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Chen, L.H.; Freedman, D.O.; Visser, L.G.

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Perspective

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COVID-19 Immunity Passport to Ease Travel Restrictions?

Lin H. Chen, MD[1,*], David O. Freedman, MD[2], and Leo G. Visser, MD, PhD[3]

[1]Division of Infectious Diseases and Travel Medicine, Mount Auburn Hospital, Cambridge, and Harvard Medical School, Boston, Massachusetts, USA, [2]Division of Infectious Diseases, William C. Gorgas Center for Geographic Medicine, University of Alabama at Birmingham, Birmingham, AL, USA and [3]Department of Infectious Diseases, Leiden University, Leiden, The Netherlands

*Corresponding Author: Lin H. Chen, MD, Mount Auburn Hospital, 330 Mount Auburn Street, Cambridge, MA 02138; Tel: 617.499.5026; Email: lchen@hms.harvard.edu

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As of May 2020, the SARS-CoV-2 Pandemic is ravaging the world.[1] Trade, travel, and most in-person interactions have come to a standstill. World Tourism Organization data show that 100% of global destinations have restrictions on travel in place; 72% of countries have completely closed their borders to international tourism.[2] Re-start strategies for future months have raised the possibility of an 'immunity certificate' (also called 'immunity passport' or 'immunity license') similar to the yellow fever vaccination certificate (International Certificate of Vaccination or Prophylaxis; ICVP issued by the World Health Organization (WHO) on the basis of the International Health Regulations). For example, if an air passenger could be documented as having recovered from SARS-Cov-2 infection or COVID-19 and is thus immune, they would be exempt from many airport, boarding gate, on-board processes, and port-of-entry procedures including many protective steps, such as face cover and quarantine/test on arrival. 'Immunity certificate' would ideally require a global standard akin to the ICVP, and possibly require the corresponding documentation to be presented electronically.

In the travel context the 'immunity certificate' should serve to protect 1) the traveler; 2) his/her fellow travelers; and 3) residents at the destination as well as in-transit locales. In assessing evidence to support the concept and feasibility of the 'immunity certificate', the following must be considered: 1) nearly all persons who have been infected will develop detectable antibodies; 2) antibodies detected are protective/neutralizing and preclude shedding of transmissible virus; 3) data establish the threshold of antibody titers necessary for protection; 4) data are available to assure that immunity is durable enough to invoke an expiry date for its validity; 5) acceptable antibody test(s) for certificate issuance comply with an international quality standard, is easily accessible and has high performance characteristics; and 6) documentation processes are highly resistant to fraud and includes a method to display exemption from certain requirements such as wearing face mask in public. An 'immunity certificate' system unable to comply with all the above criteria is unlikely to be widely accepted.

Accumulated evidence is encouraging but currently insufficient to address many of these considerations (Box 1). Extrapolating correlates of immunity and practical issues from other known virus to this unique pathogen is inadequate. The current state of knowledge on immunity and performance of available tests are summarized below.

Box 1 Current understanding about SARS-CoV-2 antibodies

What is known about SARS-CoV-2 antibodies

1) Most persons with significant disease will develop neutralizing antibodies
2) Neutralizing antibodies may protect against reinfection and reduce disease severity
3) In non-human primate model, post-infection immunity lasts at least 5 weeks
4) There are several reliable serological tests available that correlate with neutralizing antibody titers

What remains unknown about SARS-CoV-2 antibodies

1) Threshold level of antibodies for protection needs to be defined
2) Duration of protective immunity needs to be established
3) Can immune persons still shed the virus and infect others

To date, studies confirm that most persons with clinically significant COVID-19 disease will develop antibodies; data is less available for asymptomatic or mild infection. Emerging

data suggest that humans with detectable antibody to SARS-CoV-2 spike protein (SP) and nucleocapsid protein (NP) have neutralizing titers to live virus in tissue culture systems.[3,4] Media reports and studies awaiting peer review for publication show < 5% seropositivity in general population samples from over a dozen countries during or after peak pandemic activity, which speaks against widespread build-up of immunity. Only high-prevalence groups (e.g. New York City, HCWs, first responders, persons experiencing homelessness, and nursing home residents) reach > 20% seropositivity. Thus, currently only a small minority of travelers may profit from such 'immunity certificate'.

From the early epicenter of China, a rapid point-of-care lateral flow immunoassay for SARS-CoV-2 IgM and IgG derived an overall sensitivity of 88.66% and specificity of 90.63%.[5] Others evaluated IgA, IgM, and IgG by ELISA (n = 208) and determined seropositivity rates of 85.4%, 92.7% and 77.9%, respectively.[6] The median time for IgM and IgA antibody detection was 5 days (IQR 3–6) while IgG was detected 14 days (IQR 10–18) after symptom onset. The variability in seroconversion rates were also evident in another study on confirmed COVID-19 patients (n = 173), with rates of 93.1%, 82.7% and 64.7% for total antibodies, IgM and IgG, respectively.[7] Seroconversion occurred between days 11 and 14, and antibodies persisted up through 39 days after symptom onset. The presence of antibodies was < 40% among patients within 1 week of illness onset, but rapidly increased to 100.0% (total Ig), 94.3% (IgM) and 79.8% (IgG) 15 days after symptom onset.[7] These studies demonstrated that higher antibody titers were associated with more severe disease, and also that the optimal timing for serologic testing depended on the specific test and ranged from 5 days to > 3–4 weeks after symptom onset and > 2 weeks after symptom resolution.[6,7]

Investigators that measured serum antibodies to NP and SP receptor binding domain (RBD) by enzyme immunoassay along with SARS-CoV-2 viral load found different seropositivity rates depending on antibody target.[8] At 14 days or longer after symptom onset, 94% of samples were positive for anti-NP IgG, 88% for anti-NP IgM, 100% for anti-RBD IgG, and 94% for anti-RBD IgM; these IgG levels correlated with virus neutralization titer.

