

Update on the management of SARS-CoV-2 infection

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Infection and infectivity: Utility of rapid antigen tests for the diagnosis of COVID-19

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ABSTRACT

Detection of SARS-CoV-2 proteins is commercially available in the form of lateral-flow rapid antigen test for the point-of-care diagnosis of COVID-19. This platform has been validated for symptomatic and asymptomatic individuals, for diagnosis or screening, and as part of single or sequential diagnostic strategies. Although in general less sensitive than amplification techniques, antigen tests may be particularly valid during the first days of symptoms and to detect individuals with greater viral load, thereby with enhanced chances of viral transmission. The simplicity of antigen tests make them very suitable to discard infection in settings with low pretest probability, and to detect infection in case of higher chances of having COVID-19.

Keywords: SARS-CoV-2; COVID-19; rapid antigen tests; PCR; variants; infectivity

The transmission of SARS-CoV2 occurs mainly in the pre-symptomatic period and for just around 72 hours after the onset of symptoms (Figure 1). Asymptomatic infected also transmit the infection, although to a lesser extent. Other factors that have been related to greater transmission are contact with infected persons in closed environments or risks from professional exposure.

Tests that detect SARS-CoV-2 antigen (AgT) can be performed quickly and at the same point of care, and therefore can be more accessible with a faster time to result than techniques based on amplification (PCR, TMA). In contrast, AgT are less sensitive than amplification techniques (AmT). From a clinical point of view, the positivity of the AgT indicates infec-

tion with high specificity, and additionally it is related to high amounts of virus in respiratory secretions, thus indicating a greater risk of contagion. It is known that AmT remain positive for a long time, so a positive result in these techniques is not always associated with a risk of contagion (Figure 1).

It is accepted that AgT are particularly useful in the following scenarios:

- **Early stages of infection:** Although they cannot detect viruses at levels as low as AmT, AgT can be useful for people who are in the early stages of infection, when virus replication is at its highest. The WHO notes that, in settings where AmT are not available or where AmT result times are too long, AgT

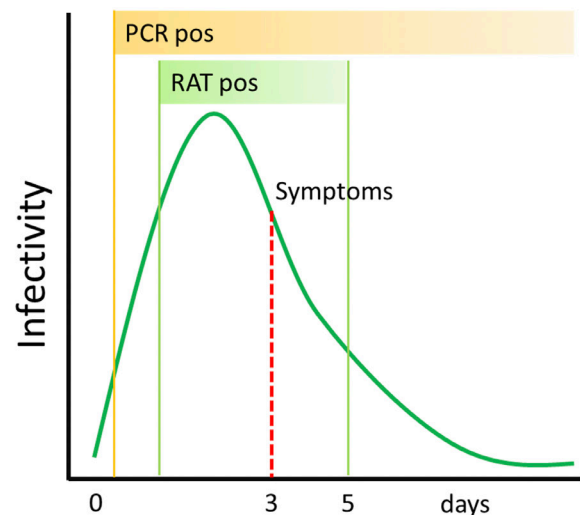


Figure 1 Dynamics of SARS-CoV-2 transmission.

PCR, polymerase chain reaction; RAT, rapid antigen test

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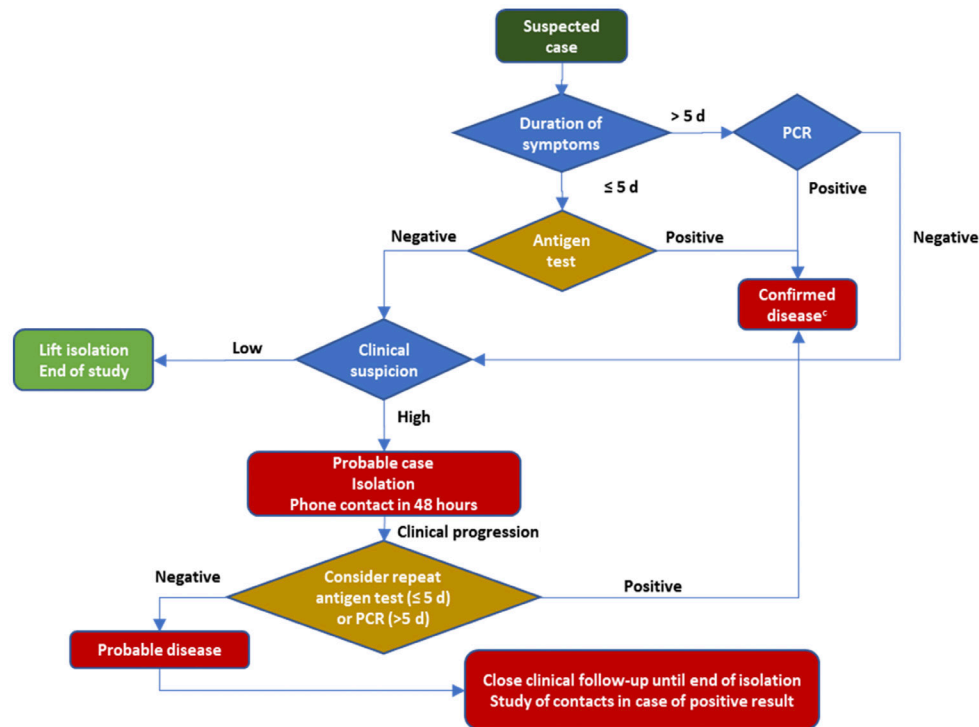


