Evaluation of the diagnostic accuracy of COVID-19 antigen tests: A systematic review and meta-analysis

Yuan-Hung Wang[a,b], Chia-Chang Wu[c,d,e], Chyi-Huey Bai[f], Shou-Cheng Lu[g], Yi-Ping Yang[h], Yi-Ying Lin[h], Wei-Yi Lai[h], Tzu-Wei Lin[h], Ying-Chun Jheng[h,*], Ming-Cheng Lee[i,*], Cheng-Chieh Chen[a,j,*]

[a]Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [b]Department of Medical Research, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC; [c]Department of Urology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [d]Department of Urology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC; [e]TMU Research Center of Urology and Kidney (TMU-RCUK), Taipei Medical University, Taipei, Taiwan, ROC; [f]Department of Public Health, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC; [g]Department of Laboratory Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC; [h]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan, ROC.; [i]Department of Medicine, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [j]Department of Pathology and Laboratory Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, ROC

Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic continues to affect countries worldwide. To inhibit the transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), testing of patients, contact tracing, and quarantine of their close contacts have been used as major nonpharmaceutical interventions. The advantages of antigen tests, such as low cost and rapid turnaround, may allow for the rapid identification of larger numbers of infectious persons. This meta-analysis aimed to evaluate the diagnostic accuracy of antigen tests for SARS-CoV-2.

Methods: We searched PubMed, Embase, Cochrane Library, and Biomed Central databases from inception to January 2, 2021. Studies evaluating the diagnostic accuracy of antigen testing for SARS-CoV-2 with reference standards were included. We included studies that provided sufficient data to construct a 2 × 2 table on a per-patient basis. Only articles in English were reviewed. Summary sensitivity and specificity for antigen tests were generated using a random-effects model.

Results: Fourteen studies with 8624 participants were included. The meta-analysis for antigen testing generated a pooled sensitivity of 79% (95% CI, 66%-88%; 14 studies, 8624 patients) and a pooled specificity of 100% (95% CI, 99%-100%; 14 studies, 8624 patients). The subgroup analysis of studies that reported specimen collection within 7 days after symptom onset showed a pooled sensitivity of 95% (95% CI, 78%-99%; four studies, 1342 patients) and pooled specificity of 100% (95% CI, 97%-100%; four studies, 1342 patients). Regarding the applicability, the patient selection, index tests, and reference standards of studies in our meta-analysis matched the review title.

Conclusion: Antigen tests have moderate sensitivity and high specificity for the detection of SARS-CoV-2. Antigen tests might have a higher sensitivity in detecting SARS-CoV-2 within 7 days after symptom onset. Based on our findings, antigen testing might be an effective method for identifying contagious individuals to block SARS-CoV-2 transmission.

Keywords: COVID-19; COVID-19 testing; Meta-analysis; SARS-CoV-2; Sensitivity and specificity

**Address correspondence. Dr. Ying-Chun Jheng, Department of Medical Research, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: cycom1220@gmail.com (Y.-C. Jheng); Dr. Ming-Cheng Lee, Department of Medicine, Cheng Hsin General Hospital, 45, Cheng Hsin Street, Taipei 112, Taiwan, ROC. E-mail address: ch6511@chgh.org.tw (M.-C. Lee); Mr. Cheng-Chieh Chen, Department of Pathology and Laboratory Medicine, Shin Kong Wu Ho-Su Memorial Hospital, 95, Wen Chang Road, Taipei 111, Taiwan, ROC. E-mail address: jack10231024@gmail.com (C.-C. Chen).*

Author contributions: Dr. Yuan-Hung Wang and Dr. Chia-Chang Wu contributed equally to this study.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 1028-1037.

Received July 31, 2021; accepted August 30, 2021.

doi: 10.1097/JCMA.0000000000000626.

1. INTRODCUTION

The coronavirus disease 2019 (COVID-19) pandemic continues to affect countries worldwide. Policies on combating COVID-19, such as vaccination, timely detection, and quarantine of infected individuals, are critical for preventing the transmission of the disease. To inhibit the transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), testing of patients, contact tracing, and quarantine of their close contacts have been used as major nonpharmaceutical interventions. Rapid identification and isolation of infectious patients with SARS-CoV-2 are crucial approaches for reducing COVID-19 community transmission. Approximately 40% of infected persons with high viral load may be asymptomatic.[1] The World Health Organization and Center for Disease Control and Prevention advised that reverse transcription polymerase chain reaction (RT-PCR) technology should be considered the standard diagnostic assay for SARS-CoV-2

detection. RT-PCR has high specificity and sensitivity to SARS-CoV-2. However, factors such as the type and quality of respiratory specimens and stage of the disease have an impact on the test accuracy. Despite its high specificity and sensitivity, RT-PCR has disadvantages, including the requirement of professional lab expertise, costly reagents, and centralized equipment. Antigen tests have been developed to detect the presence of SARS-CoV-2 proteins in respiratory samples.[2] Antigen tests are relatively inexpensive, and most of them can be used at the point of care. Antigen tests can identify individuals who are at the peak of infection, when the viral load in the body is likely to be high. Antigen tests have received Food and Drug Administration Emergency Use Authorization for use in asymptomatic and symptomatic individuals within the first 5 to 12 days after symptom onset.[3]

The advantages of antigen tests, such as low cost and rapid turnaround, may allow for the rapid identification of larger numbers of infectious persons. However, these advantages need to be balanced against the lower sensitivity, especially among asymptomatic individuals. RT-PCR should be considered after negative antigen test results in symptomatic individuals and after positive antigen test results in asymptomatic individuals.[3]

The diagnostic performance of antigen tests for the COVID-19 antigen tests remains inconclusive. Therefore, this meta-analysis aimed to evaluate the diagnostic accuracy of antigen tests for SARS-CoV-2.

2. METHODS

2.1. Literature search strategy

The systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagnostic test accuracy guidelines.[4]

We searched the PubMed, Embase, Cochrane Library, and Biomed Central databases for relevant studies. A literature search was conducted using multiple search terms including "severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 or Wuhan coronavirus" and "Antigens or antigen test or antigen detection or point-of-care testing or rapid test" and "RT-PCR or Reverse Transcriptase Polymerase Chain Reaction or COVID-19 diagnostic testing" and "sensitivity or specificity or diagnostic accuracy." We used a combination of free text and MeSH terms to identify the relevant studies. We limited our search results to studies performed on human subjects. The detailed search strategies are presented in the Supplementary File 1, http://links.lww.com/JCMA/A108.

