: 98.9%—100.0%).

3626 patients reported the accuracy of antigen tests using nasopharyngeal swab specimens.[18,19,21,22] The meta-analysis produced a pooled sensitivity of 68.3% (95% CI: 51.8%—81.2%; $I^2 = 85.7\%$) and a pooled specificity of 99.9% (95% CI: 99.6%—100.0%; $I^2 = 0\%$). According to the data of antigen tests for symptomatic patients, we performed a subgroup analysis of four studies that reported outcomes for 2775 symptomatic participants.[18,20–22] This analysis generated a pooled sensitivity of 64.5% (95% CI: 51.4%—75.8%; $I^2 = 80.8\%$) and pooled specificity of 99.7% (95% CI: 99.8%—100.0%; $I^2 = 82.5\%$). The subgroup analysis of two studies that included 881 asymptomatic participants generated a pooled sensitivity of 48.4% (95% CI: 38.5%—58.4%; $I^2 = 0\%$) and pooled specificity of 99.5% (95% CI: 95.6%—100.0%; $I^2 = 78.0\%$).[18,20] This indicates that antigen tests might have lower sensitivity in detecting COVID-19 among asymptomatic participants. The subgroup analysis for two studies that included 1214 participants and used a Ct cutoff value of 40 generated a pooled sensitivity of 66.2% (95% CI: 45.9%—81.9%; $I^2 = 70.8\%$) and a pooled specificity of 99.8% (95% CI: 86.1%—100.0%; $I^2 = 90.3\%$).[20,21] The subgroup analysis for two studies that enrolled 2060 symptomatic patients within seven days after disease onset generated a pooled sensitivity of 60.1% (95% CI: 34.6%—81.2%; $I^2 = 84.4\%$) and a pooled specificity of 99.9% (95% CI: 98.6%—100%; $I^2 = 31.1\%$). The subgroup analysis for four studies that evaluated Panbio COVID-19 Ag Rapid Test Device with 3626 participants generated a pooled sensitivity

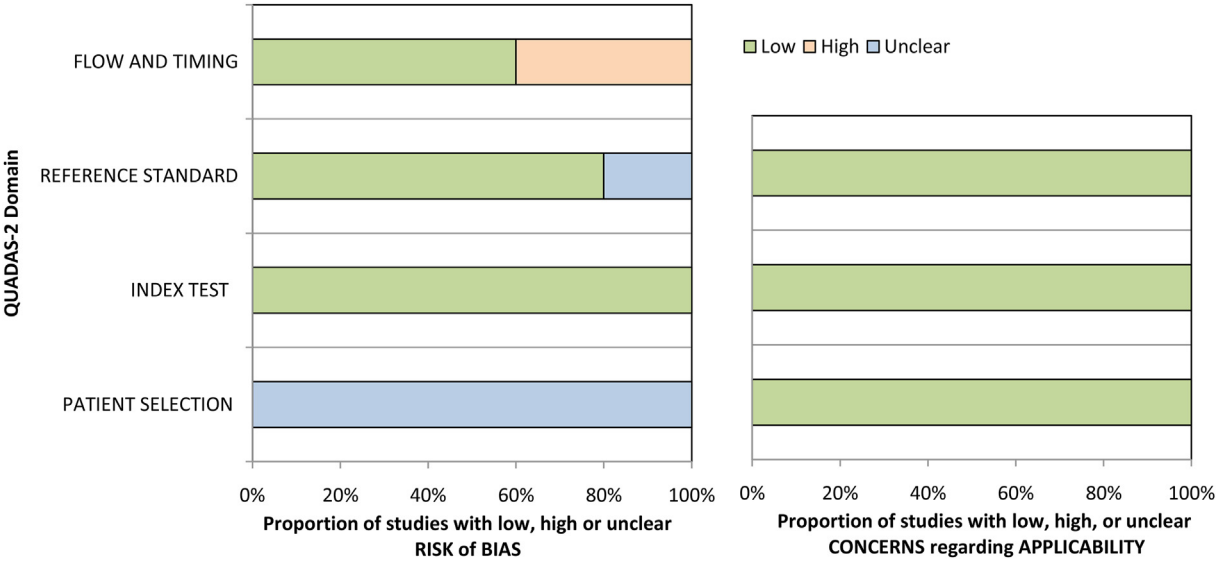

Figure 3 verall quality of included studies.

Table 2 Diagnostic accuracy of antigen tests based on subgroup analyses.

Subgroup	Number of studies	Number of patients	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	I^2 (%)
Nasopharyngeal specimen	4	3626	68.3 (51.8%–81.2%)	99.9 (99.6%–100.0%)	85.7
Symptomatic patients	4	2775	64.5 (51.4%–75.8%)	99.7 (99.8%–100.0%)	80.8
Symptom onset within 7 days	2	2060	60.1 (34.6%–81.2%)	99.9 (98.6%–100.0%)	84.4
Asymptomatic patients	2	881	48.4 (38.5%–58.4%)	99.5 (95.6%–100.0%)	0
Index test (Panbio COVID-19 Ag Rapid Test Device)	4	3626	68.3 (51.8%–81.2%)	99.9 (99.6%–100.0%)	85.7
Ct cutoff value of 40	2	1214	66.2 (45.9%–81.9%)	99.8 (86.0%–100.0%)	70.8

Ct: cycle threshold; CI: confidence interval.

of 68.3% (95% CI: 51.8%–81.2%; $I^2 = 85.7\%$) and a pooled specificity of 99.9% (95% CI: 99.6%–100%; $I^2 = 9.2\%$). Table 2 presents the diagnostic accuracy of the antigen tests based on subgroup analyses.

