Is Adding IgM Antibody to Polymerase Chain Reaction Testing Useful for COVID-19 Travel Screening?

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Since November 8, 2020, international travelers entering China have been required to present a negative nucleic acid test (NAT) and a negative serum severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin M (IgM) antibody test, known as the "double-negative test," taken within 48 hours prior to departure.[1] The new requirement for an additional IgM antibody test by the Chinese Embassy for international travelers has sparked discussions among both Chinese and international media, as well as debate within the scientific community on the usefulness of an added IgM test. What is the scientific rationale for a "double-negative test?" Does it improve the overall sensitivity in screening individuals infected by SARS-CoV-2?

Proof of a negative NAT upon arrival or within 72 hours prior to departure is not a new requirement for international travelers in the current coronavirus disease 2019 (COVID-19) pandemic. Many countries have imposed similar travel policies to minimize the risk of cross-infection during travel and thereby preserve the epidemic containment within their borders. These measures are particularly important for countries that are popular for international tourism and business. For instance, over the past Thanksgiving holiday, Hawaii required all travelers to provide a negative COVID-19 test result prior to departure. The US Centers for Disease Control and Prevention (CDC) also recently updated its Testing and International Air Travel recommendations for passengers to obtain COVID-19 testing both 1 to 3 days before and 3 to 5 days after air travel.[2] Furthermore, given that many countries are currently facing yet another new COVID-19 surge, strict travel policies will continue to be imposed. Regardless of the context of travel, as with all testing, who, what, when, and how to test matter significantly, in addition to the test performance itself.

Since the start of the pandemic, NAT for SARS-CoV-2 has been regarded as the gold standard test for COVID-19, as it is overall the most sensitive approach to detect viral presence during the first week after symptom onset. However, not all NATs perform equally. Among the more than 200 molecular diagnostic tests that received Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA), many are based on traditional reverse transcription polymerase chain reaction (RT-PCR), while others use less conventional methods such as droplet digital PCR, isothermal amplification, matrix-assisted laser desorption ionization–time-of-flight mass spectrometry, or clustered regularly interspaced short palindromic repeats technology. The limit of detection (LOD) of these tests significantly affects the detection sensitivity of SARS-CoV-2 and has been shown to vary over 3,000-fold. Each 10-fold increase in LOD is expected to increase the false-negative rate by 13%, and thus the NAT with the highest LOD may have a false-negative rate as high as 70%.[3]

There is no specification regarding which NAT travelers should use under any current travel policy. In the hospital setting, RT-PCR and nasopharyngeal (NP) swabs, being the most sensitive method and sample type, are most commonly used. However, NP swabbing needs to be performed by trained health care personnel, and inadequate collection can compromise test sensitivity. As testing demands remain high, NAT performed in laboratories on asymptomatic individuals might not be

prioritized and can still take more than 3 days to turn around, which would not allow travelers to present a negative test taken within 72 hours. In this regard, point-of-care (POC) NATs performed on nasal swabs or saliva with faster turnaround times (TATs) may be more suitable for travel screening. Despite the benefits of sampling convenience and faster TAT, POC tests are typically less sensitive compared with RT-PCR and can result in more false negatives. On November 17, 2020, the FDA granted EUA to the first at-home test by Lucira, which performs isothermal amplification on nasal swab samples to provide a positive or negative readout within 30 minutes. However, there are limited data on its sensitivity, but in practice, the LOD is likely to be significantly affected by the sample collection quality of consumers at home. Most travel policies also require test results from certified testing sites, so results obtained using at-home tests may not be permitted.

In some US cities and in other countries, there are COVID-19 testing sites set up at or near the airport to screen passengers prior to departure or following arrival. In this setting, even POC NATs may not serve to deliver prompt results for a large number of passengers due to throughput issues. Supply shortages of NAT kits remain a common hurdle to significantly ramping up testing capacity. On the other hand, SARS-CoV-2 antigen tests, which normally generate results within 15 to 30 minutes, could be the preferred test to use for airport screening. Most antigen tests that received FDA EUA are POC lateral flow immunoassays, which are also most sensitive in detecting infections during the first week after symptom onset, when patients carry the highest viral load; however, without an amplification step, antigen testing exhibits much lower sensitivity than NAT.[4] Nevertheless, antigen testing can be performed more quickly and cheaply than NAT and thereby can rapidly screen for individuals with high levels of virus requiring isolation.

