

Implications of test characteristics and population seroprevalence on 'immune passport' strategies

Daniel B. Larremore ¹, Kate M. Bubar ², Yonatan H. Grad ³

¹ Department of Computer Science and BioFrontiers Institute, University of Colorado Boulder, Boulder, CO, USA

² Department of Applied Mathematics and IQBiology Program, University of Colorado Boulder, Boulder, CO, USA

³ Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA, 02115, USA

Corresponding author: Yonatan Grad, MD, PhD, 665 Huntington Ave, Rm 715 Building 1, Boston, MA 02115. Tel 617-432-2275; email: ygrad@hsph.harvard.edu

Alternate corresponding author: Daniel Larremore, PhD, 1111 Engineering Drive, ECOT 717, 430 UCB. Boulder, CO 80309. email: daniel.larremore@colorado.edu

Brief summary

'Immune passport' strategies that use serology to reopen the economy can be undermined by low seroprevalence and imperfect test specificity. We describe the minimum requirements of a serological test for a passport program, which depend on population prevalence and R_0 .

Accepted Manuscript

Abstract

Various forms of 'immune passports' or 'antibody certificates' are being considered in conversations around reopening economies after periods of social distancing. One critique of such programs focuses on the uncertainty around whether seropositivity means immunity from repeat infection. However, an additional important consideration is that the low positive predictive value of serological tests in the setting of low population seroprevalence and imperfect test specificity will lead to many false-positive 'passport' holders. Here, we pose a simple question: how many false-positive 'passports' could be issued while maintaining herd immunity in the workforce? Answering this question leads to a simple mathematical formula for the *minimum requirements* of serological tests for a passport program, which depend on population prevalence and the value of R_0 . Our work replaces speculation in the press with rigorous analysis and will need to be considered in policy decisions that are based on individual and population serology results.

Key words

SARS-CoV-2; COVID-19; positive predictive value; immune passports; seroprevalence

Main text

Social distancing and other community quarantine measures have slowed the spread of COVID-19 but have also contributed to an economic shutdown with immense cost and growing pressures to return people to work. Among various strategies [1, 2], one is the use of 'immune passports', which would allow individuals with serological evidence of exposure to SARS-CoV-2 to return to work. This is premised on the belief that antibodies confer sufficient immunity to prevent COVID-19 infection, and carries both ethical and scientific challenges [3].

As has been increasingly recognized, the relationship between seropositivity and immune protection remains uncertain [4]. Even if we learn that seropositivity does indicate at least short-term immunity, the test characteristics of currently available SARS-CoV-2 serological tests create a distinct problem. Test characteristics refer to a test's sensitivity, which reflects its ability to correctly identify seropositive individuals, and specificity, which reflects its ability to correctly identify seronegative individuals. With imperfect specificity, a low seroprevalence will result in low positive predictive value, which is the likelihood that a positive test represents a true positive [5]. A low positive predictive value will in turn mean a large fraction of false positive tests and lead to a mix of truly seropositive and seronegative individuals who carry 'immune passports'. For example, applied to a population with 4% seroprevalence, even a test with 98.5% specificity and perfect sensitivity would produce a passport-holding population with only 73.5% true seropositive individuals. If the test sensitivity was 90%, only 71.4% of passport holders would be seropositive, with nearly 3 in 10 'passports' issued to those without SARS-CoV-2 antibodies.

This has two important implications for the 'immune passports' strategy. First, this strategy may still permit outbreaks, even when only those holding immune passports comprise the workforce. Herd immunity occurs when a large enough fraction of the population is immune that transmission does not spread widely. That fraction is typically calculated as $1-1/R_0$ [6]. R_0 , the basic reproductive number, refers to the average number of people an infected individual goes on to infect. Epidemic spread takes place when the reproductive number is greater than 1, spread is at replacement when it equals 1, and the infection dies

out when it is less than 1. Thus, intuitively, for SARS-CoV-2 estimates of $R_0=3$ [7], if more than every 2 out of 3 individuals (66.7%) are immune—the herd immunity threshold—then an infected individual will go on to infect, on average, less than one person, and the epidemic will die out. This implies that an immunity passports program in a city with 4% seroprevalence could work for a test with at least 98.5% specificity and 72% sensitivity.

Generalizing this concept, we can calculate the test characteristics needed for a given population prevalence to ensure that enough of those deemed seropositive will be truly seropositive to maintain herd immunity among passport holders (Figure). The true positive fraction among passport holders is $\frac{\theta se}{\theta se + (1-sp)(1-\theta)}$, where se is sensitivity, sp is specificity, and θ is population seroprevalence (see supplement for the derivation of all equations). For this fraction to meet or exceed the requirements of herd immunity, the test's specificity must be

$$sp > 1 - \frac{\theta}{(R_0 - 1)(1 - \theta)} se$$

corresponding to the region above a minimum test performance line. This line excludes some tests entirely: a test of 98.5% specificity and 72% sensitivity cannot be relied on for populations with prevalence below 4% at an $R_0=3$. (Figure, left). The required test sensitivity is highly dependent on R_0 : for $R_0=2.5$ and the same test specificity of 98.5%, the test sensitivity required to maintain herd immunity among the 'immune passport' carriers is only 54%, while for $R_0=3.5$ the corresponding sensitivity requirement is 90%. This suggests that, for policy considerations, a range of plausible R_0 values should be evaluated, prioritizing safety. The fact that these calculations require knowledge of population seroprevalence θ highlights the ongoing need for serological surveys.

