COVID-19 diagnostic testing in the context of international travel

Scientific brief

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World Health Organization

Background

To limit transmission and reduce morbidity and mortality from COVID-19, countries around the globe have implemented public health and social measures (PHSM) for epidemic control. One measure considered by many countries and transport sector stakeholders is testing for SARS-CoV-2 (the virus that causes COVID-19) in international travellers prior to travel, at points of entry or after travel.

Testing at borders is not a substitute for other public health measures, especially robust contact tracing systems. WHO recommends that confirmed, probable and suspected cases for COVID-19 (1) and contacts of confirmed or probable cases do not travel. WHO also advises that travelers who are unwell or any persons who are at an elevated risk for developing severe disease and dying from SARS-CoV-2 infection, including people 60 years of age or older or those with chronic diseases or underlying health conditions, are advised to delay or avoid travelling internationally to and from areas with COVID-19 community transmission.

A thorough risk assessment should be a key element of the decision-making process regarding SARS-CoV-2 testing policies for international travellers. This risk assessment should take into account an understanding of the epidemiological situations and health system capacities in the countries of origin and destination of the traveller; surveillance and case management for COVID-19 in the countries of the origin and destination of the traveller and during the travel; and arrangements for follow-up and observation of incoming travellers, including self-monitoring for the development of symptoms after arrival for up to 14 days (2). Additionally, resources and capacity to offer testing for international travellers should be assessed critically to avert negative impact on testing in high-risk settings and high-risk groups (including people at risk of developing severe disease, vulnerable populations and health workers, in line with WHO guidance (3). Countries also need to consider their capacity to manage infected travellers whose illness is detected at points of entry as per WHO interim guidance (4).

The reliability and usefulness of testing for SARS-CoV-2 depends on many factors, including the incidence of SARS-CoV-2 infection in the population being tested, the SARS-CoV-2 assay type and performance, the type and quality of the specimen tested, timing of the specimen collection as it relates to exposure to SARS-CoV-2 and the turn-around time for results.

This scientific brief examines the requirements and issues around testing as a tool for mitigating cross-border transmission of COVID-19. It provides an overview of SARS-CoV-2 diagnostic assays and their performance and suitability for potential use in SARS-CoV-2 testing prior to departure, at points of entry and on arrival.

Reliability of testing before or after travel

Negative results from pre-travel testing cannot guarantee that travellers are free from infection at the time of travel, since they may have been tested before they became infected or during the period when viral load is not yet sufficient to be detectable. The mean time from exposure to SARS-CoV-2 until symptom onset (the incubation period) is 5-6 days but may range from 1-14 days. In most individuals, the virus becomes detectable in the upper respiratory tract approximately 1-3 days before symptom onset and for days to weeks after symptoms develop (5-11). An estimated 20% (17–25%) (12) of cases, the virus may be detectable, but symptoms do not develop (13-17). Negative SARS-CoV-2 test results may generate a false sense of security both for the individual traveller and the national authorities at the traveller's destination and could lead to less diligent adherence to hand and respiratory hygiene, physical distancing use of personal protective equipment (PPE) and self-monitoring for symptoms.

Further studies are needed to determine the level of risk reduction that such testing can offer and to explore the possibility of using testing to reduce quarantine time of the traveller on arrival. WHO is conducting modelling studies and regular systematic reviews of the effectiveness and feasibility of implementing risk mitigation measures, including testing, in the context of international travel.

Potential impact of testing international travellers on national priority testing capacity

National testing capacities, including laboratory supplies, trained personnel and personal protective equipment (PPE) should be carefully evaluated when deciding whether testing of travellers should be included in national response strategies for COVID-19. Such an assessment is critical in countries that lack resources to test all suspected cases in their own populations. With those considerations in perspective, WHO has published guidance on the prioritization of testing to optimize the use of limited resources (18). Within this guidance, WHO excludes travellers as a priority group for testing in areas with community transmission and in

settings where testing capacity cannot meet needs. Investing resources in the testing of international travellers might significantly divert a country's testing capacity; and this capacity would have a greater public health impact when devoted to high-risk settings.

Costs associated with testing international travellers

Article 40 of the International Health Regulations (IHR) states that no charge shall be levied by a State Party for measures intended to ascertain the health status of a traveller examined for the protection of public health (19). Therefore, national authorities would need to identify resources and mechanisms to cover the cost of tests performed on travellers.

Available options for SARS-CoV-2 testing

Nucleic Acid Amplification Testing (NAAT), such as with real-time reverse-transcription polymerase chain reaction (rRT-PCR), is the recommended assay type for confirmation of SARS-CoV-2 infection (20).

