Review of: "The Changing Trajectory of Covid-19 and How Immunity is Evolving with It"

William Strohl

Potential competing interests: No potential competing interests to declare.

Review for COVID-19 Review:

This manuscript on the path of COVID over time is interesting, well-written, and informative. There are a few areas that might be improved as noted in the detailed sections below. Additionally, there are two lines of discussion that the authors have left out that might be good additions to their paper.

The first would be a discussion on R_0 (reproductive number) as it pertains to the various SARS-CoV-2 variants and the ever-increasing rates of infectivity as a function of time (see references Ito et al. https:// doi. org/ 10.1002/ jmv. 27560 Nishiura et al. https://doi. org/ 10. 3390/ jcm11 010030 as examples). While the authors discuss transmissibility, they do not relate their discussion to objective numbers provided in the literature.

The second area that might be important to add depth and understanding to changes in the virus would be the changes in cellular tropism and therefore organ expression profiles from Delta to Omicron. The authors may want to add a short section on the effects of cell entry tropism on the human COVID-19 disease, which likely is a contributor to the changes in both disease severity and transmissibility. For variants D614G to Delta, the tropism is skewed toward TMPRSS2-dependent entry (Hui et al https://doi.org/10.1038/s41586-022-04479-6; Meng et al https://doi. org/10.1038/s41586-022-04474-x; Zhao et al. https://doi.org/10. 1080/22221751.2021.2023329. SARS-CoV-2 Omicron variant shows less efficient replication and fusion activity when compared with Delta variant in TMPRSS2-expressed cells.), which facilitates high infectivity, cell-cell transmission, and infectivity in the deep lung, which results in a statistically higher rate of pneumonia (Hirotsu et al. Nature https://doi.org/10.1038/s43856-023-00261-5). Omicron, on the other hand, has mutations in the S1/S2 region that result in poorer use of TMPRSS-2 for entry, so omicron variants typically rely much more heavily on the cathepsin-dependent endosomal fusion mechanism of cell entry, found in greater propensity in the upper respiratory system. This results in a significantly lower preponderance of pneumonia in omicron-infected patients (Hirotsu et al. Nature https://doi.org/10.1038/s43856-023-00261-5), as well as a higher incidence of omicron in expired breath, which can help to increase transmissibility.

Some other detailed suggestions:

1. page 2, Introduction second para: “since the start of the pandemic in India, there have been 44,691,956 confirmed cases” – can you add an “as of” date to put it into perspective, since once the paper is published it will be on record forever.

2. page 4 – “dodge protection” might be better worded “elude neutralization by vaccine induced antibodies”

3. page 4 – “stick to the human ACE2” could be changed to “bind with higher affinity”

4. page 4 – “data does....” the word “data” is plural, so it should be “data do”

5. page 4, XBB.1.6 should read XBB.1.16 – this was found twice

6. page 4, Identify date of reference. “Currently, the dominant variant in the USA is XBB.1.5, with 53.8% of cases”

7. page 4, “we cannot say” is a bit loose. Perhaps “It is not known...”

8. page 4, “is still there” should be changed to “still exists”

9. page 4, last line – annual or semi-annual, yes – but seasonal no – as opposed to flu or RSV, SARS-CoV-2 is not a seasonal virus

10. Page 5 , Herd immunity has to some degree already been achieved with >90% of the population having antibodies. The problem is that herd immunity can come and go with this virus due to waning protection and new variants. You may want to cite MMWR *Weekly* / June 2, 2023 / 72(22);601–605 for number of people in US (~96%) with at least some immunity to COVID

11. Figure 1B is a nice representation – but maybe this really should be Figure 2.

12. Page 7 – “these findings suggest that vaccine manufacturers should include non-spike antigens that can target spike-antibody immune escaping variants when designing better second-generation vaccines (Figure 1B).” Note that vaccines intended to elicit T cell responses are typically very different from vaccines intended to elicit humoral responses – it may be difficult to produce a vaccine that does both well, just as has been the experience with HIV vaccines. Perhaps easily said, but very difficult to do properly.

13. “SARS-CoV-2, and human coronavirus NL63 (HCoV-NL63), utilize the human protein ACE2 as a cellular receptor to gain entry into human cells [49][50].” So does SARS-CoV.