Transmissibility of SARS-CoV-2 among fully vaccinated individuals

Vaccine effectiveness studies have conclusively demonstrated the benefit of COVID-19 vaccines in reducing individual symptomatic and severe disease, resulting in reduced hospitalisations and intensive care unit admissions.[1] However, the impact of vaccination on transmissibility of SARS-CoV-2 needs to be elucidated. A prospective cohort study in the UK by Anika Singanayagam and colleagues[2] regarding community transmission of SARS-CoV-2 among unvaccinated and vaccinated individuals provides important information that needs to be considered in reassessing vaccination policies. This study showed that the impact of vaccination on community transmission of circulating variants of SARS-CoV-2 appeared to be not significantly different from the impact among unvaccinated people.[2,3] The scientific rationale for mandatory vaccination in the USA relies on the premise that vaccination prevents transmission to others, resulting in a "pandemic of the unvaccinated".[4] Yet, the demonstration of COVID-19 breakthrough infections among fully vaccinated health-care workers (HCW) in Israel, who in turn may transmit this infection to their patients,[5] requires a reassessment of compulsory vaccination policies leading to the job dismissal of unvaccinated HCW in the USA. Indeed, there is growing evidence that peak viral titres in the upper airways of the lungs and culturable virus are similar in vaccinated and unvaccinated individuals.[2,3,5–7] A recent investigation by the US Centers for Disease Control and Prevention of an outbreak of COVID-19 in a prison in Texas showed the equal presence of infectious virus in the nasopharynx of vaccinated and unvaccinated individuals.[6] Similarly, researchers in California observed no major differences between vaccinated and unvaccinated individuals in terms of SARS-CoV-2 viral loads in the nasopharynx, even in those with proven asymptomatic infection.[7] Thus, the current evidence suggests that current mandatory vaccination policies might need to be reconsidered, and that vaccination status should not replace mitigation practices such as mask wearing, physical distancing, and contact-tracing investigations, even within highly vaccinated populations.

I declare no competing interests.

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With interest we read the paper by Anika Singanayagam and colleagues[1] assessing the secondary attack rate (SAR) of SARS-CoV-2 in 204 vaccinated and unvaccinated household contacts exposed to 138 vaccinated and unvaccinated index cases. Here, we want to point out the importance of adjusting for age when comparing vaccinated and unvaccinated individuals.

The authors report a similar SAR among household contacts exposed to fully vaccinated and unvaccinated index cases (25% and 23%). Although not explicitly stated by the authors, this finding hints towards no effect of vaccination on transmission and was reported as such by the media in the UK and the Netherlands—and possibly other countries.[2,3] However, age is a confounding factor in this observation if age is associated with both vaccination status and the risk of transmitting SARS-CoV-2. Indeed, the study indicates a higher peak viral load with increasing age, consistent with lower infectiousness in children. In addition, although the age distribution of all included index cases and contacts is not presented, table S2 in the appendix to the Article provides data for a subset of participants testing positive for SARS-CoV-2, showing that a large proportion (78%) of unvaccinated participants were younger than 18 years, whereas none of the vaccinated participants were. These findings together suggest that the infectiousness of the included unvaccinated index cases was lower than that of the included vaccinated participants because of younger age. Therefore, the presumed lack of vaccine effect on transmission might be largely due to confounding by age, which the authors did not address. In our analysis of vaccine effectiveness against transmission in the Netherlands, adjustment for age of index cases and contacts indeed had a large effect on vaccine effectiveness estimates.[4] Therefore, vaccine effectiveness against transmission reported by Singanayagam and colleagues is probably an underestimate.

Also, the reported vaccine effectiveness against SARS-CoV-2 infection (34%) is likely confounded

by age, as vaccination status is associated with age, and younger age is associated with reduced susceptibility to acquiring SARS-CoV-2 infection.[5]

In these times, when evidence-based confidence in vaccines is crucial to reduce the impact of the COVID-19 pandemic on mortality and morbidity, data on effects of vaccination should be adequately and unambiguously reported by the scientific community in order to avoid misinterpretation of the data by the public and the media.

We declare no competing interests.

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The important analysis by Anika Singanayagam and colleagues[1] demonstrated that individuals fully vaccinated against SARS-CoV-2 with breakthrough infections have similar peak viral loads to unvaccinated people and might infect other fully vaccinated individuals within the same household. Of particular concern, vaccines that permit transmission do not confer sterilising immunity, thus potentially resulting in accumulation of large viral loads and increased risk of immune escape.[2] By mainly targeting the SARS-CoV-2 spike protein, vaccines can favour propagation of variants with immune-escape mutations.[3] Single point mutations in the receptor-binding domain of the viral spike protein are sufficient to facilitate the immune escape and transmission of resistant viruses.[2] By further examining the unpublished whole-genome sequencing data of vaccinated and unvaccinated participants in the study by Singanayagam and colleagues,[1] invaluable information could be gleaned about whether the current first-generation COVID-19 vaccines potentially exerted selective pressure for resistant SARS-CoV-2 variants.

Tracing the whole-genome sequencing data of all unvaccinated participants chronologically from the pre-alpha-variant (B.1.1.7) phase (September–November, 2020), to the alpha-variant phase (December, 2020, to March, 2021), and to the delta-variant (B.1.617.2) period (May 25–Sept 15, 2021) would likely reveal a trend of increasing number of mutations that converge towards the resultant whole-genome sequence aligned with delta lineage-defining mutations presented in figure 2 of the Article.[1] To determine if vaccines possibly contributed to this genetic drift, the whole-genome sequencing data from patients who tested PCR positive (vaccinated and unvaccinated) can be compared with data from their respective contacts over time from the pre-alpha to the delta phases.

Identical whole-genome sequences between PCR-positive participants and their respective contacts demonstrates direct viral transmission without mutation. Clearly distinct whole-genome sequences between both groups indicate cross-infection of contacts by a different viral lineage. Slight variations in whole-genome sequences between both groups show mutation has occurred, in which case the vaccination status of the contact should be examined. If mutation occurred predominantly among vaccinated contacts but not within unvaccinated contacts, it suggests vaccine-induced mutation has developed. Because the sample size in the research by Singanayagam and colleagues[1] is relatively small, it will be worrisome if a fair number of vaccinated contacts of PCR-positive participants are identified with mutations, especially with the amino acid mutations summarised in the appendix.

See **Online** for appendix

The earliest detection of the delta variant was in India on Oct 14, 2020,[4] before India's vaccination commencement on Jan 16, 2021.[5] However, with fastidious propagation of these variants over time by non-sterilising vaccines targeting the spike protein, it is still reasonably plausible that selective pressure could have contributed to the current dominance of the delta variant.

It would be much appreciated if Singanayagam and colleagues would consider analysing their unpublished whole-genome sequencing data as suggested above. If theoretical risk of evolutionary escape from the existing COVID-19 vaccines[2] translates into real-life evidence, which could be verified via whole-genome sequencing data from this study,[1] then it will be prudent to expedite resources towards second-generation COVID-19 vaccines that exert sterilising immunity, in addition to non-pharmacological interventions.

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