

Antigen Testing Every 3 Days A Path to Manage Schools, Businesses and Enhance Public Safety

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Rethinking Covid-19 Test Sensitivity — A Strategy for Containment – Antigen Tests

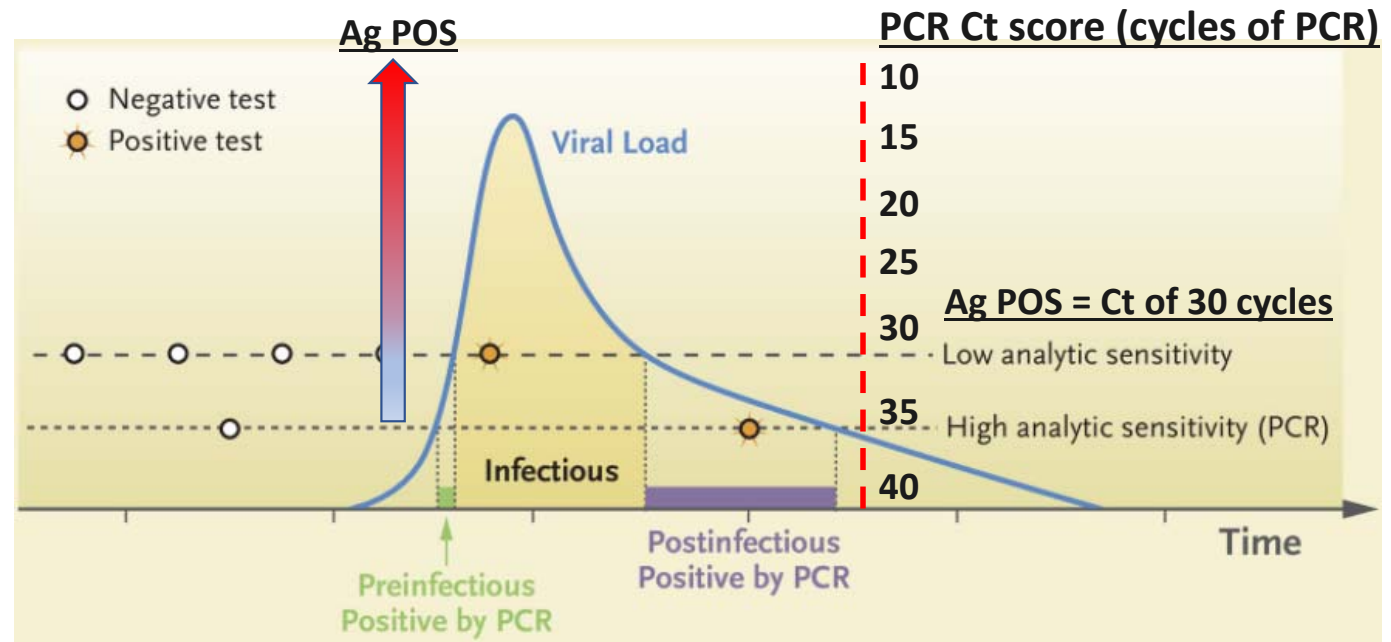
NEJM: .Michael J. Mina, M.D., Ph.D. et.al.,

Question:

High-Frequency Testing with Low Analytic Sensitivity tests (Antigen) versus Low-Frequency Testing with High Analytic Sensitivity (PCR)?

We are doing the later, but we need to do the higher frequency of testing with low sensitivity tests.

<https://www.nejm.org/doi/full/10.1056/nejmp2025631>



A typical infection trajectory (blue line) is shown in the context of two surveillance methods (circles) with different analytic sensitivity.

The low-analytic-sensitivity assay (Antigen) is administered frequently and the high-analytic-sensitivity assay (PCR) infrequently. **Both testing regimens detect the infection (orange circles), but only the high-frequency test detects it during the transmission window** (shading; “INFECTIOUS”).