As a patient's viral load decreases over time, the clinical sensitivity of nucleic acid and antigen tests declines. A recent study found that the clinical sensitivity of NATs decreases from more than 90% during the first 5 days after symptom onset to 70% to 71% during days 9 to 11 and to 30% at day 21.[5] In contrast, the clinical sensitivity of antibody tests increases after the first week following symptom onset. The diagnostic accuracy of antibody tests is only 30.1% within 7 days after symptom onset, whereas it increases to 72.2% after 8 to 14 days and to 91.4% after 15 to 21 days.[6] Therefore, while antibody testing is not particularly useful for diagnosis early in the course of COVID-19 infection, it can be complementary to NAT after 1 to 2 weeks following symptom onset. How contagious COVID-19 patients are after the first week of symptom onset is still not well understood. The CDC suggests that patients with COVID-19 likely remain infectious no longer than 20 days after symptom onset. Adding an antibody test could help detect a recent or resolving infection that still has the potential to mediate spreading of the virus but has somehow eluded detection by NAT. However, how long IgM and immunoglobulin G (IgG) antibodies against SARS-CoV-2 remain present after infection is also largely unknown. A recent study by Iyer et al[7] demonstrated that IgM antibodies against the RBD region of the SARS-CoV-2 spike protein were short-lived, with median times to seroreversion of 49 days after symptom onset. In most other viral or bacterial infections, IgG antibodies usually remain detectable for years or a lifetime while IgM antibodies decline after several months. This feature makes IgM potentially helpful to be used in combination with NAT to extend the detection window of a recent infection or exposure with some degree of temporal specificity vs testing for IgG antibodies.

In places where new cases of COVID-19 are rare and need to be more carefully monitored and followed by contact tracing, employing a more stringent screening strategy may be particularly useful. As discussed, a testing panel combining nucleic acid and IgM testing may increase the overall sensitivity of detecting acute and recent COVID-19 cases. However, IgM antibodies can remain detectable for up to several months in patients who have recovered from COVID-19. With the added requirement of a negative IgM test result, individuals previously infected with COVID-19 could unnecessarily be denied entry after recovery for as long as their IgM antibodies remain detectable. In countries or regions where new COVID-19 case numbers are high and contact tracing is not conducted on every positive case, it is most critical to identify the individuals with higher viral loads via screening; in this scenario, nucleic acid or antigen testing performed within 3 days of travel is most helpful, and IgM testing might not provide additional value.

At present, no single ideal test can specifically detect all cases of SARS-CoV-2 infection—including individuals who are asymptomatic—within a narrow cross section in time, even for a defined population. Nucleic acid, antigen, and antibody tests all have limitations in SARS-CoV-2 detection. There is unlikely a "one-size-fits-all" solution that could be implemented on a national level to control the global COVID-19 pandemic.

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We are continuously learning to meaningfully deploy optimal testing strategies, in addition to face masking, social distancing, handwashing, and isolation. Public health policy, informed by scientific evidence, is as important as effective medical treatment regimens for handling the crisis. With the uptick in new COVID-19 cases worldwide and a busy holiday travel season, changes and additions to testing requirements on travelers are expected. The recent availability of COVID-19 vaccines will also inevitability add another dimension to travel screening considerations, although an additional vaccination requirement in favor of solely requiring single or combination testing will likely simplify these deliberations. Even so, clinical testing remains an important asset in our response to the pandemic. There are both pros and cons to implementing combination testing such as the "double-negative test," and the decision to enact such measures depends on both context and how the screening results will be acted upon. Testing accessibility and timely turnaround of results remain key to successful control of cross-infection among travelers.

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