



RESEARCH NOTE

Pre-vaccination testing could expand coverage of two-dose COVID vaccines [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Recent evidence indicates that a single dose of mRNA-based vaccines produce similar immune responses in people with evidence of past infection compared with two doses in immunologically naive individuals. For COVID-19 vaccines with two dose regimens, point-of-care antibody testing for prior infection when administering the first dose could enable expanded vaccine access in a cost-effective manner. Generally, antibody tests with sensitivity and specificity well below that typically accepted for product licensure would still enable expanded vaccine coverage, though to be cost-beneficial total test cost (*i.e.* procurement and administration) needs to be less than roughly a third of total vaccine dose cost. For highly sensitive (90%) and specific (99%) tests, coverage could be expanded by more than 33%. Tests with the appropriate performance characteristics are plausible, though likely need setting specific tailoring.

Keywords

COVID-19, SARS-CoV-2, Vaccination, Point-of-Care Antibody Testing, Rapid Serological Testing

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 1		
11 May 2021	report	report
1. Thomas Crellen , University of Oxford, Oxford, UK		
2. Ana Bento , Indiana University School of Public Health-Bloomington, Bloomington, USA		

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Pearson CAB:** Conceptualization, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Clifford S:** Conceptualization, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Pulliam JRC:** Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Eggo RM:** Methodology, Project Administration, Resources, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Many countries have experienced high SARS-CoV-2 infection attack rates and currently have limited vaccine supplies. For example, countries participating in the CO-VAX facility expect to receive vaccine coverage for only 20% of their populations¹, with any additional coverage depending on availability and cost. However, recent evidence indicates that a single dose of the mRNA-based vaccines (*e.g.* the Pfizer or Moderna products) produce immune responses in people with evidence of past infection (*i.e.* seropositive) that are at least comparable to the response elicited by two doses in immunologically naive individuals²⁻⁶.

If effects observed in these studies are validated, the use of a point-of-care antibody test when administering the first dose could allow for more efficient use of available vaccine doses. This benefit depends on test performance, cost, and the seroprevalence in the population being vaccinated. Intuitively, the advantage will increase with greater seroprevalence because there is more opportunity to reallocate the second dose. To be a better option than buying more doses, administering a test should cost less than a single vaccine dose, but how much less will depend on test specificity (to avoid giving too few doses) and sensitivity (to benefit from reallocating doses), as well as seroprevalence. Several rapid, point-of-care antibody tests⁷⁻¹⁰ are available that may ultimately be able meet these requirements; however, further testing and development may be needed to validate and tailor tests for use in different contexts¹¹⁻¹³. Data to evaluate vaccine effectiveness for a single dose conditional on antibody testing could be collected in countries pursuing a delayed second dose scheme, like the United Kingdom.

Methods

Calculations performed in R (4.0.3)¹⁴, with visualizations prepared using `data.table`¹⁵, `ggplot2`¹⁶, and `patchwork`¹⁷.

Coverage with testing

To analyze the direct benefit of this dose-sparing approach, we conservatively assume seronegative individuals are fully vaccinated (*i.e.* protected at the efficacy of the vaccine) only after two doses, and seropositive individuals after one dose. With a test, most seropositive individuals get one dose instead of two, freeing up doses to protect more people. Given a fixed supply, the number of additional people that could be protected depends on both test performance and the seroprevalence in the population of interest.

To evaluate this relationship, we model the population as having a homogeneous distribution of potentially test-detectable prior SARS-CoV-2 infection, characterized by a population-level seroprevalence, $\rho_+ = 1 - \rho_-$. We model a test that is characterized by sensitivity (the true-positive rate, the complement of the false negative rate $\text{TPR} = 1 - \text{FNR}$), and specificity (the true-negative rate, the complement of the false positive rate $\text{TNR} = 1 - \text{FPR}$). For practical applications, these values will be entangled, since we know that *e.g.* SARS-CoV-2 antibody responses decline with time¹⁸.