2.2. Inclusion and exclusion criteria

Studies that evaluated the diagnostic accuracy of antigen testing for SARS-CoV-2 with reference standards were included, whereas review articles were excluded. Respiratory specimens were collected from symptomatic and asymptomatic individuals. Studies that defined RT-PCR as a reference standard were included. Only articles in English were reviewed. We conducted a literature search with no time restrictions. We included studies that provided sufficient data to construct a 2 × 2 table on a per-patient basis. We excluded case reports, case series, proposals, protocols, conference abstracts, and in-house tests. The last literature search was performed on January 2, 2021. One reviewer initially screened the titles and abstracts for potentially eligible studies. After eliminating irrelevant studies, two reviewers independently examined the full-text articles that met the inclusion criteria. Disagreements between the reviewers were resolved through joint discussions.

2.3. Quality assessment

We assessed the quality of the included studies using a tool known as the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[5] Antigen tests for SARS-CoV-2 virus were the index tests and RT-PCR test results for SARS-CoV-2 were the reference standards. QUADAS-2 consists of the following four domains: patient selection, index test, reference standard, and flow and timing. Each domain contained questions that allowed an assessment of the risk of bias. The quality of the diagnostic test comprises the risk of bias and the applicability of the study. Bias may occur if systematic deviation in the design or conduct of a study distorts the outcome. A study may have limited applicability if the clinical features or spectra of patients enrolled in the study differ from the review title. A study was considered high quality if each domain in that study exhibited a low risk of bias. Based on QUADAS-2, studies that did not record consecutive patient enrolment were considered to have an unknown risk of bias in the patient selection. Studies with a case-control design might have overestimated the diagnostic accuracy.

2.4. Statistical analysis

We extracted data of true positives, true negatives, false positives, and false negatives from each included study to construct 2 × 2 tables to calculate the values of the pooled sensitivity and pooled specificity. The sensitivity of a test is defined as the proportion of people with the disease (target condition) who show a positive result, whereas the specificity of a test is the proportion of people without the disease (target condition) who show a negative result.[6]

We conducted a meta-analysis using a random-effects model to calculate the summary sensitivity and specificity on a per-patient basis. We also plotted the summary receiver operating characteristic (SROC) curve to demonstrate the overall diagnostic performance of the index tests. The closer the curve approaches the upper-left corner, the higher the overall performance.[7] A perfect test has an area under the curve (AUC) of 1. The AUC of an excellent test should be ≥0.97. An AUC of 0.93 to 0.96 is highly suitable, and an AUC of 0.75 to 0.92 is suitable.[8] Summary estimates, including the pooled sensitivity and specificity, were generated with the associated 95% CI. Possible causes of heterogeneity between studies were explored through prespecified subgroup analysis, which included the following: specimen type, patients in the community, asymptomatic participants, and symptomatic individuals. All analyses were performed using the MetaDiSc ver. 1.4, and MetaDTA software.[9,10] Between-study heterogeneity commonly exists in a meta-analysis. The bivariate SROC models were used by the MetaDTA software. The random-effects bivariate binomial model is a generalized linear mixed-effect model with an unstructured between-study covariance matrix.[11,12] The circles of the SROC plot in MetaDTA are displayed as pie charts summarizing the risk of bias of individual studies based on the QUADAS-2 tool. The first quadrant of a circle represents patient selection, the second quadrant represents the index test, the third quadrant represents the reference standard, and the fourth quadrant represents the flow and timing. Circles on the SROC plot are colored depending on their quality assessment score: green for low, red for high, and gray for unclear risk of bias.[10] A p value <0.05 was considered statistically significant.

3. RESULTS

Fourteen studies with 8624 participants were retrieved.[3,13–25] Fig. 1 depicts the flowchart of the literature search. Table 1 presents the detailed characteristics of the studies. All studies in the meta-analysis used a prospective study design and five studies enrolled participants in the hospital.[15,18,19,22,25] Two studies evaluated the diagnostic performance of antigen tests with nasal swab specimens.[3,13] Nine studies assessed the accuracy of antigen tests with nasopharyngeal swab specimens.[15,17–19,21–25]

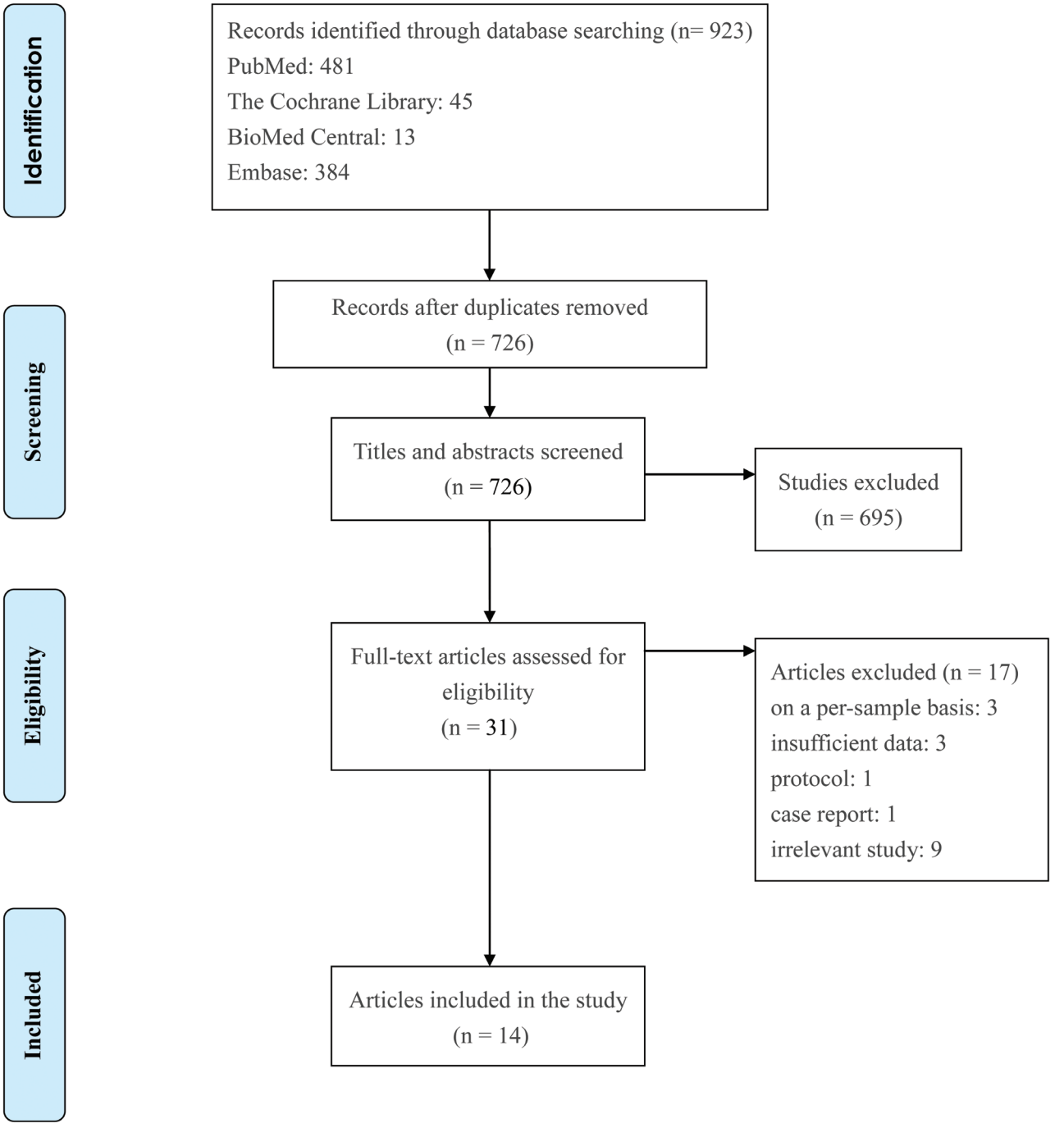

Fig. 1 Flowchart of literature search.