The window during which polymerase chain reaction (PCR) detects infections before infectivity (green) is short, whereas the corresponding post-infectious but PCR-detectable window (purple), long causing unnecessary quarantine/controls.

Antigen Tests are Not RT-PCR: They Are Not Seeing the Same Thing

Are They Being Used Correctly? Maybe Not

A POS PRC Test is a cycle count of 39 or lower. Forty cycles without some detection is a NEG Test.

Delta infections are showing 1000x the viral load of previous Alpha variant infections and without symptoms.

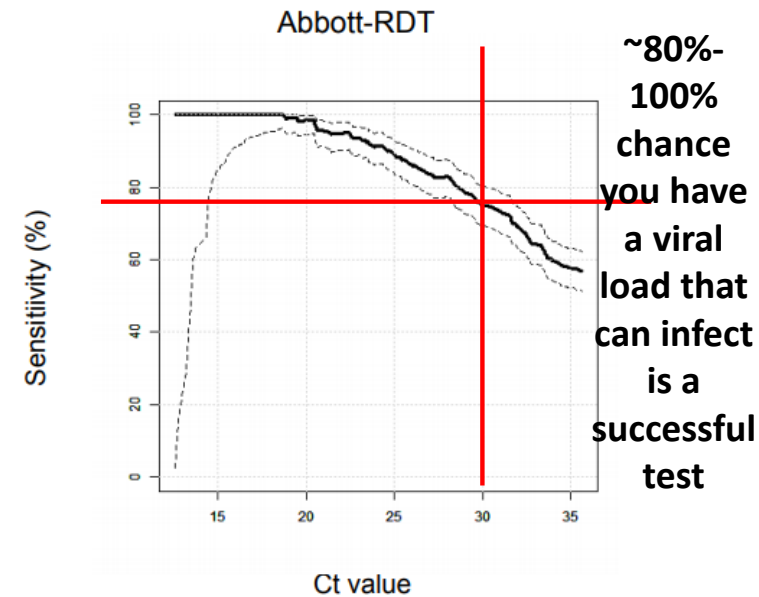
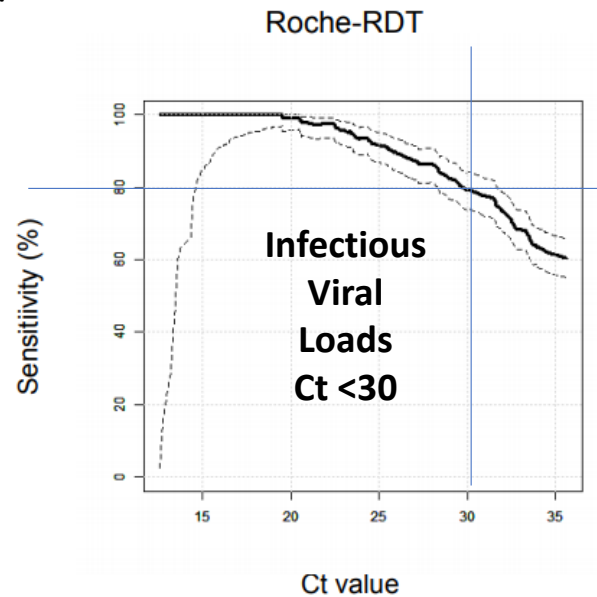
What can a rapid antigen test tell us?

A German study doubts the antigen tests are useful. In fact: Cycle threshold (Ct) values under 30 are representing sample viral loads in excess of >6 log₁₀ RNA copies/ml).

Below this Ct value of viral copies the probability of a POS culture drops off and this also represents a lower probability of transfer of an infectious level of virus to another person.

This is the desired outcome and not whether the antigen test predicts a POS or equivalent PCR sample.

Infectious vs Non-Infectious is KEY!



