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

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Potential competing interests: No potential competing interests to declare.

The article is a narrative review of the current state of Covid-19 immunity. A summary of this kind is useful though there are some details that need attention. The biggest issue for me is that the paper is not structured in a way that clearly separates out:

1. What we know and can rely on
2. What is to be determined but is a promising new direction
3. What is controversial

Without the big picture being clear, the reader can get lost in the detail.

Figure numbering is odd: why 1A and 1B when they are separate figures?

There are a few minor language issues. A consistent problem is the use of “however”: this signifies a bigger break than a comma; either a semicolon or the start of a new sentence. Please fix this consistently.

A few other typos:

• The dynamic of the virus-host interaction–>The dynamic of virus-host interaction

• three major mutations on its spike protein that makes this variant–>three major mutations on its spike protein that make this variant

• controversy between the efficacy of therapeutic monoclonal antibodies and polyclonal preparations–>controversy as to the efficacy of therapeutic monoclonal antibodies versus polyclonal preparations

• sub variants–>subvariants

• Researchers at the University of Tübingen in Germany have atrial going to investigate the safety–>Researchers at the University of Tübingen in Germany have a trial that is going to investigate the safety

• type 1 interferon–>type I interferon

• antibody detection; There is–>antibody detection. There is

A few other issues

Cite a reference for Evusheld.

Early promise of convalescent plasma does not appear to have held up in general https://journals.asm.org/doi/full/10.1128/cmr.00200-21 though it does appear to have benefits for the immunocompromised https://jamanetwork.com/journals/jamanetworkopen/article-abstract/2800275

While monoclonal antibodies have shown promise **https://doi.org/10.1002/jmv.27623** this is a very expensive therapy; if it contributes to the overall immunity landscape, that is useful but has to be weighed against lower-cost alternatives like vaccines.

Herd immunity is an unattainable goal with current levels of transmissibility. When the original variant was estimated to have R0=2.5, the herd immunity level was 60% of the population. For Omicron, even before the more contagious subvariants, R0 was over 8, meaning that the “herd immunity” level is 87.5% of the population https://pubmed.ncbi.nlm.nih.gov/35262737/ – in practical terms, almost everyone has to be infected to reach herd immunity, assuming that infection prevents reinfection.

Antibody tests, unless they are specifically targeting testing for vaccine efficacy, generally target the Nucleocapsid protein not the Spike Protein https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8242647/

A good question is why the main target of vaccines is the spike protein, which is relatively non-conserved. A vaccine targeting a more conserved protein would be less susceptible to immune escape. However, a protein with a strong role in infection is better disrupted by the immune system than one with a secondary role in disease or is not involved in infection at all. The protein most involved in infection has to be relatively unconserved to allow new variants to emerge so it is not clear what the optimal choice is; possibly a vaccine targeting both the N and S proteins would be stronger than one targeting only one of them. More here on the N protein: https://virologyj.biomedcentral.com/articles/10.1186/s12985-023-01968-6

ACE2 and haematological conditions: interesting and worthy of further study, given that the worst comorbidities (other than age) tend to be haematological. You could add clotting to the list.

“One known exception is cutaneous Leishmaniasis” – there are other better-known instances where a single exposure leads to lifelong immunity: https://www.livescience.com/why-lifelong-immunity.html

While mRNA viruses do in general have a high mutation rate, this is variable https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6107253/

SARS-Cov-2 is not particularly fast at mutating as it has a proofreading mechanism and inherently has a much slower mutation rate than influenza https://doi.org/10.24875/bmhim.20000183 – its apparently fast rate of mutation arises from the high number of concurrent infections.

The real issue is if it becomes endemic, will mutations stabilise? Theoretically, if a high proportion of the population has

some level of immunity, new infections should reduce. It is hard to know if we are there yet as routine testing has declined with lower instances of severe cases (both because Omicron is less virulent and because of the increasingly complex immunity landscape with multiple prior variants and vaccines).

To make this a good paper, some tidying of presentation to make the contribution clearer would be useful.