Nine studies provided cycle threshold (Ct) values of positive RT-PCRs.[3,14–17,19–21,24] Six studies reported threshold values of Ct.[13–16,18,20] Table 2 lists the statistical data. The meta-analysis for antigen tests generated a pooled sensitivity of 79% (95% CI, 66%-88%; 14 studies, 8624 patients) and a pooled specificity of 100% (95% CI, 99%-100%; 14 studies, 8624 patients; Fig. 2). The AUC of the SROC curve for the antigen test was 0.99, indicating that the antigen test might be suitable for diagnosing COVID-19 (Fig. 3). Sensitivity and specificity were jointly modeled. The random effect intraclass correlation was –0.179. Sensitivities and specificities of antigen tests for SARS-CoV-2 from the included studies are presented in Supplementary File 2, http://links.lww.com/JCMA/A108.

3.1. Quality assessment

The strength of the evidence in this meta-analysis relied on its rigid-quality assessment. We applied QUADAS-2, which has four domains, to evaluate the quality of the studies in our meta-analysis. Regarding patient selection, six studies enrolled patients randomly or consecutively; 10 studies avoided a case-control study design, which might have led to an overestimated diagnostic accuracy. Based on the rules in this domain, four

Table 1

Characteristics of studies

Study	Study design	Patient population	Participants (total /data extraction)	Age median (range)	Days postsymptom onset median (range)	Specimen type	Product, antigen detection technology	Viral antigen detected	Reference standard	Ct value of positive RT-PCR median (range)	Threshold value (Ct)
Pray et al[3]	Prospective	Asymptomatic and symptomatic persons at 2 universities	(1105/1098) symptomatic: 227 asymptomatic: 871	15-24 (88.4%) ≧25 (11.8%)	3	Nasal swabs	Sofia SARS Antigen, fluorescent immunoassay	NA	RT-PCR	23.7 (mean)	NA
Pilarowski et al[13]	Prospective	Participants in an urban commercial transport hub	(3302/3302)	<13, 13-18, >18	NA	Nasal swab	BinaxNOW™ COVID-19 Ag Card	NA	RT-PCR	NA	35
Gremmels et al[14]	Prospective	Community-dwelling subjects with mild symptoms of respiratory tract infection	(1369/1367) (Utrecht study site)	36.4 (Utrecht study site)	NA	Throat/ nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device, immunochromatography	Nucleocapsid protein	RT-PCR	24.74 (mean), (E-gene, Utrecht study site)	32
Scohy et al[15]	Prospective	Hospitalized patients	(148/148)	57.5 (0-94)	4 (0-34)	Nasopharyngeal swab	COVID-19 Ag Respi-Strip, membrane technology	Nucleoprotein antigen	RT-PCR	32.5 (18-38) (no symptoms)	40
Porte et al[16]	Prospective	Patients with respiratory symptoms, travel or contact with a case	(1453/127)	38 (1-91)	2 (0-12)	Nasopharyngeal swab, oropharyngeal swab, sputum	Bioeasy 2019-Novel Coronavirus, lateral flow assay	Nucleocapsid protein	RT-PCR	17.7	40
Lambert-Niclot et al[17]	Prospective	NA	(138/138)	NA	NA	Nasopharyngeal swab	COVID-19 Ag Respi-Strip, membrane technology	Nucleoprotein antigen	RT-PCR	21	NA
Diao et al[18]	Prospective	Hospitalized patients or outpatients with suspected COVID-19 symptoms	(253/251)	NA	NA	Nasopharyngeal swab	Fluorescence immunochromatographic	Nucleocapsid protein	RT-PCR	NA	40
Linares et al[19]	Prospective	Emergency department, primary healthcare	(255/255)	NA	<5, <7, ≥7	Nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device, immunochromatography	Nucleocapsid protein	RT-PCR	23.28 (0-37.8)	NA
Chaimayo et al[20]	Prospective	Suspected COVID-19 patients	(454/454)	58 (16-95)	3 (0-14)	Nasopharyngeal and throat swabs	Standard™ Q COVID-19 Ag kit, chromatographic immunoassay	Nucleocapsid (N) antigen	RT-PCR	23.41 (10.49-35.02) (envelope gene)	40
Albert et al[21]	Prospective	Adults and children with compatible signs or symptoms appearing within the prior week	(412/412)	31(1-91)	3 (1-7) (RT-PCR+/ RAD+)	Nasopharyngeal swab	Panbio COVID-19 Ag Rapid Test Device, immunochromatography	Nucleoprotein	RT-PCR	14.5 (4-25.8) (adult)	NA
Krüttgen et al[22]	Prospective	Hospitalized patients	(150/150)	NA	NA	Nasopharyngeal swab	SARS-CoV-2 Rapid Antigen Test, lateral flow assay	NA	RT-PCR	NA	NA
Cerutti et al[23]	Prospective	Suspected COVID-19 patients in ER, travelers	(330/330)	Patients: 44.6 (mean) travelers: 35.9 (mean)	NA	Nasopharyngeal swabs	Standard Q COVID-19 Ag kit, chromatographic immunoassay	Nucleoprotein	RT-PCR	NA	NA

(*Continued next page*)

Table 1 (Continued)

Study	Study design	Patient population	Participants (total /data extraction)	Age median (range)	Days postsymptom onset median (range)	Specimen type	Product, antigen detection technology	Viral antigen detected	Reference standard	Ct value of positive RT-PCR median (range)	Threshold value (Ct)
Gupta et al[24]	Cross-sectional, prospective	Patients symptomatic for COVID-19, asymptomatic/ presymptomatic contacts of laboratory-confirmed cases between 5 and 10 d of exposure outpatient department	(330/330)	34.1 ± 12.6 (SD)	≤5 d: 192, >5 d: 12	Nasopharyngeal swabs	Standard Q COVID-19 Ag kit, chromatographic immunoassay	NA	RT-PCR	21.4 (10-35.4)	NA
Nalumansi et al[25]	Cross-sectional, prospective	Hospitalized patients	(262/262)	34 (mean)	NA	Nasopharyngeal swabs	Standard Q COVID-19 Ag kit, chromatographic immunoassay	NA	RT-PCR	NA	NA

COVID-19 = coronavirus disease 2019; Ct = cycle threshold; ER = emergency rooms; NA = not available; RAD = rapid antigen diagnostic immunoassay; RT-PCR = reverse transcription polymerase chain reaction; SARS = severe acute respiratory syndrome; SD = standard deviation.