Cycle threshold (Ct) values in rRT-PCR for SARS-Cov-2 RNA versus the sensitivities of the Roche-RDT (left) and Abbott-RDT (right). **The solid lines indicate sensitivities, the dotted lines represent the upper and lower bounds of the corresponding 95% confidence intervals. Ct scores <30 denote 80-100% of POS.**

<https://www.medrxiv.org/content/10.1101/2021.08.04.21261609v1.full.pdf>

Novel Antigen Rapid Diagnostic Tests for SARS-CoV-2 Can Stop The Spread

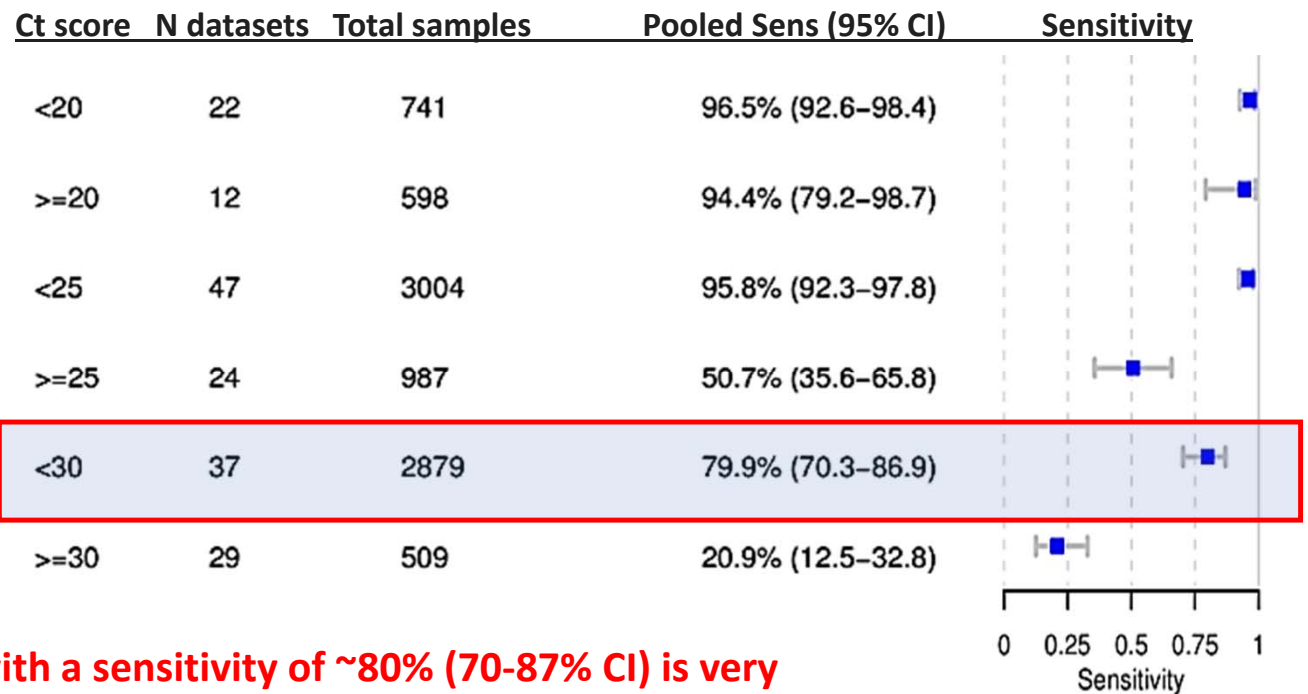
What Makes the Antigen Test Useful? 2X/Week will stop the spread

Ag-RDTs detect the vast majority of SARS-CoV-2-infected persons within the first week of symptom onset and those with high viral load.

They can have high utility for diagnostic purposes in the early phase of disease, screening out those who are of high viral load, making them a valuable tool to fight the spread of SARS-CoV-2.

A school can provide Ag-RD tests to every student for use at home. Taking the test on Monday and Thursday mornings before school would dramatically impact the school risk.

