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

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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 imperfect specificity of currently available SARS-CoV-2 serological tests creates a distinct problem: in populations with low prevalence, the low positive predictive value will result in a large fraction of false positive tests and thus lead to a mix of truly seropositive and seronegative individuals who carry 'immune passports'. For example, applied to a population with 4% seroprevalence (as estimated for Los Angeles, California, in a press release about an as yet unavailable study [5], 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 $1\text{-}1/R_0$, which, for SARS-CoV-2 estimates of $R_0$=3 [6], predicts herd immunity when 66.7% or more of the population is immune, implying 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 $\theta$ is population seroprevalence. 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 B). Note that the test sensitivity required is highly dependent on $R_0$. For $R_0$=2.5 and a test specificity of 98.5%, the test sensitivity required to maintain herd immunity among the 'immune passport' carriers is 54% (Figure A), but for $R_0$=3.5 the corresponding sensitivity requirement is 90% (Figure C). This suggests that, for policy considerations, a range of plausible $R_0$ values should be evaluated to aid in prioritizing safety. The fact that these calculations require knowledge of population seroprevalence $\theta$ highlights the ongoing need for serological surveys more broadly.

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 mixing of passport holders with individuals who have continued to work in essential roles, 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 [1,7].

A second consequence of mistakenly identifying individuals as seropositive is the impact of outbreaks among passport holders. Not only will perceived re-infection exacerbate scientific 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 generally.

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 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.

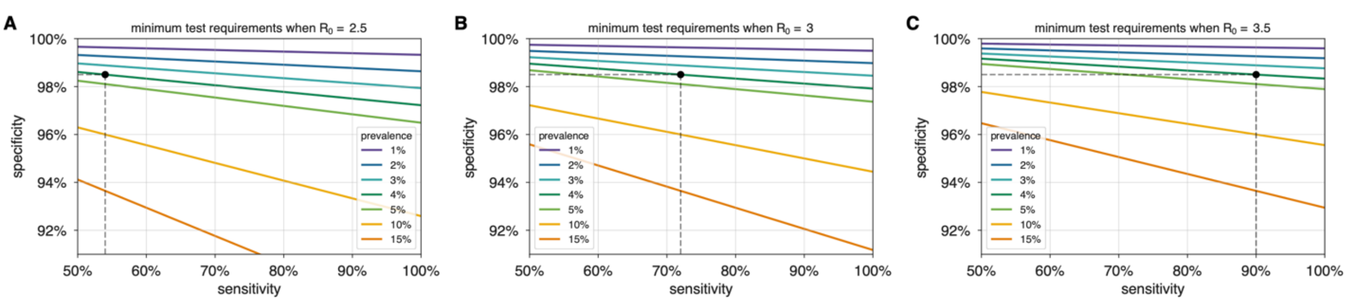


**Figure. Test sensitivity and specificity characteristics at varying population seroprevalence needed for herd immunity among those who test seropositive**. For a given population prevalence (see key), the combination of test sensitivity and specificity have to be on or to the right of each line to ensure that the fraction of true positives is above the herd immunity threshold for a given $R_0$ (2.5 in panel A, 3 in panel B, 3.5 in panel C). Dotted lines indicate the sensitivity needed for a test with specificity of 98.5% [6].

## REFERENCES

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