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Perspective

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SARS-CoV-2 testing to assure safety in air travel

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Background

The COVID-19 pandemic and subsequent lockdowns have led to a dramatic decline in travel with austere economic impact (https://www.e-unwto.org/doi/epdf/10.18111/wtobarometereng.2020.18.1.5). Travellers are discouraged from travel due to country travel restrictions, quarantine, inconsistent testing requirements—some of which could change at short notice—and thus complex planning needed which may become obsolete at short notice. Some inconsistencies can be attributed to the gradually evolving understanding about SARS-CoV-2, its transmission and infectivity, whereas others are due to non-scientific but equally important country-specific considerations. The previously unknown pathogen is now recognized to be transmitted mainly by droplet and aerosol during close contact.[1] SARS-CoV-2 appears most infectious with the highest viral load one day prior to symptom onset to 5–7 days from symptom onset.[1,2] However, infectivity could start even earlier before symptom onset and 40–45% of infections are asymptomatic.[3,4]

Relating to air travel, most reports of on-board transmission have occurred during the period before masking was recommended, but transmission has also been reported on flights with required (but not completely implemented) masking.[5–7] Cruises have suffered high incidence of infection,[8] and travel has contributed to superspreading events.[1] The International Civil Aviation Organization (ICAO, a United Nations specialized agency which serves as the global forum of States for international civil aviation) has recommended guidance to States and aviation stakeholders to implement a multi-layer strategy of mitigation measures to counter the spread of COVID-19, addressing all aspects of aviation including airports, airlines, aviation personnel, passengers and cargo operations. It includes the publication of the ICAO *Manual on Testing and Cross-border Risk Management Measures*. (https://www.icao.int/covid/cart/Pages/default.aspx).

Options for Diagnostic Assessment to Make Air Travel Safer

The main categories of SARS-CoV-2 diagnostics are molecular, antigen, and antibody tests.[9] Importantly, no test is 100% accurate. False-negative molecular or antigen tests may lead to relaxed precautions by infected individuals, resulting in spread of COVID-19. The availability of tests, samples to be tested, procedures for testing, and speed of return vary and continue to evolve; each setting may be best suited for particular tests (https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html). Molecular tests (or nucleic acid amplification tests, NAAT) detect viral RNA and include polymerase chain reaction (PCR) as well as isothermal amplification tests. PCR testing is considered the gold standard, most sensitive for detecting acute infection but positivity persists beyond the period of infectivity. Isothermal amplification tests can be performed more rapidly than PCR tests but have lower sensitivity and generally can be positive from symptom onset for up to 7 days. Antigen tests detect viral protein and positivity theoretically reflects the presence of live virus and transmissibility. It is most likely to be positive in cases with high viral load, in early symptomatic cases up to 5 days from symptom onset. Despite less sensitive than molecular tests, many antigen tests allow rapid point-of-care testing. As more and different tests are being approved by regulatory/health authorities, specifying a particular test to use for travel purposes could become challenging. ICAO therefore established performance-based recommendations for testing (>95% sensitivity and specificity),