Ag-RDT sensitivity increase to 95.8% (95% CI 92.3% to 97.8%) when restricted to the analysis to **samples with high viral loads** (i.e., a Ct value < 25; “infectious”)



A test that finds Ct scores of <30 with a sensitivity of ~80% (70-87% CI) is very useful tool to reduce the risk of infected students (test 2 x/week prior to school)

<https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003735>

<https://journals.plos.org/plosmedicine/article/figure?id=10.1371/journal.pmed.1003735.g006>

Change in Saliva RT-PCR Sensitivity Over the Course of SARS-CoV-2 Infection

Antigen tests may be a first-pass screen to check an asymptomatic person

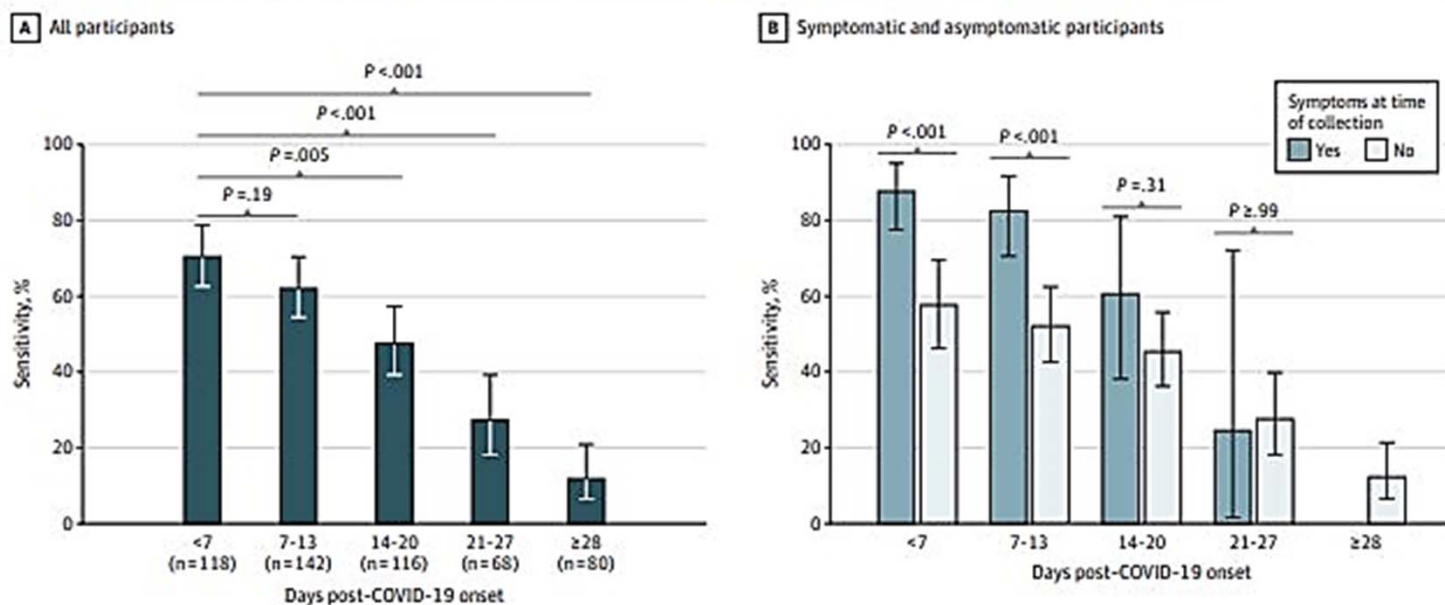
RT-PCR testing of saliva is sensitive for detecting SARS-CoV-2 in symptomatic individuals during initial weeks (14-21 d) of infection (>50%).

However, sensitivity in asymptomatic carriers was less than 60% at all time points.

As COVID-19 testing strategies in workplaces, schools, and other shared spaces are optimized, low saliva sensitivity in asymptomatic infections must be considered.

The data suggests saliva-based RT-PCR should not be used for asymptomatic COVID-19 screening.