Table 2

Statistical data of included studies

Study	True positive	False positive	False negative	True negative
Pray et al[3]	39	16	18	1025
Pilarowski et al[13]	201	13	3	3085
Gremmels et al[14]	101	0	38	1228
Scohy et al[15]	32	0	74	42
Porte et al[16]	77	0	5	45
Lambert-Niclot et al[17]	47	0	47	44
Diao et al[18]	152	0	49	50
Linares et al[19]	44	0	16	195
Chaimayo et al[20]	59	5	1	389
Albert et al[21]	43	0	11	358
Krüttgen et al[22]	53	3	22	72
Cerutti et al[23]	77	0	32	221
Gupta et al[24]	63	1	14	252
Nalumansi et al[25]	63	13	27	159

studies were judged to have a low risk of bias in the patient selection domain.[13,15,23,24] Regarding index tests, four studies reported that index tests were interpreted without knowledge of the results of the reference standard.[13,14,16,18] All of these studies were judged to have a low risk of bias in the index domain.[13,14,16,18] Regarding the reference standard, all studies presented that the reference standard likely correctly classified the target condition. Regarding the flow and timing domains, 12 studies demonstrated that all patients received a reference standard, and 10 studies indicated that all patients were included in the analysis. Nine articles were judged to have a low risk of bias in the flow and timing domains. Regarding the applicability, patient selection, index tests, and reference standards of the studies in our meta-analysis matched our review title. Table 3 presents the quality of the studies. Fig. 4 demonstrates the risk of bias of individual studies in the meta-analysis. Fig. 5 summarizes the overall quality of studies in the meta-analysis. The quality assessment process is presented in Supplementary File 3, http://links.lww.com/JCMA/A108.

3.2. Investigation of heterogeneity

The participant population and the duration from symptom onset to specimen collection may represent sources of heterogeneity in the meta-analysis. Subgroup analyses were performed to identify the sources of heterogeneity. Specimen types for antigen tests may have an impact on the diagnostic accuracy. Two studies with 4400 patients discussed the accuracy of antigen tests using nasal swabs.[3,13] The meta-analysis produced a pooled sensitivity of 92% (95% CI, 51%-99%; two studies, 4400 patients) and a pooled specificity of 99% (95% CI, 98%-100%; two studies, 4400 patients). Moreover, nine studies with 2276 patients reported the accuracy of antigen tests using nasopharyngeal swabs.[15,17–19,21–25] The meta-analysis produced a pooled sensitivity of 68% (95% CI, 57%-77%; nine studies, 2276 patients) and a pooled specificity of 100% (95% CI, 95%-100%; nine studies, 2276 patients). The participant population in the meta-analysis included hospitalized patients and individuals in the community. Disease prevalence may vary between patient populations. According to the accuracy data of antigen tests for patients in the community, we performed a subgroup analysis of four studies that involved 6097 participants from the community.[3,13,14,23] It generated a pooled sensitivity of 84% (95% CI, 58%-95%; four studies, 6097 patients) and a pooled specificity of 100% (95% CI, 97%-100%; four studies, 6097 patients), respectively. Antigen tests may have a high sensitivity for

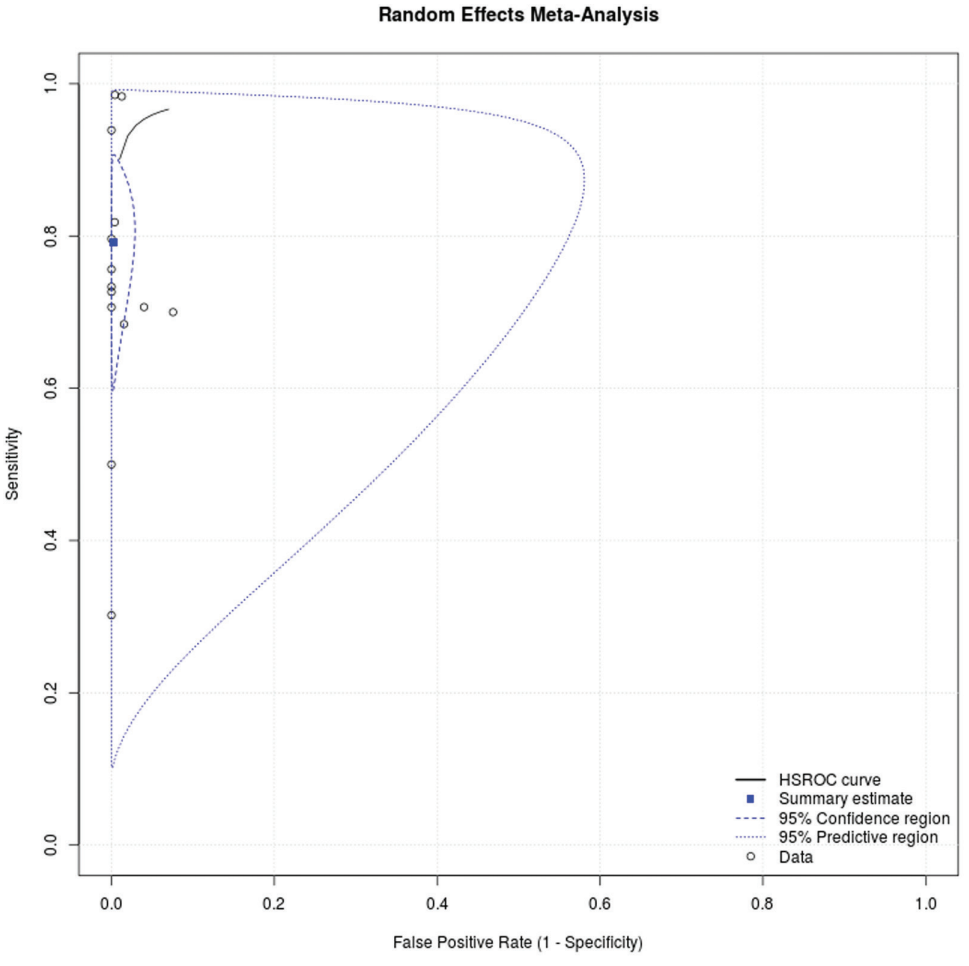

Fig. 2 Pooled sensitivity and specificity of antigen test for SARS-CoV-2. HSROC = hierarchical summary receiver operating characteristic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

