Why do we need a pan-sarbecovirus vaccine?

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January 28, 2022
The current situation

Current vaccines are based on wild-type antigens
We’ve now been through several VOCs: Alpha, beta, gamma, delta, and now omicron, with other regionally important variants (e.g., lambda and mu)
Omicron combines reduced (though still significant) virulence, greater transmissibility, and significant evasion of previous immune responses
In spite of moving quickly, by the time an omicron vaccine is available, much of omicron’s damage will have been done
Overall, this will increase worldwide immunity against SARS-CoV-2
While it is possible that a future variant will be derived from omicron, we can’t be sure
Implications

Over time, we expect increased worldwide immunity against SARS-CoV-2. Those who survive COVID infection may have significant protection against severe disease. Some believe that this heralds a (at least short term) change from pandemic to endemic COVID.

Even if that is correct, it doesn’t mean the next clinically important variant won’t evolve, but might just mean that it will take longer.

While it is possible that a future variant will be derived from omicron, we can’t be sure:

Future variants are likely to be even more transmissible
There’s a good chance future variants will be more evasive of previous immunity
Virulence of future variants is uncertain

It’s even possible that another bat sarscovirus will jump to the human population

We need to be prepared for all possibilities.
There’s been increasing interest in pan-sarbecovirus vaccines

Key questions:
How badly are they needed?
What are the most promising approaches?
How rapidly can they be developed?
If they are developed, how can they be reliably and efficiently evaluated?
What research is needed to facilitate all of this?
How can the worldwide community contribute to eliminating the future threat of pandemic sarbecoviruses?
Conclusions - 1

Structural similarity between sarbecoviruses should enable development of a pan-sarbecovirus vaccine. Additional variants may arise, and this occurs more quickly than variant-specific vaccines can be developed and deployed. T cell responses may be an important component of pan-sarbecovirus vaccines.

Omicron derives much of its growth advantage from immune escape properties. Omicron infection is less severe than previous variants, with lower incidence of ICU admission and death (but is certainly not mild). Nonetheless, there is a significant burden on hospitals and effect on healthcare staff.

In South Africa, omicron infection led to reduced hospital admissions plus reduced severity of infection among those admitted, including in children (with possible exception ages 1-4). This mirrors similar findings elsewhere.

Germinal center responses: memory (diversification) and plasma cells (selected for affinity). Four classes of neutralizing monoclonals bind spike in different places. Variant mutations eliminate neutralization of dominant classes 1 and 2. RBD-specific Memory B Cells and neutralizing function of Abs increase over time, especially with boosting. But breadth doesn’t change over time.
Conclusions - 2

Natural immunity provides substantial protection against delta infection and hospitalization, well in excess of that provided by vaccination alone. Prior infection seems roughly similar to booster in efficacy against infection. Prior infection gave durable protection, and was >90% effective against severe infection with omicron but with broad confidence intervals (Qatar), which may have contributed to perception of reduced virulence.

Very high urgency for pan-sarbecovirus vaccines: Current vaccines are becoming less effective against evolving variants, and waning even of booster vaccine response indicates that we don’t have a practical vaccine for the future. Although severe disease is critical, a pan-sarbecovirus vaccine may have a better chance of blocking transmission and facilitating herd immunity, and are expected to be more durable (facilitating vaccine deployment). Consider combination vaccines.

Conclusions - 3

There are many additional beta-sarbecoviruses that could potentially develop capacity to replicate in humans. More work on defining the spectrum of viruses that are out there is important. Persistent infections in immunocompromised individuals may contribute to viral evolution. Antigenic imprinting is an important issue in cross-protection. N protein is well conserved, but S also induces cross protective responses.

In spite of loss of some humoral epitopes with omicron, T cell responses are conserved across variants. In animal models, omicron infection is milder and more transmissible than prototype or previous variants, and outcompetes delta with immune selection pressure. Animal models remain important and useful.

mRNA and NR viral vector vaccines are highly effective against severe disease caused by delta, alpha. Boosters were also highly effective against severe disease caused by delta. nAbs seem well correlated with protection against infection, but less well with severe disease. Hybrid immunity preserves neutralization and gives high protection. Omicron is less resistant to T cell responses. Booster vaccination provides additional protection against infection and increases protection against severe disease, though booster effect on infection appears to wane fairly quickly.
Conclusions - 4

A variety of strategies may induce broader immune responses. These include different antigen presentation strategies as well as inclusion of additional antigens. Mosaic nanoparticles can present multiple antigens and select for responses to more conserved RBD domains (e.g., class 3 and class 4 at base). Overall, data indicate that developing a pan-sarbecovirus vaccine is very feasible.

It may not be necessary to cover all sarbecoviruses in order to have a useful vaccine (e.g., not all use ACE-2). Neutralization panels would need to be used - but not all viruses are available or simple to use, suggesting value of pseudotyped particles. Assay standardization would be helpful.

Cross reactive T cell responses from other coronaviruses play a role in protection and vaccine response. It’s nonetheless difficult to standardize and identify clinical correlates of T cell responses.

Innate antibody-mediated immune responses are important for protection in natural infection and likely for vaccines. They are more resilient against VOCs (e.g., omicron) in non-spike domains.
Conclusions - 5

Advanced statistical methods may provide the opportunity to obtain more rapid and reliable data from observational vaccine effectiveness studies.

There is clearly a need for additional vaccines. Several manufacturers are proceeding with vaccines that could be “variant-proof” or address sarbecoviruses more broadly.

Goal is to extend durability & diversify immunogens and responses. Vaccines, due to broadly acting responses, are working well against severe infection. Major benefit of next generation vaccines could be in reducing infection and transmission. Vaccines could be made available based on current humoral immunobridging criteria if they met criteria for non-variant-proof vaccines. Continued investment is critical. Equity and access are essential to meet goals. The problem of SARS-CoV-2 is not over.

Key themes around facilitation: 1. Global coordination, collection & sharing of information & reagents, 2. Commitment to discovery research linked to global clinical outcomes, genomic surveillance 3. Investment/finances, case for global access. Suggestion to prioritize in favor of “variant-proof” vaccines over the short term, including development of correlates for T cell mediated protection. Importance of broad vaccine candidate repertoire (including adjuvants). Funding (like OWS) to de-risk vaccine development efforts.
Key questions about pan-sarbecovirus vaccines:

How badly are they needed? **Urgently**

What are the most promising approaches? **Many approaches are highly promising and feasible**

How rapidly can they be developed? **This will depend on resources. Novel platforms may require significant manufacturing development. Ease and speed of manufacture is critical.**

If they are developed, how can they be reliably and efficiently evaluated? **Answers are clearer for vaccines that induce humoral responses.**

What research is needed to facilitate all of this?

- Define range of sarbecoviruses that we would like to protect against
- Assays, animal model work
- More work on mediators of protection: CMI, non-neutralizing responses, mucosal immunity
- Optimizing the candidate vaccines
- Human studies

How can the worldwide community contribute to eliminating the future threat of pandemic sarbecoviruses? **We are not yet even done with COVID. It’s critical to continue these discussions and strongly support efforts towards this goal.**