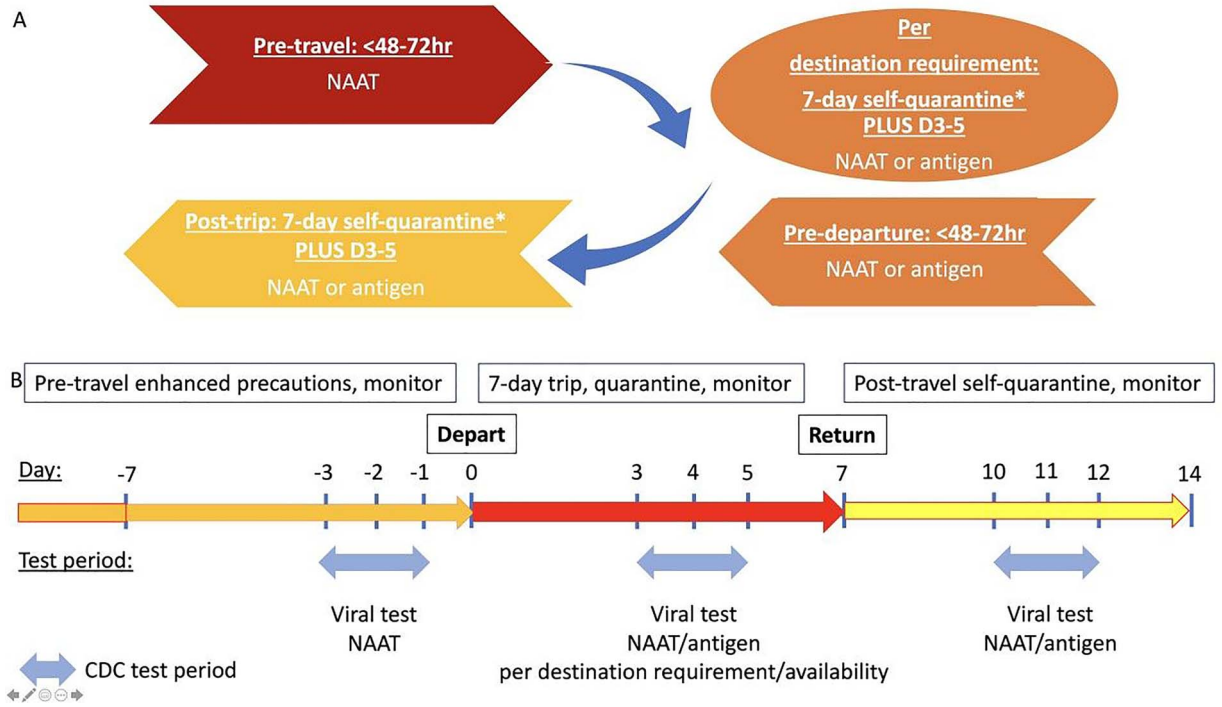

Figure 1. (A). Proposed testing strategy to assure safety in travel and to meet destination requirements. (B). Strategy for a 7-day trip. (NAAT, the type of test recommended may vary depending on test availability and updated performance characteristics; although current antigen tests may not be as sensitive as NAAT, they may have greater availability, be more easily accessible and may be more affordable; currently, some health authorities only endorse PCR testing). *Self-quarantine may range from self-monitoring to required quarantine depending on location

which is aligned with the ICAO risk-based approach to mitigate the spread of COVID-19. Pre-boarding, witnessed testing with rapid antigen might reassure the passenger/traveller is most likely not transmitting the virus at least for the duration of the flight, but need to take into account practical considerations.

In contrast, antibody tests do not indicate current infectiousness. They document previous infection to SARS-CoV-2; usually, the result becomes positive ~14–21 days after symptom onset. Some antibodies possibly protect people from becoming infected for some time. Levels may be low and wane quickly after asymptomatic infection. However, many characteristics of SARS-CoV-2 antibody tests need elucidation including cross-reactivity with seasonal or endemic coronaviruses, correlation with immunity, the threshold level needed for protection, and duration of protection.[10] Current evidence supports their use mainly for epidemiologic survey.

Diagnostic Tests and Quarantine Requested by the Authorities of the Destination Country

Destination countries have a legitimate interest to minimize the risk of importation of coronavirus infections, but these quarantine and testing requirements imposed by each country or state vary greatly. Rational and coordinated strategies for testing and quarantine, along with consistent advice to reduce the risk of exposure and spread, may help to assure safer travel and the resumption of travel. Coordination could start at bilateral or multilateral level between city pairs, different regions within a country or between countries (e.g. Australia and New Zealand), and then be expanded further (e.g. the ICAO Public Health Corridor concept). Figure 1 shows a proposed testing strategy.

Many countries/destinations call for molecular test <48–72 hours pre-travel, some countries specify PCR. For this setting, a proposal is to accept molecular tests performed in healthcare settings because they are the most reliable. If this is not done or unacceptable by the destination, then a molecular test or rapid antigen test performed on arrival to destination may help to establish the traveller as uninfected. However, false-negative tests remain a concern, including the scenario that the traveller may still be in the incubation period.