Figure. Saliva Sensitivity by Collection Timing After COVID-19 Onset Overall and in Symptomatic and Asymptomatic Individuals



Saliva sensitivity in all 524 nasopharyngeal-positive paired samples from 256 participants (A) and participants who were symptomatic vs asymptomatic at time of specimen collection (B) grouped by collection timing after COVID-19

onset, defined as the earliest of either first symptom or first reverse transcriptase-polymerase chain reaction positivity. Error bars indicate 95% CIs.

However, routine twice weekly Antigen tests that suggest infectious Ct scores and without symptoms, may be useful to reduce PCR testing to when there is a reason.

<https://jamanetwork.com/journals/jama/fullarticle/2783249>

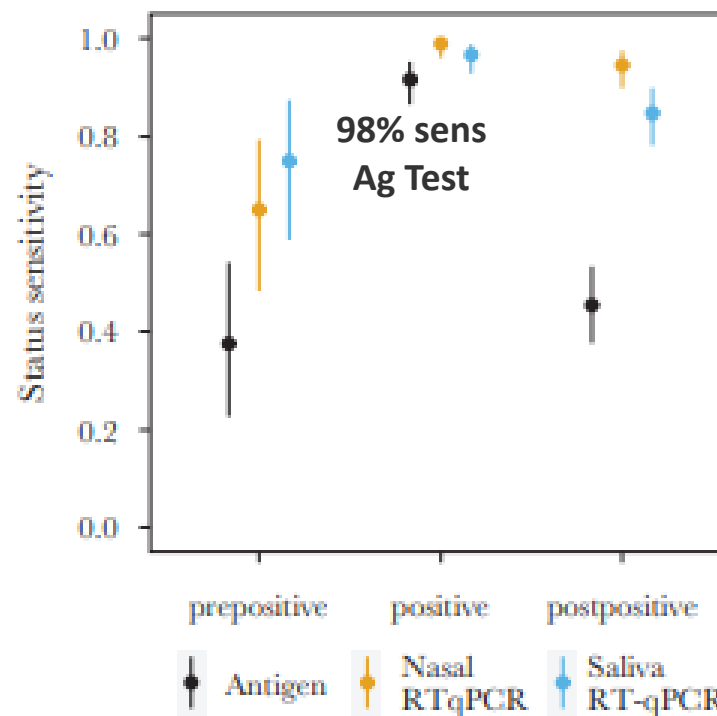
Antigen Testing Every 3 Days Is Highly Sensitive for Identifying “Infectious”

A recent campus-based [study](#) suggests that rapid SARS-CoV-2 antigen testing could help curb community spread by detecting asymptomatic infections. The study found that antigen testing—which is faster and cheaper than gold-standard polymerase chain reaction (PCR) testing—is **highly sensitive for detecting SARS-CoV-2 infections when conducted at least every few days.**

The study involved 43 on-campus students and employees of the University of Illinois at Urbana-Champaign who had mild or asymptomatic infections and positive nasal virus cultures. Participants submitted daily samples for 14 consecutive days, and antigen testing was performed with **the 15-minute point-of-care Quidel Sofia SARS Antigen Fluorescent Immunoassay.**

Nasal and saliva PCR testing were more sensitive than antigen testing with nasal samples early in the course of infection. However, **antigen testing’s sensitivity reached 98% when conducted at least every 3 days**, bringing it on par with PCR testing at the same frequency.

<https://jamanetwork.com/journals/jama/fullarticle/2782881>



Antigen testing finds the “infectious” Subject (Ct <30) as well as PCR with 98% sensitivity.