If we assume, pessimistically, that a single dose is not protective when given to seronegative individuals, then in our model the people protected per dose (PPD) is:

$$\text{PPD} = 0.5 * (\text{TNR}\rho_- + \text{FNR}\rho_+) + 1 * \text{TRP}\rho_+ + 0 * \text{FRP}\rho_-$$

which we can re-arrange in terms of complementary parameters:

$$\begin{aligned} 2\text{PPD} &= (\text{TNR}(1 - \rho_+) + (1 - \text{TRP})\rho_+) + 2\text{TRP}\rho_+ \\ &= \text{TNR} - \text{TNR}\rho_+ + \rho_+ - \text{TRP}\rho_+ + 2\text{TRP}\rho_+ \\ &= \text{TNR} - \text{TNR}\rho_+ + \rho_+ + \text{TRP}\rho_+ \\ &= \text{TNR} + \rho_+ (1 + \text{TRP} - \text{TNR}) \end{aligned} \quad (1)$$

Recall that without testing, two doses are required for vaccine immunity, *i.e.* $\text{PPD} = 0.5$. This corresponds to the situation where $\text{TNR} = 1$ (because the “test” is simply that everyone gets two doses) and $\text{TPR} = 0$ (because no one gets a single dose). Relative to this baseline, the relative change in PPD due to introducing testing is:

$$\begin{aligned} \Delta_{\text{PPD}} &= \frac{2\text{PPD}(\text{TNR}, \text{TRP}, \rho_+)}{2\text{PPD}(1, 0, \sim)} - 1 \\ &= \text{TNR} + \rho_+ (1 + \text{TRP} - \text{TNR}) - 1 \end{aligned} \quad (2)$$

Assuming a single dose is non-protective in seronegative individuals helps ensure that the model represents the *minimal* benefit, and thus decisions continue to be beneficial even after accommodating real-world factors that are impractical to model. This limiting assumption implies that introducing testing can reduce the number of people effectively vaccinated. As practical matter, this is only a problem with extreme combinations of sero-prevalence and test performance, which are not generally relevant for the settings where this scheme is worth considering. The constraining relation is $\Delta_{\text{PPD}} > 0$ or $\text{TNR} + \rho_+ (1 + \text{TRP} - \text{TNR}) > 1$. For example, in a population with 20% seroprevalence, using a test with low specificity, 50%, would be detrimental even with a perfectly sensitive test.

Costs

Though testing will increase the overall cost of the vaccine program (relative to a fixed number of available vaccine doses), decision-makers should consider the cost per fully vaccinated person. One way to make that decision is to estimate which is the less expensive way to expand coverage: expanding the supply by buying more vaccine doses or more efficiently using the existing supply with testing. We model the total cost per vaccine dose of V (*i.e.* production, logistics, and administration) and total cost per test of T . On the margin, imagine purchasing one more protected person: that can be accomplished for $2V$ (*i.e.* two doses to get a fully vaccinated person without testing) or for some expected number of tests, nT , to allow re-allocation of unnecessary second doses from

seropositive recipients. Restricting our consideration to situations with positive Δ_{PPD} , we can think about the relationship between n and Δ_{PPD} .

If testing increases the PPD by *e.g.* 10%, then using 20 tests (on average) would add another fully immunized individual. Even in a situation where the test is perfect and everyone is seropositive (*i.e.* testing increases PPD by 100%), two tests are still required: one to free up the second dose from an individual and one to confirm that the next recipient in line only needs one. We can generalize this relationship to $n = \frac{2}{\Delta_{PPD}}$. Thus, using tests is preferred when

$$\frac{2}{\Delta_{PPD}} \leq 2V \rightarrow \frac{T}{V} \leq \Delta_{PPD} \quad (3)$$

Results

Expanded coverage

Using Equation 2, we find that using a pre-vaccination antibody testing program could substantially expand vaccine coverage in populations with relatively high seroprevalence. Rearranging Equation 2 and considering a high specificity (99% or TNR = 0.99) test, only moderate seroprevalence and sensitivity are required to observe gains:

$$\rho_+ (0.01 + TPR) > 0.01 \quad (4)$$

With this high specificity and a 40% seroprevalence ($\rho_+ = 0.4$) in the population of interest, only $TPR > 0.015$ (or sensitivity of 1.5%) is necessary to expand coverage, though of course such low performance does not expand coverage much. However, a test with sensitivity more typical of licensed medical assays (90%) would expand coverage by 35% (*e.g.* increasing a COVAX-like coverage of 20% to 27%). Given that the test is not needed to determine treatment, but rather more efficiently allocate doses, lower sensitivity (*e.g.* 70%) might be substantially less expensive, and even that lower performance would expand coverage by 27% (*e.g.* increasing a COVAX-like coverage of 20% to 25%). In each of the three dimensions, coverage gains increase linearly: higher seroprevalence means more opportunity to reallocate doses, higher sensitivity means taking better advantage of that opportunity, and higher specificity decreases the (assumed) loss of protection. Figure 1A shows this trend for seroprevalence (moving left to right on plot) and sensitivity (shifting from lower to higher trend lines).