A longitudinal COVID-19 virological analysis of 9 patients with mild to moderate disease found active virus replication in upper respiratory tract with high viral load during the first week of symptoms, which correlated with seroconversion in 50% of patients after 7 days and 100% of patients after 14 days.[3] Another assay on 40 confirmed SARS-CoV-2 serum samples for neutralizing, SP-specific, and NP-specific antibodies, detected seroconversion 2 weeks after illness onset.[4] The ELISA assays correlated with plaque reduction neutralization tests; IgA ELISA showed highest sensitivity; however, validation studies found that commercial S1 IgG or IgA ELISAs were of lower specificity, and sensitivity varied.[4]

To date, the largest human study was conducted in New York City with 1343 participants whose median interval from symptom onset to serum antibody test was 24 days (range 3–70), and median interval from symptom resolution to antibody test was 15 (4–77).[9] Antibody titers were higher with longer interval between symptom onset and testing and with longer symptom duration. IgG antibodies developed from 7–50 days after symptom onset and 5–49 days after symptom resolution. High antibody titers developed at a median of 24 days after symptom onset and a median of 15 days after symptom resolution.

Early encouraging results on the use of convalescent plasma to treat COVID-19 provide support for seroprotection based on antibody-containing plasma of recently-recovered COVID-19 patients.[10] In animal model, 9 rhesus macaques infected with SARS-CoV-2 developed neutralizing antibody responses as well as SP by ELISA (including many subclasses) which persisted to at least 35 days; cellular immune responses were also documented.[11] When rechallenged at 35 days, all animals developed rapid anamnestic response, no viral replication, and little or no clinical disease.[11]

An important unanswered question is the duration of antibody persistence. It is injudicious to apply data from other coronaviruses to SARS-CoV-2. Disease from 4 human coronaviruses that cause common cold is milder and reinfections do occur.[12] Two other coronaviruses that cause severe disease, SARS-CoV-1 (Severe Acute Respiratory Syndrome 2003) and MERS-CoV (Middle East Respiratory Syndrome 2012), offer comparison with SARS-CoV-2, and have demonstrated neutralizing antibodies for up to 2 years and 34 months, respectively.[12]

On the practical side, antibody tests are either point-of-care rapid tests or high throughput antibody tests that are run on large autoanalyzer platforms to detect IgM and/or IgG. In the U.S. the FDA performance assessment found several high-throughput tests for antibody detection (not immunity) to be more robust; some IgG tests have achieved sensitivity and specificity or positive and negative predictive values over 99.5%. Worldwide, hundreds of point-of-care rapid tests have been marketed without submission for any regulatory approval, with unknown sensitivity. All rapid point-of-care antibody tests formally reviewed by the FDA have inferior performance compared to high-throughput platforms. False positives for IgG and IgM antibodies may occur due to cross-reactivity with antibodies of other pathogens, including other human coronaviruses, and would imperil the person and their contacts if they curtail preventive measures. The use of such point-of-care tests that have not been validated or have not been correlated with virus neutralization, either pre-travel or at ports of entry or airports of departure, cannot be recommended. On the other hand, some point-of-care rapid antigen tests may be used in the travel industry to detect active infection.

Of course, appropriate counselling by a competent travel clinic in this era of COVID-19 risk becomes more important than ever. At the same time, many other enterprises may soon be in the business of providing 'immunity certificate' if certification becomes recognized in the context of certain kinds of employment, or attendance at educational institutions or large gathering events. Currently in the U.S. one nationwide lab provider offers direct-to-consumer walk-in COVID-19 high-throughput antibody testing.

The practicalities of widely accepted 'immunity certificate' to facilitate international travel are unlikely to be resolved soon. The WHO, European Centre for Prevention and Control (ECDC), *b* Air Transport Association (IATA), and International Civil Aviation Organization (ICAO) do not advocate their implementation under present circumstances and test performance. As more data accrue and population herd immunity rates rise in the future, it is conceivable that the ICVP may be recognized

and used to document immunity[13]; travel clinics would play a greater role in such use of the ICVP. This use of the ICVP however may cause great confusion should a vaccine against SARS-CoV-2 become available and an internationally recognized certification becomes necessary to document actual vaccination. Also, individual airports, airlines, or national authorities may see fit to recognize some form of vaguely specified letters or certification of immunity on an ad hoc basis for either domestic or international travel. Travel clinics may be called upon to provide such documentation in the near future and must assess the performance characteristics of the tests and understand the immune response to COVID-19, the timing and duration of antibody response, and whether the antibodies tested are of appropriate levels and correlate with protective immunity. No consistent global standard or recommendation for immunity certificate exists at present. Expertise from International Society of Travel Medicine constituency, with profound understanding of rapid COVID-19 developments, can contribute greatly towards recommendations for safe opening of travel.

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