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RAPID DIAGNOSTIC TESTS FOR COVID-19

RAPID DIAGNOSTIC TESTS (RDTs) CAN DETECT EITHER ANTIGEN (Ag) OR ANTIBODY (Ab), AND BOTH TEST TYPES HAVE IMPORTANT ROLES GIVEN THE CURRENT EPIDEMIC CONTEXT (COMMUNITY TRANSMISSION)

A combination of different test types is needed to facilitate patient management and public health planning for effective control of COVID-19. Tests that **directly detect the virus (polymerase chain reaction [PCR] or Ag) should be prioritized for diagnosis and monitoring**; while tests that detect the immune response to the virus **(Ab)**, can be complementary for clinical care, but **should be prioritized for seroprevalence and epidemiological purposes**. Importantly, the utility of any test is dependent on several factors: 1) the test performance (i.e. sensitivity and specificity), 2) the epidemiological context in which it is used (i.e. the disease prevalence), and 3) the timing of test use in relation to disease kinetics (especially true for Ab tests). (See page 4 for more details.)

GENERAL INFORMATION ON Ag- AND Ab-DETECTION RDTs FOR COVID-19

- RDTs can enable fast (15–40 minutes), decentralized access to testing, but generally have decreased performance compared with lab-based tests:
  - Tests with the **highest possible sensitivity must be prioritized** to minimize false negatives, as these may lead to missing cases.
  - High **specificity** is also important, **particularly as prevalence decreases.**

- Ag tests directly detect SARS-CoV-2 virus, will be positive within a few days after infection, and will become negative as the patient clears the infection and recovers. Therefore, **Ag tests are useful for detection of active infection.**

- Ab tests detect the host response to the virus and take several more days to become positive – they are likely to be most accurate 10–14 days post infection. **Ab tests cannot distinguish between active and previous infection.** Current data are limited on the correlation between antibody detection and immunity/protection.

- **Positive results from either Ag or Ab tests, together with the presence of respiratory symptoms**, indicate that an individual is likely to be actively infected with SARS-CoV-2 (dependent on the positive predictive value of the test). Without waiting for confirmatory testing, the individual should undergo home isolation, or healthcare facility admission if symptoms require advanced care.
  - In individuals **without symptoms and no known contact** with a person suspected to have COVID-19 in the past 14 days, a positive Ab test followed by a negative PCR test indicates prior infection.

- **Negative results from either Ag or Ab tests should be interpreted with caution (dependent on the negative predictive value of the test)**; for suspect cases with negative results, consider accessing a more sensitive test for confirmation (i.e. PCR), and/or home isolation followed by a second test at a later date.

SUGGESTED USES FOR Ag- AND Ab-DETECTION RDTs GIVEN OUR CURRENT UNDERSTANDING

- **Ag RDTs** should be prioritized for **case management** to enable decentralized testing, especially when access to PCR testing is limited.

- **Ab RDTs** should be prioritized for **seroprevalence surveys** to inform public health measures and testing of contacts to establish previous spread of the virus.

Suggested use		Ag	Ab
Case management in high prevalence/ active outbreak settings	Triage suspect cases **Positive:** no confirmatory testing required **Negative:** confirmatory testing with PCR recommended, if available	✓	
	Aid diagnosis in symptomatic cases presenting late (≥10 days post-symptom onset) In addition to PCR/Ag, not a replacement		✓
	Monitor active infection	✓	
Public health measures	Screen contacts for infection	✓	
	Screen contacts for previous exposure (≥10 days post exposure)		✓
	Seroprevalence surveys to define levels of population exposure,* including vaccine trial support		✓

* Insufficient data supporting effectiveness of protection or duration of immunity.

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UNIQUE FEATURES OF SARS-COV-2 THAT ARE IMPORTANT TO CONSIDER WHEN USING RDTs

- SARS-CoV-2 is a **respiratory pathogen**, unlike malaria, HIV, dengue, Zika or chikungunya viruses.

- The immune response to SARS-CoV-2 may be atypical:
  - Other viruses: IgM is detectable in the blood during active infection and then wanes after a few weeks, whereas IgG levels rise after the acute phase.
  - SARS-CoV-2: Preliminary studies suggest that **IgM and IgG rise** during early infection and may remain high for weeks, though more data are needed.

- Respiratory specimens may contain high levels of virus **days before the onset of symptoms**, even in **individuals who remain asymptomatic**.

- In a pandemic situation, where there are no specific treatments and the goal is to minimize spread of the infection by breaking the chain of transmission, tests with the **highest possible sensitivity** must be selected to minimize the possibility of missing any active cases:
  - To reduce the burden on confirmatory testing in high prevalence settings, a positive result from a screening test (even with low specificity and thus a higher probability of false positivity) may not require confirmation.
  - In this scenario, all individuals who screen positive should undergo home isolation, or be admitted to a healthcare facility if symptoms are severe and warrant hospitalization.