Paying for testing versus more doses

Similar to expanding coverage, using Equation 3, we find that regions with relatively high seroprevalence could more effectively expand coverage with antibody testing than additional doses with a relatively high threshold for test cost. Per Equation 3, the cost threshold is identical to the coverage expansion, and as such also increases linearly with seroprevalence and test performance. Figure 1B shows this trend for

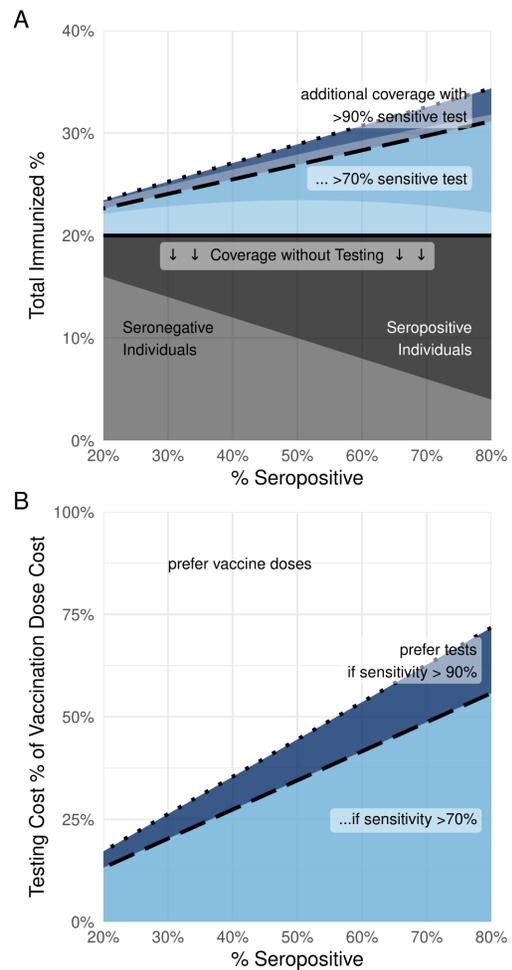


Figure 1. Example benefits of testing. A) Assuming roughly 20% of the population (light grey region) could be vaccinated without any testing: with a highly specific test (99%), testing can expand the percentage covered by increasing amounts depending on seroprevalence and test sensitivity (light blue: 70% sensitive, dark blue: 90% sensitivity). While many individuals still go unvaccinated (white background), further incremental vaccine supply would result in similarly extended coverage under pre-vaccination testing approach. **B)** Testing can also expand the vaccinated fraction for lower costs, again depending on the vaccine-eligible population's seroprevalence and the test's performance. For a highly specific test, and relatively high seroprevalence, *e.g.* 40%, a test that is less than 27% (if >70% sensitive) to 35% (if >90% sensitive) the cost of a vaccine dose is a cheaper way to expand coverage than buying more doses of vaccine. The cost advantage of testing grows with increasing seroprevalence and test performance.

seroprevalence (moving left to right on plot) and sensitivity (shifting from lower to higher trend lines).

Recalling the high seroprevalence (40%), high specificity (99%), and high sensitivity (90%) scenario, the cost threshold would be 35% of the cost of vaccination. Considering a per dose cost of roughly 15 USD (a rough direct price for the

mRNA vaccines¹⁹, but ignoring the additional administration and logistics costs), a test that cost around 5 USD or less would be a better investment to expand coverage. Even at a lower sensitivity (70%), the cost threshold remains plausible at 4 USD or less per test.