COVID-19 detection among participants in the community. We assumed that viral load was related to patients' symptom status, and the diagnostic accuracy of antigen testing to the viral load. The subgroup analysis of three studies that involved asymptomatic participants generated a pooled sensitivity of 89% (95% CI, 62%-98%; three studies, 4730 patients) and pooled specificity of 99% (95% CI, 98%-100%; three studies, 4730 patients), respectively.[3,13,24] We performed a subgroup analysis based on the antigen test data for patients within 5 days after symptom onset. The subgroup analysis of three studies that reported specimen collection within 5 days after symptom onset produced a pooled sensitivity of 83% (95% CI, 74%-89%; three studies, 479 patients) and a pooled specificity of 100% (95% CI, 96%-100%; three studies, 479 patients).[3,19,24] Antigen tests might have higher pooled sensitivity in the detection of SARS-CoV-2 among symptomatic patients with no more than 5 days of evolution. Four studies in the meta-analysis reported data regarding the antigen tests for participants within 7 days after symptom onset; we performed the following subgroup analysis. The subgroup analysis of four studies that reported specimen collection within 7 days after symptom onset demonstrated a pooled sensitivity of 95% (95% CI, 78%-99%; four studies, 1342 patients) and a pooled specificity of 100% (95% CI, 97%-100%; four studies, 1342 patients).[13,16,19,21] Antigen tests may have higher pooled sensitivity in detecting SARS-CoV-2 in symptomatic patients with no more than 7 days of evolution. The subgroup analysis of studies using Ct cutoff value less than 35 produced a pooled sensitivity of 93% (95% CI, 93%-93%; two studies, 4669 patients) and pooled specificity of 100% (95% CI, 99%-100%; two studies, 4669 patients) of antigen test for COVID-19.[13,14] Another subgroup analysis of studies using Ct cutoff value less than 40 produced a pooled sensitivity of 85% (95% CI, 47%-97%; four studies, 980 patients) and pooled specificity of 100% (95% CI, 94%-100%; four studies, 980 patients) of antigen test for COVID-19.[15,16,18,20] Antigen tests may have higher sensitivity for COVID-19 with Ct cutoff value less than 35, based on the subgroup analyses. The subgroup analysis of studies using Panbio COVID-19 Ag produced a pooled sensitivity of 74% (95% CI, 69%-79%; three studies, 2034 patients) and pooled specificity of 100% (95% CI, 0%-100%; three studies, 2034 patients) of antigen test for COVID-19.[14,19,21] Another subgroup analysis of studies using Standard Q COVID-19 Ag kit produced a pooled sensitivity of 97% (95% CI, 83%-99%; four studies, 1376 patients) and pooled specificity of 95% (95% CI, 81%-99%; four studies, 1376 patients) of antigen test for COVID-19.[20,23–25] The statistical data of the subgroup analyses are presented in Supplementary File 4, http://links.lww.com/JCMA/A108.

4. DISCUSSION

Our major findings indicated that antigen tests have moderate sensitivity and high specificity for detecting SARS-CoV-2. Immunological tests (IgM and IgG) showed promising sensitivity

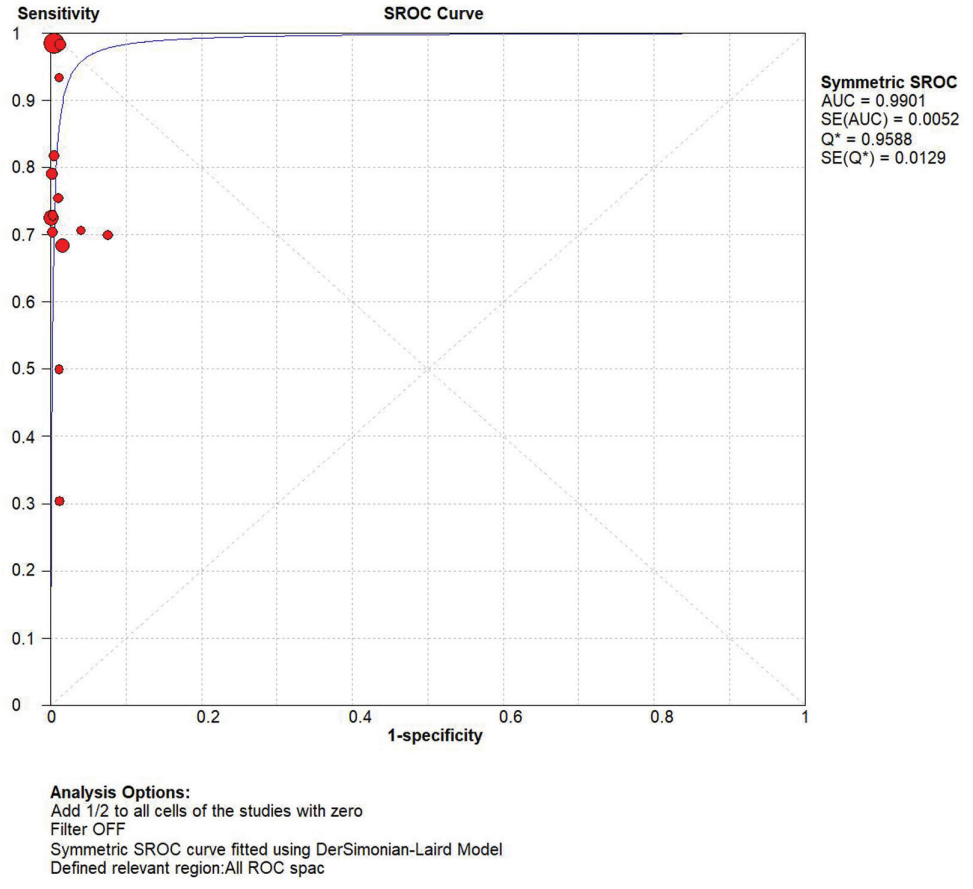

Fig. 3 The SROC curve for antigen tests. AUC = area under the curve; ROC = receiver operating characteristic; SE = standard error; SROC = summary receiver operating characteristic.

for COVID-19.[26] However, higher levels of antibodies are seen in the second and third week of symptom onset.[27] RT-PCR is the standard diagnostic method for SARS-CoV-2 detection. A previous study reported that RT-PCR positivity may persist over 3 weeks after illness onset when most mild cases yield a negative result. However, a positive RT-PCR result demonstrates only the detection of SARS-CoV-2 RNA and does not necessarily indicate the presence of replicating virus.[27]

According to the subgroup analyses, antigen tests may have higher sensitivity in detecting SARS-CoV-2 within 7 days after symptom onset, which indicates that antigen tests may be suitable for viral detection during the early disease phase. In another subgroup analysis of studies involving data from patients within 5 days after symptom onset, antigen tests also showed high sensitivity in detecting SARS-CoV-2 in the population. In the absence of effective treatments or vaccines for COVID-19, identifying as many infected individuals

Table 3

Quality of studies

	Risk of bias				Applicability concerns		
Study	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**
Pray et al[3]	U	U	L	H	L	L	L
Pilarowski et al[13]	L	L	L	L	L	L	L
Gremmels et al[14]	U	L	L	H	L	L	L
Scohy et al[15]	L	U	L	L	L	L	L
Porte et al[16]	U	L	L	H	L	L	L
Lambert-Niclot et al[17]	U	U	L	H	L	L	L
Diao et al[18]	U	L	L	H	L	L	L
Linares et al[19]	U	U	L	L	L	L	L
Chaimayo et al[20]	U	U	L	L	L	L	L
Albert et al[21]	U	U	L	L	L	L	L
Krüttgen et al[22]	H	U	L	L	L	L	L
Cerutti et al[23]	L	U	L	L	L	L	L
Gupta et al[24]	L	U	L	L	L	L	L
Nalumansi et al[25]	H	U	L	L	L	L	L

H = high risk of bias; L = low risk of bias; U = unclear risk of bias.