Figure 2 Indication of antigen test in symptomatic individuals.

with minimal sensitivity and specificity of $\geq 80\%$ and $\geq 97\%$, respectively, can be used for diagnosis SARS-CoV-2; in such cases, the test should be done within the first 5 to 7 days of the onset of symptoms [1]. Used for clinical diagnosis in symptomatic patients, positive AgT indicate SARS-CoV-2 infection with high reliability (Figure 2) [2]. However, the negative result may be false as a consequence of the lower sensitivity of the AgT, so if the clinical suspicion is high, an AmT should be performed within the following 48 hours and the patient should be isolated during that time.

According to a study [3], between days 0 to 10 of the acute phase of infection, only a third of patients present elevated levels of RNA in respiratory secretions, which would result in a positive AgT; the other two-thirds have a low viral load so that the AgT most likely will be negative. After 10 days of infection, 90% of patients have such a low RNA level that the AgT will also be negative; finally, there are 10% of patients who, after 10 days of infection may have high levels of RNA and still positive AgT.

-Closed environments: AgT can also be useful in the study of outbreaks, particularly in high-risk closed environments (nursing homes, schools, prisons, etc.); if the frequency of testing is high enough, even despite the lower sensitivity of AgT, it has been shown that AgT can be used successfully to reduce cumulative infection rates [4]. If used for serial testing in this setting, negative AgT does not need to be confirmed by

AmT and positive results are diagnostic.

If AgT are used in situations in which the probability of infection is lower (screening of asymptomatic patients or low cumulative incidence in the community) the negative result is reliable because in these settings the negative predictive value of the test increases. However, any circumstance that increases the likelihood of pre-test infection, such as close family contact or high infection rates in the community, should lead to confirmation with AmT any negative AgT.

According to a recent systematic review, the sensitivity of AgT is higher in cases with symptoms compared to asymptomatic contacts (72% versus 58%) and is higher during the first week compared to the second week after the onset of symptoms (78% versus 51%). The sensitivity is also higher in samples with a higher estimated level of viral RNA (95% with Ct <25 versus 41% with Ct > 25). The specificity in general is high (greater than 99%) [5]. In another study, the sensitivity and specificity of AgT, taking AmT as a reference, was 41% and 98%, respectively, in asymptomatic individuals, and 80% and 99% among symptomatic individuals [6]. The mean Ct value for samples that had a negative AgT but a positive AmT result was higher than that of the samples that were consistently positive (Ct of 32 versus 24), confirming that the sensitivity of AgT is higher for high levels of virus in respiratory secretions. There are no studies in this regard, but it is foreseeable that AgT will be more cost-effective for the detection of variants

that are associated with higher levels of RNA [7,8]; in contrast, AgT will probably be less useful for the diagnosis of reinfections or infection in vaccinated patients, situations in which viral RNA levels are expected to be lower.

In another study it has been shown that a positive AgT indicates the presence of viable virus in the sample more reliably than a positive AmT; among 38 samples positive for AmT, AgT was positive in 27/28 samples with positive culture, but only in 2/10 samples with negative culture [9]). Viable virus can also be isolated from a AgT negative samples; in another study, 9% of clinical samples positive for AmT were negative for AgT [10]. Negative AgT are not entirely reliable in indicating that a person with a proven infection is not infectious.

Most AgT target the nucleocapsid protein for the detection of SARS-CoV-2. Mutations found in viral variants are mostly located in the spike protein, but there are several changes in the nucleocapsid protein that could affect the performance of AgT. In several studies, the variant B.1.1.7 (British) was equally well detected by all AgT tested (namely Abbott Panbio, Fortress, Innova, Roche, and Surescreen). No such studies are available for the variant B.1.351 (South African) or B.1.617.2 (Indian) [11].

In summary, AgT are especially useful in these situations:

- To detect infection in patients with active symptoms.
 - In patients with high viral load, such as variant-infected patients; probably sensitivity will be lower in the case of reinfections or in the infection of the vaccinated patient.
- In the study of outbreaks, particularly if the test is repeated every 3-5 days.
 - To rule out infection if there is a low pretest probability.
 - The performance of AgT needs to be monitored as new viral variants emerge.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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