The Study:

<https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab337/6311835>

Antigen Testing Every 3 Days Is Highly Sensitive for SARS-CoV-2

Testing daily, other day, third day, fourth, fifth, sixth and weekly

Testing every THIRD day still provided 100% detection and SENS drops to 80% with WEEKLY tests
Antigen testing finds the “infectious” Subject (Ct <30) as well as PCR with 98% sensitivity

Testing Frequency	No. Before or While VC+ ^a		Nasal Antigen				Saliva RT-qPCR				Nasal RT-qPCR			
			Probability of Detection		No. Positive		Probability of Detection		No. Positive		Probability of Detection		No. Positive	
			Any Time ^b	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+	Any Time	Before or While VC+
Daily	43	22	1	0.909	43	20	1	0.955	43	21	1	1	43	22
Every other day	86	44	1	0.841	86	37	0.988	0.909	85	40	1	0.909	86	40
Every third day	129	66	1	0.803	129	53	0.984	0.833	127	55	1	0.848	129	56
Every fourth day	172	88	0.959	0.739	165	65	0.983	0.761	169	67	1	0.784	172	69
Every fifth day	215	110	0.921	0.682	198	75	0.981	0.709	211	78	0.995	0.727	214	80
Every sixth day	258	132	0.864	0.621	223	82	0.965	0.644	249	85	0.992	0.667	256	88
Weekly	301	154	0.797	0.558	240	86	0.963	0.597	290	92	0.987	0.597	297	92

Abbreviations: RTqPCR, quantitative reverse transcription polymerase chain reaction; VC+, viral culture positive,

^aBefore or while VC+ refers to detection of the individual before or during the time in which their viral culture was positive.

^bAny time refers to detection of the individual at any point in the 14-day testing period.

“VC+” is viral culture POS

The Study:

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Antigen Testing Every 3 Days Is Highly Sensitive for SARS-CoV-2

Testing daily, other day, third day, fourth, fifth, sixth and weekly

Daily sensitivity of each test platform relative to the day of first positive viral culture result. Shaded areas represent the 95% confidence interval around the observed proportion. Abbreviation: RT-qPCR, quantitative reverse transcription polymerase chain reaction.

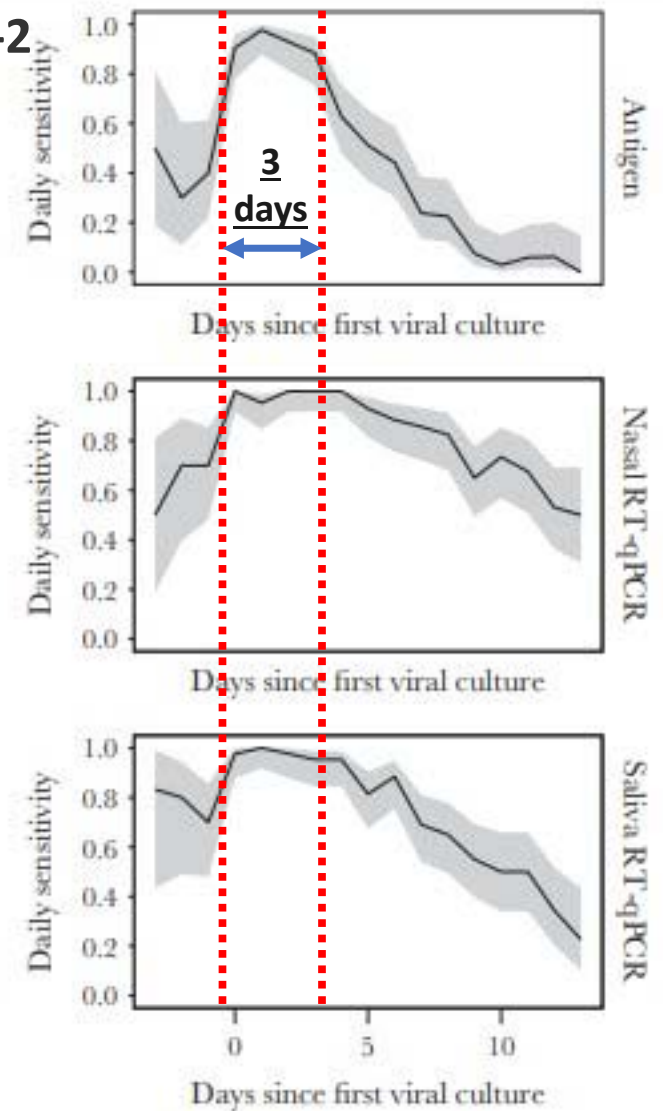
The data supports a window of Antigen discovery opportunity between D0 and D3 of viral POSitivity (**Ag test sens @ 98% vs PCR at D1-D3**)

Note the Saliva PCR POS declines faster than the Nasal sensitivity. The Antigen sensitivity declines rapidly as the infection wanes after Day 5.