Discussion and conclusions

Where a pre-vaccination antibody testing programme is implemented, vaccine administration could be adapted to include a rapid, point-of-care antibody test before the first dose. The test result could be delivered at the end of the normal monitoring period for severe acute reactions in recipients, allowing them to be advised whether they need a follow-up dose based on their test result. For tests with imperfect specificity, some individuals with no past infection history would only receive a single dose; for our analysis, we conservatively assume these people get no protection, though studies indicate at least short-term protection². Other studies have suggested that past exposure alone is sufficiently protective, and that testing could be used to administer vaccines only to seronegative individuals²⁰. While theoretically plausible, such an approach seems practically and politically untenable, could exacerbate existing inequity in COVID-19 health burdens, and does not account for potential effects like waning immunity or immune escape variants where a single dose may boost protection^{3,6}.

We have framed this analysis in terms of a population of interest. While that population could be an entire country, it could likewise be a sub-national region and/or a particular age or employment group. The pre-vaccination testing approach is most beneficial for populations with high prior burden where there is still high risk of infection, but improperly communicated could lead to the perception of these groups receiving inferior treatment and further exacerbating health inequities. While increased vaccine availability or more globally equitable distribution would reduce the need for dose-sparing

methods, pragmatic solutions to expand coverage like testing may enable more efficient use in the current vaccine context. Indeed, approaches like this could be adopted in higher-income settings, where testing may require less calibration and other infrastructure advantages could offset the costs, thus freeing up vaccine supply globally.

In this analysis, we have tried to offer a conservative estimate of the potential benefits of using testing. We have focused on the directly protected individuals and the direct costs, but expanding vaccination could also increase indirect protection by reducing transmission broadly²¹. Likewise, expanded vaccination could reduce the incidence of severe disease and associated costs and consumption of health service resources. We expect that a more sophisticated model incorporating these kinds of effects will predict higher testing benefits, though there are additional nuances that would dampen returns (*e.g.* accounting for prioritization of older populations who have high disease risk but likely lower past exposure rates). Given that our approach indicates substantial potential benefits despite being conservative, we recommend further development of rapid, point-of-care antibody testing and vaccine effectiveness studies to verify protection of seropositive individuals after single doses.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Code availability

Source code available from <https://github.com/cmmid/covidTest-Vac>

Archived source code at time of publication: <https://doi.org/10.5281/zenodo.4725815>²².

License: MIT

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Version 1

Reviewer Report 02 July 2021

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Ana Bento 

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I really enjoyed this study. In the current context, where vaccine availability is very different depending on the country, this can potentially have real applications to public health interventions and prioritization. It is very simple but elegant.

As a further step, I would introduce heterogeneity in susceptibility, test seeking and eventually introduction of VOCs.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: mathematical models of infectious disease. Vaccine implementation design

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 June 2021

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Thomas Crellen 

Big Data Institute, University of Oxford, Oxford, UK

This short report provides a quantitative assessment of when it is cost effective to use a single vaccine dose plus an antibody test, instead of two vaccine doses, under the assumption that these provide comparable immune responses across the population. Overall the methods and analysis are appropriate for a short paper.

I have a few minor comments.

1. In terms of the "real world application" of this approach, the population will be heterogeneous in terms of past exposure and immune response following infection + a single dose. A key heterogeneity will be age. Does past infection + a single vaccine dose provide a comparable antibody response to 2 doses in very old (e.g. 80+) individuals?
2. Could a bit more thought on how population heterogeneity would affect the analysis / results be added to the introduction or discussion?
3. Another important consideration is whether the duration of immunity from 1 dose + past infection is comparable to that from 2 doses.
4. The results could be much better presented in terms of providing a "key results table". I find Figure 1 quite unclear and I suggest that this could be improved given that it is the only Figure.
5. For panel A, I don't find the comparison between blanket 2 dose vaccination and testing + vaccination very clear. Additionally, where does the assumed 20% coverage without testing come from? Why is the proportion of the population vaccinated considered only up to a maximum of 30%? A seroprevalence of >50% also seems implausible - are there any locations where COVID seroprevalence surveys are this high?
6. For Panel B, I would expect the "Testing cost % of vaccinated dose cost" to **decrease** with higher seroprevalence, but the opposite is shown on the Figure. It's unclear to me how the coloured areas relate to test sensitivity.

7. Overall I would encourage the presentation of results to be much clearer. E.g. a table or figure which shows for different antibody test sensitivities and seroprevalence how the cost effectiveness of testing + 1 dose compares with blanket 2 dose vaccination.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology, pathogen genomics, statistical modelling.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