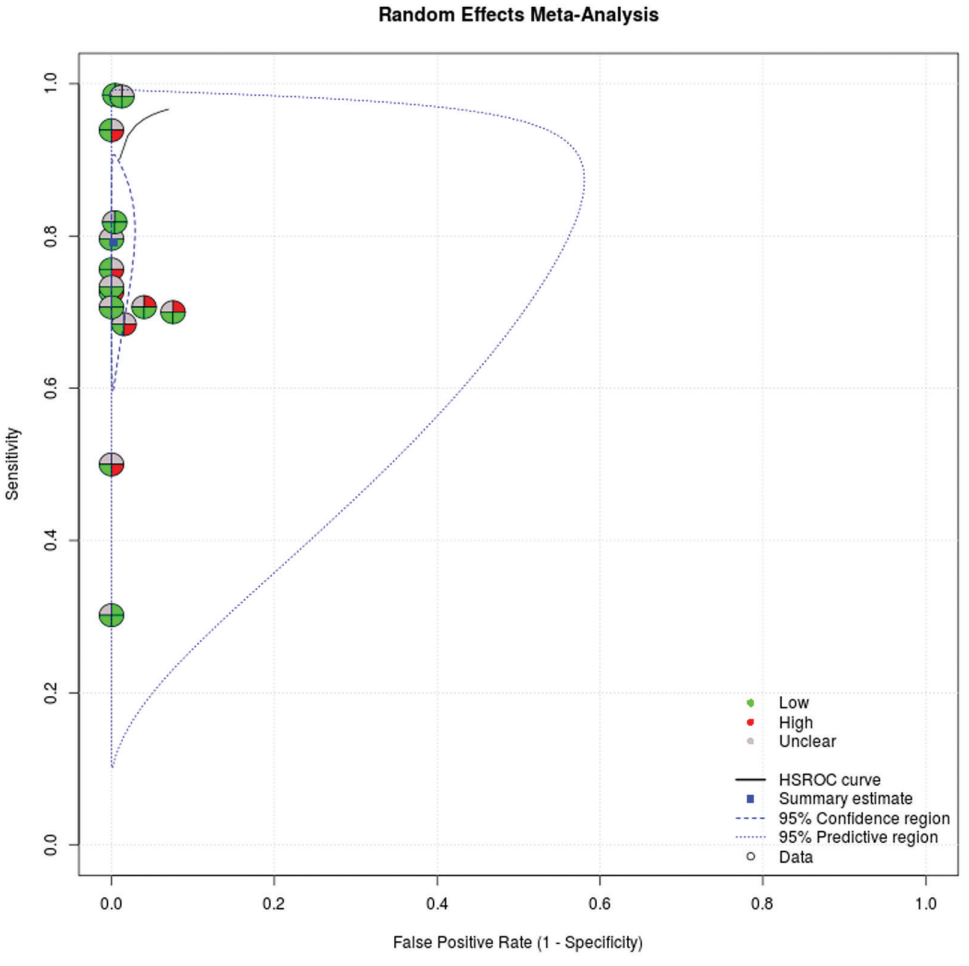

Fig. 4 SROC curve showing the summary estimate and risk of bias of individual studies. HSROC = hierarchical summary receiver operating characteristic.

as possible (both symptomatic and asymptomatic) and then isolating them is the most effective approach to prevent disease transmission.[28] Our meta-analysis provided evidence that antigen tests are effective in identifying potentially infected people in the community.

Rapid and reliable diagnostic methods are crucial during the COVID-19 pandemic, as a large-scale diagnostic capacity becomes critical for containing outbreaks and reducing disease mortality. Deploying on-site and rapid tests is ideal for urgent patient triaging and contact tracing.[28] Fast and accurate laboratory testing of SARS-CoV-2 is essential for early quarantine, early treatment, and blocking COVID-19 transmission.[29] An antigen test is easy, cheap, and scalable. It can be useful in monitoring the infection status and has the potential to reduce community transmission. Antigen tests can be applied for the surveillance of asymptomatic and presymptomatic individuals. Frequent use of antigen tests might help identify infected individuals and reduce COVID-19 transmission, which is one of the strategies for pandemic control.[2] COVID-19 vaccine will have to be distributed as quickly as possible to the vast majority of people worldwide.[30]

Owing to the absence of effective COVID-19 treatment, the only currently available approach to reduce SARS-CoV-2 transmission is to identify and isolate contagious persons.[31] Rapid diagnosis for clinical treatment and management (including protection of first-line staff) and prompt identification of infected individuals for quarantine purposes are key benefits of using antigen tests in suspected individuals. Contact tracing becomes feasible so that patients can be isolated to minimize SARS-CoV-2 spread.[32] Diagnostic testing plays a role in COVID-19 outbreak control. To end the pandemic, accurate application of diagnostic testing in high volumes and rapid use of the results may help implement the appropriate therapy and prevent further spread.[33] Antigen tests may increase overall COVID-19 testing capacity and have the advantages of shorter turnaround times and reduced cost, compared with RT-PCR tests.[34]

Antigen tests detect SARS-CoV-2 proteins, and positive antigen test results indicate the presence of the virus. Antigen tests are most likely to perform better in patients with high viral loads (Ct values ≤25), which usually appear in the presymptomatic (1-3 days before symptom onset) and early symptomatic phases of COVID-19 (within the first 5-7 days of illness).[35] Antibodies are detectable approximately 8 days after disease onset. Antibody testing could yield positive results in the middle or late stages of COVID-19. The use of antibody tests without RT-PCR tests in the first week of the symptomatic phase may fail to diagnose COVID-19.[36]

Individuals with confirmed COVID-19 are asked to quarantine for 14 days after exposure to limit asymptomatic transmission. This method may be a social and economic burden for the individual and society, which may result in low adherence and reduced effectiveness. A study reported that quarantine until an RT-PCR or antigen test on day 7 after exposure (with early release if negative) may avert transmission similar to the standard 14-day quarantine period.[37] The testing of asymptomatic healthcare workers has been suggested to reduce nosocomial transmission