OPERATIONAL CHARACTERISTICS AND OVERVIEW		
	Antigen (Ag)	**Antibody (Ab) (IgA, IgM and/or IgG)**
How does it work?	Directly detects the presence of the virus, indicating **active infection** (i.e. replication of the virus)	Detects the body's immune response to the virus, in the form of antibodies (IgA, IgM, IgG or in combination), which are produced during **active infection**, but also persist after the virus is no longer detected, indicating **previous infection**
Sample type	Nasopharyngeal, nasal, or oropharyngeal swab; potentially oral fluid or stool	Fingerstick blood, venous blood; potentially oral fluid
Where and who performs?	Trained healthcare workers, wearing appropriate personal protective equipment (PPE) at decentralized points of need	
Benefits	Enables fast, **decentralized access to direct testing** for the virus, relieving the burden on the laboratory testing system If used for contact tracing, provides an **objective marker to define chains of transmission**	Best biomarker for **estimation of the number of people previously infected**: enables more accurate estimates of case fatality rates, serial sampling can be used to estimate incidence In **high prevalence** settings, may be useful to **triage symptomatic patients in a later phase of disease** and reduce the burden on the laboratory testing system (relieve bottlenecks): positive results can trigger clinical action; negative results should reflex to PCR for confirmatory testing, if available In **low prevalence** settings, the use of Ab tests to triage symptomatic patients is unlikely to be beneficial due to low PPV

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TEST UTILITY IS RELATED TO THE TEST PERFORMANCE (SENSITIVITY/SPECIFICITY) AS WELL AS THE EPIDEMIC SETTING (i.e. PREVALENCE IN THE POPULATION)

The number of true positives and true negatives is dependent on the prevalence of the population being tested, as illustrated in the table on the next page.

INTERPRETATION OF TEST RESULTS		
	Antigen (Ag)	**Antibody (Ab) (IgA, IgM and/or IgG)**
A true positive result…	Means SARS-CoV-2 is present; the person is actively infected and should home isolate or be admitted to a healthcare facility → Continue contact tracing to define chains of transmission and contain disease spread	Indicates an active or past infection → In the absence of symptoms or recent (past 14 days) exposure, indicates previous infection and potential immunity;* followed by a negative PCR test, confirms previous infection and excludes active infection
A true negative result…	Means the person is uninfected → If the test has a low negative predictive value, in the presence of symptoms, the result may be a false negative; home isolate while waiting for a confirmatory PCR test, or a re-test with an Ag RDT in a few days → If the test has a low negative predictive value in the absence of symptoms, monitor for onset of symptoms and consider a confirmatory test	Means the person has no detectable Ab and therefore has not been infected or is early in the course of active infection before antibodies can be detected (i.e. window period) → Difficult to interpret if used to screen for active infection: in the presence of symptoms, could mean that the person is early in the course of active infection, before antibodies can be detected (i.e. window period); follow with a confirmatory test that directly detects the virus (i.e. PCR or Ag)
A false positive result…	Means the person is uninfected, but will be unnecessarily directed to home isolate or be admitted to a healthcare facility to manage symptoms If in the presence of symptoms, means that the person is ill with another febrile/respiratory illness and may not be appropriately treated	If used to screen for active infection, means that the person is uninfected, but will be unnecessarily directed to home isolate or be admitted to a healthcare facility to manage symptoms If in the presence of symptoms, means that the person is ill with another febrile/respiratory illness and may not be appropriately treated If used to screen for exposure during contact tracing or sero-surveys, means that the person is still susceptible and could be put at risk and pose a risk to others
	❗ Tests with poor specificity/high cross-reactivity could be falsely reactive due to other endemic infections	
A false negative result…	Means that the person is infected, but is missed → The person may not receive the care needed and will contribute to community transmission if not in isolation	If used to screen for active infection, means that the person is infected and likely too early in the infection for antibodies to be detected (i.e. window period), so is missed → The person may not receive the care needed and will contribute to community transmission if not in isolation If used to screen for exposure during contact tracing or serosurveys, means that the person has been infected, but no action is taken

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As seen below, a test with **high performance** (95% sensitivity and 98% specificity), when applied to a **low-prevalence setting,** will result in roughly the same number of true positives and false positives (PPV: ~50%), whereas when applied to a higher prevalence population would result in a much higher positive predictive value (PPV: 95%), with the majority of positive results associated with actual cases. Alternatively, the use of a **mid-or lower-performing test** might be considered for a **high prevalence population** (PPV: 68-78%), but would lead to such high numbers of false positives when testing a **low prevalence population that this would likely do more harm than good**. Across a range of sensitivities and prevalence, the negative predictive value remains relatively high, but the consequence of missed cases for epidemic control and case management can be detrimental.

Cohort	Pre-test probability (prevalence)	Sensitivity	Specificity	Cases	Non-cases	True positive (TP)	False negative (FN)	True negative (TN)	False positive (FP)	PPV	NPV
High performance											
1,000	2.0%	95%	98%	20	980	19	1	960	20	49.2%	100%
1,000	5.0%	95%	98%	50	950	48	2	931	19	71.4%	100%
1,000	10.0%	95%	98%	100	900	95	5	882	18	84.1%	99%
1,000	30.0%	95%	98%	300	700	285	15	686	14	95%	98%
Mid performance											
1,000	2.0%	85%	90%	20	980	17	3	882	98	14.8%	100%
1,000	5.0%	85%	90%	50	950	43	8	855	95	30.9%	99%
1,000	10.0%	85%	90%	100	900	85	15	810	90	48.6%	98%
1,000	30.0%	85%	90%	300	700	255	45	630	70	78%	93%
Low performance											
1,000	2.0%	75%	85%	20	980	15	5	833	147	9.3%	99%
1,000	5.0%	75%	85%	50	950	38	13	808	143	20.8%	98%
1,000	10.0%	75%	85%	100	900	75	25	765	135	35.7%	97%
1,000	30.0%	75%	85%	300	700	225	75	595	105	68%	89%

The expected prevalence of active or previous COVID-19 infection will vary across populations being tested and is therefore an important consideration when selecting tests and interpreting results. Example prevalence ranges for some target populations are summarized below.

Target population	Example prevalence range
Symptomatic healthcare workers	High to very high (10 – ≥ 30%)
Healthcare workers with significant exposure	High (10%)
Contacts of index patient	Low to high (2 – 10%)
Community testing/contact tracing of hotspots	Medium to high (5 – ≥ 10%)
Symptomatic general population	Low (2%)
Asymptomatic general population	Very low to low (≤ 2%)