- Many molecular tests for SARS-CoV-2 that are well-characterized and demonstrate high sensitivity and specificity are available. This means that if tests are properly performed and provided that the standards for sampling, transportation and capacities of laboratories are met, the risk of false-negative and false-positive results from NAAT is low. The infrastructure and biosafety requirements for molecular testing in a laboratory are stringent (20). Some NAAT systems have the capacity for fully automated testing that integrates sample processing and RNA extraction, amplification and reporting, and may be performed in near-to-patient locations. However, these generally have a low sample throughput and are therefore not practical for screening large numbers of passengers with a single instrument because this approach may cause crowding at points of entry and disrupt physical distancing.
- Pooling of specimens could be used to reduce the cost of testing in population groups with a low/very low expected prevalence of SARS-CoV-2 infection (20). However, this might increase turnaround times because test-positive pool samples will need to be re-tested individually. Pooling also dilutes the viral RNA concentration of individual samples, potentially leading to some false negative results.
- As noted above, testing travellers before departure does not ensure that they will not be shedding virus at the actual time of travel. Likewise, a negative NAAT result on samples obtained from an international traveller on arrival does not exclude the possibility that the individual was recently infected with SARS-CoV-2 and is incubating the disease. Modelling data shows a minor additional benefit of serial testing at different points in time (21, 22).
- Viral RNA might be detected for weeks to months following infection and depending on severity of disease in a small subset of patients (23). Most patients, who have clinically recovered and who have mounted an antibody response to the virus, are not considered to remain infectious. Thus, if rRT-PCR were used in this situation as a as condition for travel, a positive test would result in their exclusion.

Direct immunoassay detection of viral protein antigens, including laboratory-based versions (e.g. ELISA) and rapid diagnostic test (RDT) format.

Rapid diagnostic tests detecting viral proteins have the potential to expedite and simplify the detection of SARS-CoV-2 active infection. WHO has published interim guidance on the use of antigen-detecting RDTs in the diagnosis of COVID-19 (24).

- Antigen-detecting tests have a lower sensitivity than NAAT but allow rapid detection of the most infectious patients (with the highest viral load in the respiratory tract). Like NAAT, antigen-detecting RDTs (Ag-RDTs) are likely to perform best in samples collected on or around the time of development of symptoms. The sensitivity of Ag-RDTs appears to be highly variable among the brands of RDTs used, ranging from 0 to 94% (22, 23), whereas the specificity of various RDT brands has consistently been reported to be high (≥97 to 100%) (24, 25).
- Use of Ag-RDTs is not recommended in settings or populations with low expected prevalence of disease where confirmatory testing by NAAT is not readily available. The prevalence of SARS-CoV-2 infection among travellers is expected to be low compared to the general population, considering that symptomatic individuals and case contacts should already have been prevented from travelling. The test population has an influence on the sensitivity and specificity of a test, and evaluations of using SARS-CoV-2 Ag-RDTs at points of entry are limited.
- Test performance from antigen detection assays performed in other populations (e.g. symptomatic individuals soon after symptom onset), will likely not be predictive of performance in point of entry testing. Sensitivity is likely be lower among travellers who appear to be in good health (with more cases going undetected). Conversely, the percentage of positive results being falsely positive would be higher (meaning, there is a low positive predictive value). For example, when using a test with 80% sensitivity and 98% specificity in a population where the prevalence of the infection is 1/1000 (26), the positive predictive value (proportion of travellers with a positive test who are truly infected) is only around 4%. It is therefore recommended to confirm Ag-RDT positive results with NAAT in populations with low prevalence of COVID-19.

Serological tests for IgM/IgG/IgA antibody detection, including ELISA, immunofluorescence assay and RDTs

WHO recommends against the issuance of so-called "immunity passports" for individuals who have a positive serological test showing antibodies against SARS-CoV-2 (27). A positive serological test result only indicates previous infection, and a negative test for antibodies cannot exclude an active infection with SARS-CoV-2.

Operational challenges of implementing testing requirements

Implementation of safe and reliable SARS-CoV-2 testing to mitigate the risk of cross-border transmission poses substantial operational and logistical challenges at all points of entry, including:

- A need for investment in staff trained in sample collection, biosafety, testing and result interpretation.
- Crowding within points of entry premises may increase the risk of transmission of SARS-CoV-2 and other communicable diseases among travellers and points of entry staff.
- Challenges to verifying the authenticity of test results across different countries.
- For pre-departure testing, false positives may result in unnecessary cancelations of travel for the passenger; and false negatives may result in transmission of disease during travel and quarantine following positive testing on arrival.
- For ground crossings, it may be easy to bypass official check points by taking a detour along unstaffed sections of a border. Additionally, travellers who are sick and do not want to be prevented from travelling may try to bypass ground crossing testing sites.
- Resources may be diverted from more urgent public-health needs.

WHO monitors emerging evidence about this critical topic and will update this scientific brief as new information becomes available.

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