Public health officials and policymakers may be unable to choose test characteristics, either due to cost, or due to testing materials already in hand. Nevertheless, one can solve the equation above for seroprevalence instead,

$$\theta > \frac{\left(1 - \frac{1}{R_0}\right)(1 - sp)}{se - \left(1 - \frac{1}{R_0}\right)(se + sp - 1)}$$

Given a test with known sensitivity and specificity, immune passport programs become feasible only when seroprevalence is sufficiently high: with a 99% specific and 100% sensitive test, a community with $R_0=3.5$ requires at least a seroprevalence of 2.5% to support an immune passport program. A test with 98.5% specificity in the same community requires at least a 3.7% seroprevalence. For communities with contact rates that lead to higher values of R_0 , the minimum feasible seroprevalence correspondingly increases (Figure, right).

The calculations here assume that only those who test positive would hold passports. To the extent that policies to dial down social distancing result in the mixing of passport holders with those without passports who are susceptible (for example, essential workers who have escaped infection), similar calculations can aid in setting expectations for the size of subsequent outbreaks. Incorporating serological data into modeling efforts will be crucial to inform policy and decision making [1, 8].

The requirements for serological tests for 'immune passport' programs may become less restrictive as the pandemic proceeds. First, seroprevalence will increase, leading to higher positive predictive values. Second, as individuals and communities adopt behaviors (e.g., mask-wearing and social distancing) that limit transmission, the reproductive number will decrease. Both of these factors would expand the range of acceptable tests for seropositivity.

A second consequence of mistakenly identifying individuals as seropositive is the impact of outbreaks among passport holders. The extent to which seropositivity implies immunity has been unclear. Thus, not only will perceived re-infection exacerbate this confusion about the relationship between seropositivity and immune protection, but public frustration with outbreaks among the supposed immune could erode trust in an immunity passport program and 'back to work' plans.

The nature and dynamics of immune responses to SARS-CoV-2 infection remain to be elucidated, further clouding the picture of immune passports. Recent work has indicated the possible rapid waning of anti-SARS-CoV-2 antibodies [9] and the need for continued evaluation of markers of exposure and correlates of protection. However, the issues we present here hold independent of the marker itself and are general issues that reflect the interaction among test characteristics, R_0 , and prevalence.

In sum, when considering the use of serological studies to inform strategies for lifting broad community quarantine measures, attention must be paid to the test characteristics, the local seroprevalence, and the local contact rates to understand the associated risks and to guide decision-making. These issues will remain until the widespread availability of tests with near-perfect sensitivity and specificity.

Accepted Manuscript

NOTES

This work was supported in part by the Interdisciplinary Quantitative Biology (IQ Biology) PhD Program at the BioFrontiers Institute, University of Colorado Boulder and by the Morris-Singer Fund for the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health.

COI declaration: The authors declare no conflicts.

Accepted Manuscript

REFERENCES

1. Kraay ANM, Nelson K, Zhao C, Weitz JS, Lopman BA. Modeling serological testing to inform relaxation of social distancing for COVID-19 control. medRxiv **2020**:2020.04.24.20078576.
2. Weitz JS, Beckett SJ, Coenen AR, et al. Modeling shield immunity to reduce COVID-19 epidemic spread. Nat Med **2020**; 26:849-54.
3. Phelan AL. COVID-19 immunity passports and vaccination certificates: scientific, equitable, and legal challenges. Lancet **2020**; 395:1595-8.
4. Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. medRxiv **2020**:2020.04.14.20065771.
5. Manrai AK, Bhatia G, Strymish J, Kohane IS, Jain SH. Medicine's uncomfortable relationship with math: calculating positive predictive value. JAMA Intern Med **2014**; 174:991-3.
6. Anderson RM, May RM. Infectious diseases of humans : dynamics and control. New York: Oxford University Press, **1991**.
7. Imai N, Cori A, Dorigatti I, et al. Report 3: Transmissibility of 2019-nCoV, **2020**. URL: <https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-transmissibility-25-01-2020.pdf>
8. Larremore DB, Fostick BK, Bubar KM, et al. Estimating SARS-CoV-2 seroprevalence and epidemiological parameters with uncertainty from serological surveys. medRxiv **2020**:2020.04.15.20067066.
9. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med **2020**. doi:10.1038/s41591-020-0965-6

FIGURE LEGEND

Figure. The relationship between sensitivity, specificity, seroprevalence, and R_0 places limits on the feasibility of ‘immune passport’ programs. Left: Minimum test sensitivity and specificity

characteristics needed for herd immunity among those who test seropositive are shown for a given population prevalence. The combination of test sensitivity and specificity must be on or above each line to ensure that the fraction of true positives is above the herd immunity threshold for a given R_0 ($R_0=3$ shown). Dotted lines indicate the sensitivity needed for a test with specificity of 98.5% [7]. **Right:**

Minimum seroprevalence requirements needed for herd immunity among those who test seropositive are shown for varying R_0 and specificity values. The combination of R_0 and seroprevalence must be on or above each line to ensure that the fraction of true positives is above the herd immunity threshold for a given sensitivity (100% sensitivity shown). Dotted lines indicate the seroprevalence needed for an R_0 of 3.5 at 99% specificity.