Upon arrival to destination, a traveller is generally required to quarantine and/or self-monitor for a period of time. Data from systematic serial testing of travellers are instructive to optimize the timing of the post-arrival testing. For instance, Saudi Arabia implemented mandatory 14-day quarantine of returning travellers in dedicated quarantine facilities, paired with SARS-CoV-2 PCR testing on Day 1 and Day 12–13.[11] Among 1928 returning travellers, 0.7% tested positive on Day 1, and 0.5% of the initial negatives tested positive on Day 12–13. Hong Kong also instituted mandatory quarantine and entry screening of returnees at airport on Day 1 and Day 10. Among roughly 1400 imported COVID-19 cases identified through entry screening, the positivity rates for the first test (Day 1) is 0.35% and second test (Day 10) is 0.1% (Jasper Chan, personal communication). A model has suggested that a 7-day quarantine combined with symptom monitoring and a test on Day 3–4 post-arrival is 95–99% effective in reducing travel-related risk, and a 14-day quarantine can reduce risk by 97–100%.[12] Having

internationally accepted, standardized quarantine period can ease the confusion travellers encounter. Some destinations allow release from quarantine based on a post-arrival negative SARS-CoV-2 test at 10–14 days after arrival. The USA and Europe have updated testing and quarantine guidance incorporating a 7-day quarantine in combination with testing (https://www.cdc.gov/coronavirus/2019-ncov/travelers/testing-air-travel.html; https://www.ecdc.europa.eu/en/publications-data/guidelines-covid-19-testing-and-quarantine-air-travellers). In the evolving guidance, the US permits viral testing (NAAT or antigen) for air travellers, whereas Europe currently only endorses PCR testing.

Until vaccination is widespread, serial testing will be essential because of the significant proportion of infected persons that never develop symptoms. However, challenges and pitfalls face such strategies, not the least is the expense associated with testing. Also, testing is still not readily available in all locations, and at times it may require great effort to obtain test and much time to get result. Although it is far more reliable than questionnaire or temperature screening, serial testing paired with strict quarantine has still repeatedly found PCR positivity.[11,13] The plethora of licenced tests (or tests that received emergency use authorization by the Food and Drug Administration, FDA) are wide ranging, require specific sample type, have particular indication, and confuse medical professionals. For instance, rapid antigen tests in the USA received Emergency Use Authorization (EUA) for symptomatic persons, and the EUA specified nasal swab for one test, whereas another specified nasopharyngeal swab only. The EUA did not include testing for asymptomatic persons. Tests available in one country may not be recognized or accepted in other countries. The many manufacturers mean varying performance characteristics. Thus, destination countries may only trust their testing when travellers arrive and may reject pre-travel, pre-boarding tests.

Documentation

Uniformity in documentation will be important for the test results (e.g. units, metric, timing, interpretation) and COVID-19 vaccination when they become available. Serologic responses are being clarified, and documentation of an individual's immune status may also be useful in the future. The existing International Certificate of Vaccination or Prophylaxis under the World Health Organization (WHO) International Health Regulations,[14] which applies to yellow fever, meningococcal and poliomyelitis vaccination for travellers, can be expanded to document the COVID-19 vaccination and possibly test results. Documentation for COVID-19 regulated by a UN organization would globally be better accepted given the multiple independent electronic systems developed by the International Air Transport Association (https://www.iata.org/en/pressroom/pr/2020-11-23-01/), the World Economic Forum (CommonsPass) (https://thecommonsproject.org/commonpass), or others on the horizon. Guidance will be needed to assure uniform documentation worldwide at least for international travel both before and after the implementation of COVID-19 vaccination.

Many issues regarding documentation need to be addressed urgently (Table S1), including standardizing test reporting formats, recognizing vaccines and appropriate dosing/schedule that are endorsed by international health authorities, identifying reliable personnel and platforms that only authenticate information from trusted sources, and ensuring that the platforms are protected from fraud.

Conclusion

Control of COVID-19 needs multi-layered preventive strategies. Travel-associated risk management needs consideration of the entire curb-to-curb process. Sensible and well-timed surveillance testing would support the safe shortening of existing quarantine requirements for travel. It is important to note that WHO does not consider travellers as COVID-19 contacts, and recommends self-monitoring rather than quarantine. Large-scale data are needed regarding transmission on masked flights, and on serial screening test results during quarantine periods to inform the in-flight risk, optimize quarantine duration and standardize testing strategies.

Supplementary data

Supplementary data are available at *JTM* online.

Authorship

All authors contributed equally to the conception, and writing and revising the manuscript.

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Conflict of Interest

L.C. reports advisor fees from Shoreland Inc.

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