4. Discussion

Our major findings indicate that antigen tests have moderate sensitivity and high specificity for detecting SARS-CoV-2 in the pediatric population. If a test (in this case, an antigen test) has high specificity and yields a positive result, a clinician can be certain that the disease (in this case, COVID-19) is present.[26] Antibody testing (IgM and IgG) has promising sensitivity (0.66–0.97) for COVID-19.[27] Moreover, higher antibody levels were found to occur in the second week after symptom onset. Antibody testing is crucial for patients with mild-to-moderate illness who may present late, beyond the first two weeks after symptom onset. The antibody levels began to increase from the second week of symptom onset. Antibody testing also plays a crucial role in understanding the seroprevalence of COVID-19 in the community and identifying individuals immunoreactive against SARS-CoV-2.[28] RT-PCR is the standard diagnostic tool for SARS-CoV-2 detection. False-negative RT-PCR results mainly occurred because of inappropriate specimen collection timing in relation to symptom onset and deficiency in the sampling technique.[28] Symptomatic patients should undergo antigen testing and consider retesting if they have a negative antigen test result, particularly if they have a high pretest probability of SARS-CoV-2 infection. Asymptomatic individuals with known exposure to SARS-CoV-2 are recommended to undergo antigen testing within 5–7 days after exposure. If the antigen test result is negative, these asymptomatic individuals are recommended to undergo testing again two days later.[29]

Children were less frequently symptomatic, had fewer symptoms, and had a shorter duration of symptoms than adults.[30] The viral loads of children with asymptomatic SARS-CoV-2 infection or mild disease were slightly lower than those of adults with similarly mild SARS-CoV-2 infections. Although symptomatic children have higher viral loads than asymptomatic children, viral loads have not been predictive of disease severity in children.[31] Based on the subgroup analysis of our meta-analysis, antigen tests might have moderate sensitivity in detecting SARS-CoV-2 in symptomatic pediatric patients. In another subgroup analysis of studies involving asymptomatic pediatric participants, antigen tests showed lower sensitivity for detecting SARS-CoV-2 in the asymptomatic pediatric population. The current meta-analysis provided evidence of the moderate sensitivity of antigen tests in identifying symptomatic individuals in the pediatric population. Although the subgroup analysis for studies that used a Ct cut-off <25 could not be performed, one study reported that the sensitivity of the antigen test for SARS-CoV-2 with a Ct cut-off <25 was 93.8% (15/16).[20]

The average viral load was lower in the pediatric population than in the adult population, and the lowered viral load could impact SARS-CoV-2 transmission and the sensitivity of the antigen tests in children. This could cause a lower sensitivity of antigen tests in the pediatric population.[32] A retrospective cross-sectional cohort study reported that SARS-CoV-2 viral load increases with age, which could cause lower sensitivity of antigen tests in the pediatric population. Furthermore, SARS-CoV-2 antigen tests have lower sensitivity in children than in adults.[33] viral load is the most critical factor determining the sensitivity of antigen test for SARS-CoV-2.[34] Serial testing might be one of the strategies to compensate for the lower sensitivity antigen test in children. A one-time antigen test may not be effective for identifying asymptomatic children. Hence, serial testing might detect infections in children who subsequently develop high viral loads.[20] Moreover, effective COVID-19 screening depends mainly on the frequency of testing and rapid turnaround time and is only slightly improved by test sensitivity.[35]

Antigen tests could increase the overall COVID-19 testing capacity and have the advantages of shorter turnaround times and lower costs.[36] Antigen tests are most likely to have high performance in patients with high viral loads (Ct values ≤ 25), which usually appear in the presymptomatic (1–3 days before symptom onset) and early symptomatic (within the first 5–7 days of illness) phases of COVID-19.[37]

Antigen testing has evolved recently. For example, the sensitivity of the SARS-CoV-2 antigen test with a self-collected nasal swab is comparable with that of a professional-collected nasopharyngeal swab.[38] Sensitivity of antigen test with self-testing was 82.5%, whereas the sensitivity with professional-sampled antigen test was 85.0%.[38] Patients suspected of COVID-19 may be able to

perform the antigen test and test by themselves.[38] To minimize false negatives of antigen tests, the negative specimens of antigen tests could be retested using RT-PCR.[39] Dinnes et al. reported that there are proposals for repeated use of antigen tests in asymptomatic children; however, they found no data or studies evaluating the accuracy of any of these serial screening strategies.[40] Our study evaluated the diagnostic accuracy of COVID-19 antigen tests for children, including asymptomatic children.

Although this meta-analysis demonstrated that antigen tests had moderate sensitivity for detecting SARS-CoV-2 in the pediatric population, our study had some limitations. The Ct cut-off values of the studies in the meta-analysis were limited. The Ct values of SARS-CoV-2 infected individuals were limited. Statistical data of antigen tests stratified by Ct cut-off values were limited. Furthermore, no study in the meta-analysis had information on the SARS-CoV-2 variants. Studies in the meta-analysis discussed a limited number of antigen test products, and the meta-analysis outcomes may not be generalizable to other test kits. Few studies in the meta-analysis discussed the accuracy of antigen tests stratified by Ct values.

In conclusion, our major findings indicate that antigen tests have moderate sensitivity in detecting SARS-CoV-2 in infants, children, and adolescents. However, antigen tests are less sensitive for detecting SARS-CoV-2 in asymptomatic pediatric patients with COVID-19. Therefore, further studies that calculate the accuracy of antigen tests stratified by Ct values and involve more manufacturers are required to improve the understanding of the applicability of antigen tests for SARS-CoV-2 detection.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.07.012.