Testing every THIRD Day will thus capture the Peak productivity period of the viral infection for time of highest protein expression. (dotted red lines indicate the 3 day window of opportunity)

The Study:

<https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab337/6311835>



Antigen Test

Specifications:

Most are <30 min and at home use.

They nearly all can detect the spike protein at or near Ct scores of 30.

Notes:

Ct, cycle threshold;

LoD, limit of detection;

N/A, not available (not found);

TCID, tissue culture infective dose.

a: US Food and Drug

Administration – Emergency Use

Authorizations for Medical

Devices (FDA-EUA); b CE.

Company	Device	Time	LoD	Sensitivity	
				Overall	Specific conditions
Abbott Diagnostics ^a	BinaxNOW COVID-19 Ag Card	~15 min	22.5 TCID50/swab	0.97 (95%CI, 0.85–1.00)	Ct _≥ 33: 0.83 (0.36–1.00)
Amedica SA ^b	Amela Covid-19 Antigen test	~30 min	N/A	N/A	–
ArcDia International Ltd ^b	mariPOC SARS-CoV-2	~20 min	N/A	0.92 (95%CI, N/A)	–
Becton Dickinson ^a	BD Veritor System for Rapid Detection of SARS-CoV-2	~15 min	140 TCID50/swab	0.84 (95%CI, 66–95)	–
Beijing Kewei Clinical Diagnostic Reagent ^b	Kewei COVID-19 Antigen Rapid Test Kit	~15 min	N/A	0.85 (95%CI, N/A)	–
Beijing Savant Biotechnology ^b	SARS-Cov-2 Antigen Fluorescence Rapid Detection Kit	~15 min	50 ng/mL	N/A	–
Coris BioConcept ^b	COVID-19 Ag Respi-Strip	~15 min	N/A	0.60 (95%CI, 0.48–0.71)	Ct<25: 0.77 (0.61–0.88)
Liming Bio-Products ^b	Strongstep COVID-19 Antigen Rapid Test Device	~15 min	N/A	0.73 (95%CI, 0.60–0.83)	–
LumiraDx UK Ltd ^a	LumiraDx SARS-CoV-2 Ag Test	~12 min	32 TCID50/swab	0.98 (95%CI, 0.92–1.00)	–
PCL Inc ^b	PCL COVID19 Ag Rapid FIA	N/A	N/A	N/A	–
Quidel Corporation ^{a,b}	Sofia SARS Antigen FIA	~15 min	113 TCID50/swab	0.97 (95%CI, 0.83–1.00)	–
RapiGEN Inc ^b	Biocredit COVID-19 Ag	5–8 min	N/A	0.90 (95%CI, 0.79–0.97)	–
SD Biosensor Inc	Standard F COVID-19 Ag FIA	~30 min	7.81 × 10 ¹⁻² TCID50/mL	N/A	–
SD Biosensor Inc	Standard Q COVID-19 Ag FIA	15–30 min	1.25 × 10 ³⁻² TCID50/mL	0.97 (95%CI, 0.91–0.99)	–
Shenzhen Bioeasy Biotechnology ^b	Bioeasy 2019-nCoV Ag	~15 min	N/A	N/A	–
Sugentech, Inc ^b	SGTi-flex COVID-19 Ag	~20 min	530 TCID50/swab	0.80 (95%CI, 0.61–0.91)	–
Verify Diagnostics ^b	COVID-19 Antigen Rapid Test Device	~15 min	N/A	0.80 (95%CI, 0.74–0.86)	–