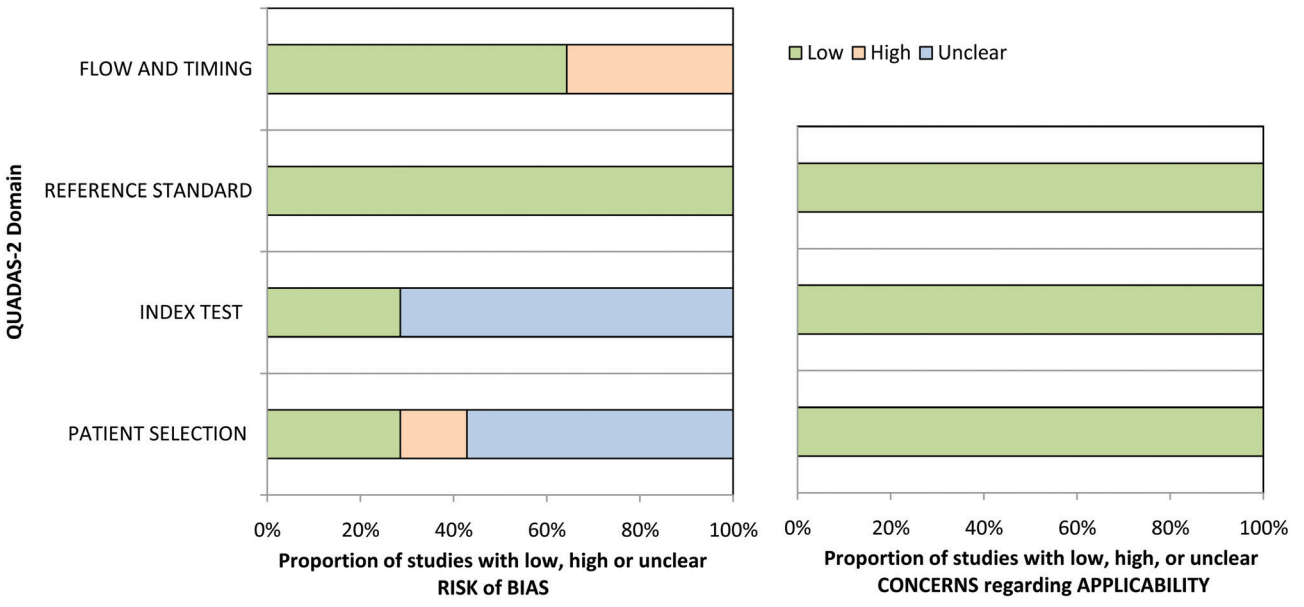

Fig. 5 Overall quality of studies in the meta-analysis. QUADAS = Quality Assessment of Diagnostic Accuracy Studies-2.

of COVID-19.[38] Therefore, antigen tests can be used for screening and serial testing (every 2-3 days) of residents and staff in healthcare, home care, and long-term care facilities in areas where there is ongoing community transmission. When an initial case is confirmed in a resident or staff member of a closed setting, comprehensive testing for all residents and staff should be considered.[34]

Several published studies have discussed the diagnostic performance of antigen testing for COVID-19 to provide evidence for allied healthcare to contain the COVID-19 pandemic. Schuit et al[39] reported that SARS-CoV-2 antigen tests are capable to detect close contacts of people with confirmed SARS-CoV-2 infection from day 5 onward. Dinnes et al[40] reported that sensitivities of antigen tests for COVID-19 are highest in the first week of illness, when the viral loads are higher in individuals with signs and symptoms. Antigen testing can be considered as a replacement for laboratory-based RT-PCR methods when immediate medical decisions about patient care must be made, or where RT-PCR cannot be performed promptly.[40] Antigen tests have promising diagnostic performance for mass population testing and can be used to identify infectious individuals to break the potential transmission of SARS-CoV-2 in the community.[41] The performance of antigen test is inconsistent and dependent on the manufacturer. The operator might not have an impact on diagnostic performance.[42] Antigen tests have high diagnostic performance in the early phase of disease. Antigen tests detect the vast majority of SARS-CoV-2–infected persons with high viral load.[43] Moreover, our meta-analysis indicated that antigen tests may have higher sensitivity in detecting SARS-CoV-2 within 7 days after symptom onset. This systematic review and meta-analysis have added to the clinical evidence supporting the clinical use of antigen tests for COVID-19 diagnosis.

Although this meta-analysis showed that antigen tests may be effective in detecting SARS-CoV-2, our study has some limitations. The Ct cutoff values of RT-PCR in the included studies were limited and inconsistent. Most studies in the meta-analysis did not report whether patient enrollment was consecutive or random. No studies in the meta-analysis reported SARS-CoV-2 variants.

In conclusion, our major findings indicated that antigen tests have excellent specificity and high sensitivity in detecting SARS-CoV-2 in patients with COVID-19 infection within 7 days after symptom onset. Antigen testing may be an effective strategy to interrupt SARS-CoV-2 transmission.

ACKNOWLEDGMENTS

We thank Graduate Institute of Clinical Medicine and Shuang Ho Hospital of Taipei Medical University for supports in statistical analyses, information collection, and grant (110FRP-01). The grant was partly from Cheng Hsin General Hospital (110-CY11012/108-CY10813).

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A108.

REFERENCES

1. Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. *Ann Intern Med* 2020;**173**:362–7.
2. Toptan T, Eckermann L, Pfeiffer AE, Hoehl S, Ciesek S, Drosten C, et al. Evaluation of a SARS-CoV-2 rapid antigen test: potential to help reduce community spread? *J Clin Virol* 2021;**135**:104713.
3. Pray IW, Ford L, Cole D, Lee C, Bigouette JP, Abedi GR, et al. Performance of an antigen-based test for asymptomatic and symptomatic SARS-CoV-2 testing at two university campuses - Wisconsin, September-October 2020. *MMWR Morb Mortal Wkly Rep* 2021;**69**:1642–7.
4. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al and the PRISMA-DTA Group. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA* 2018;**319**:388–96.
5. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36.
6. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. *Acta Paediatr* 2007;**96**:338–41.
7. Chartrand C, Leeflang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. *Ann Intern Med* 2012;**156**:500–11.
8. Jones CM, Athanasiou T. Summary receiver operating characteristic curve analysis techniques in the evaluation of diagnostic tests. *Ann Thorac Surg* 2005;**79**:16–20.

9. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol* 2006;**6**:31.
10. Freeman SC, Kerby CR, Patel A, Cooper NJ, Quinn T, Sutton AJ. Development of an interactive web-based tool to conduct and interrogate meta-analysis of diagnostic test accuracy studies: MetaDTA. *BMC Med Res Methodol* 2019;**19**:81.
11. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. *J Clin Epidemiol* 2006;**59**:1331–2.
12. Chu H, Chen S, Louis TA. Random effects models in a meta-analysis of the accuracy of two diagnostic tests without a gold standard. *J Am Stat Assoc* 2009;**104**:512–23.
13. Pilarowski G, Marquez C, Rubio L, Peng J, Martinez J, Black D, et al. Field performance and public health response using the BinaxNOW TM Rapid SARS-CoV-2 antigen detection assay during community-based testing [published online ahead of print December 26, 2020]. *Clin Infect Dis*. Doi:10.1093/cid/ciaa1890.
14. Gremmels H, Winkel BMF, Schuurman R, Rosingh A, Rigter NAM, Rodriguez O, et al. Real-life validation of the Panbio™ COVID-19 antigen rapid test (Abbott) in community-dwelling subjects with symptoms of potential SARS-CoV-2 infection. *Eclinicalmedicine* 2021;**31**:100677.
15. Scohy A, Anantharajah A, Bodéus M, Kabamba-Mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. *J Clin Virol* 2020;**129**:104455.
16. Porte L, Legarraga P, Vollrath V, Aguilera X, Munita JM, Araos R, et al. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. *Int J Infect Dis* 2020;**99**:328–33.
17. Lambert-Niclot S, Cuffel A, Le Pape S, Vauloup-Fellous C, Morand-Joubert L, Roque-Afonso AM, et al. Evaluation of a rapid diagnostic assay for detection of SARS-CoV-2 antigen in nasopharyngeal swabs. *J Clin Microbiol* 2020;**58**:e00977–20.
18. Diao B, Wen K, Zhang J, Chen J, Han C, Chen Y, et al. Accuracy of a nucleocapsid protein antigen rapid test in the diagnosis of SARS-CoV-2 infection. *Clin Microbiol Infect* 2021;**27**:289.e1–4.
19. Linares M, Pérez-Tanoira R, Carrero A, Romanyk J, Pérez-García F, Gómez-Herruz P, et al. Panbio antigen rapid test is reliable to diagnose SARS-CoV-2 infection in the first 7 days after the onset of symptoms. *J Clin Virol* 2020;**133**:104659.
20. Chaimayo C, Kaewnaphan B, Tanlieng N, Athipanyasilp N, Sirijatuphat R, Chayakulkeeree M, et al. Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand. *Virol J* 2020;**17**:177.
21. Albert E, Torres I, Bueno F, Huntley D, Molla E, Fernández-Fuentes MÁ, et al. Field evaluation of a rapid antigen test (Panbio™ COVID-19 Ag Rapid Test Device) for COVID-19 diagnosis in primary healthcare centres. *Clin Microbiol Infect* 2021;**27**:472.e7–472.e10.
22. Krüttgen A, Cornelissen CG, Dreher M, Hornef MW, Imöhl M, Kleines M. Comparison of the SARS-CoV-2 rapid antigen test to the real star Sars-CoV-2 RT PCR kit. *J Virol Methods* 2021;**288**:114024.
23. Cerutti F, Burdino E, Milia MG, Allice T, Gregori G, Bruzzone B, et al. Urgent need of rapid tests for SARS CoV-2 antigen detection: evaluation of the SD-Biosensor antigen test for SARS-CoV-2. *J Clin Virol* 2020;**132**:104654.
24. 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.
25. 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.
26. Lisboa Bastos M, Tavaziva G, Abidi SK, Campbell JR, Haraoui LP, Johnston JC, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. *BMJ* 2020;**370**:m2516.
27. Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. *JAMA* 2020;**323**:2249–51.
28. Cheong J, Yu H, Lee CY, Lee JU, Choi HJ, Lee JH, et al. Fast detection of SARS-CoV-2 RNA via the integration of plasmonic thermocycling and fluorescence detection in a portable device. *Nat Biomed Eng* 2020;**4**:1159–67.
29. Yan Y, Chang L, Wang L. Laboratory testing of SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCoV): current status, challenges, and countermeasures. *Rev Med Virol* 2020;**30**:e2106.
30. Subbarao K. COVID-19 vaccines: time to talk about the uncertainties. *Nature* 2020;**586**:475.
31. Cheng MP, Papenburg J, Desjardins M, Kanjilal S, Quach C, Libman M, et al. Diagnostic testing for severe acute respiratory syndrome-related coronavirus 2: a narrative review. *Ann Intern Med* 2020;**172**:726–34.
32. Bhopal RS. COVID-19 zugzwang: potential public health moves towards population (herd) immunity. *Public Health Pract (Oxf)* 2020;**1**:100031.
33. Vandenberg O, Martiny D, Rochas O, van Belkum A, Kozlakidis Z. Considerations for diagnostic COVID-19 tests. *Nat Rev Microbiol* 2020;**19**:171–83.
34. Options for the use of rapid antigen tests for COVID-19 in the EU/EEA and the UK. Available at https://www.ecdc.europa.eu/en/publications-data/options-use-rapid-antigen-tests-covid-19-eueea-and-uk. Accessed July 30, 2021.
35. WHO. Antigen-Detection in the Diagnosis of SARS-CoV-2 Infection Using Rapid Immunoassays: Interim Guidance. Available at https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays. Accessed July 30, 2021.
36. Uwamino Y, Wakui M, Aoki W, Kurafuji T, Yanagita E, Morita M, et al; Keio Donner Project Team. Evaluation of the usability of various rapid antibody tests in the diagnostic application for COVID-19. *Ann Clin Biochem* 2021;**58**:174–80.
37. Quilty BJ, Clifford S, Hellewell J, Russell TW, Kucharski AJ, Flasche S, et al; Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. *Lancet Public Health* 2021;**6**:e175–83.
38. Chow A, Htun HL, Kyaw WM, Lee LT, Ang B. Asymptomatic healthcare worker screening during the COVID-19 pandemic. *Lancet* 2020;**396**:1393–4.
39. Schuit E, Veldhuijzen IK, Venekamp RP, van den Bijllaardt W, Pas SD, Lodder EB, et al. Diagnostic accuracy of rapid antigen tests in asymptomatic and presymptomatic close contacts of individuals with confirmed SARS-CoV-2 infection: cross sectional study. *BMJ* 2021;**374**:n1676.
40. Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, et al; Cochrane COVID-19 Diagnostic Test Accuracy Group. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev* 2021;**3**:CD013705.
41. Peto T; UK COVID-19 Lateral Flow Oversight Team. COVID-19: Rapid antigen detection for SARS-CoV-2 by lateral flow assay: a national systematic evaluation of sensitivity and specificity for mass-testing. *Eclinicalmedicine* 2021;**36**:100924.
42. Mistry DA, Wang JY, Moeser ME, Starkey T, Lee LYW. A systematic review of the sensitivity and specificity of lateral flow devices in the detection of SARS-CoV-2. *BMC Infect Dis* 2021;**21**:828.
43. Brümmer LE, Katzenschlager S, Gaeddert M, Erdmann C, Schmitz S, Bota M, et al. Accuracy of novel antigen rapid diagnostics for SARS-CoV-2: a living systematic review and meta-analysis. *PLoS Med* 2021;**18**:e1003735.