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Authors' reply

We thank Carlos Franco-Peredes, Mirjam Knol and colleagues, and Humphrey Ko for their interest in our Article.[1] We reported that one in four household contacts exposed to fully vaccinated index cases with breakthrough delta (B.1.617.2)-variant infections, and one in four fully vaccinated household contacts exposed to delta-infected index cases, become infected. These are appreciable risks, which led us to conclude that fully vaccinated individuals remain susceptible to infection and, when breakthrough infection occurs, can efficiently transmit infection in household settings. While we also assessed the secondary attack rate (SAR) among unvaccinated contacts and contacts exposed to unvaccinated index cases, comparing these with the aforementioned SARs, and the corresponding calculation of vaccine effectiveness, were purely exploratory analyses. Our study was not sufficiently powered for such comparisons, as evidenced by the wide confidence intervals, which overlapped between groups. Therefore, extrapolation of our data to comment on the effect of vaccination in a wider context or at a population level requires careful consideration of our study's limitations and caveats.

We are aware of the relationship between age and infectiousness of index cases and susceptibility to infection in contacts. Indeed, our viral load kinetic data revealed a correlation between age and peak viral load, helping to explain the increased infectiousness of older adults relative to children.[2] Given that our study was a snapshot of SARS-CoV-2 delta-variant transmission in real-life UK households, most unvaccinated participants were children and teenagers, whereas most vaccinated participants were adults, owing to the age prioritisation of national vaccine rollout. Accordingly, we could not directly compare the infectiousness of vaccinated breakthrough infections with age-matched unvaccinated cases nor the SAR in vaccinated contacts with age-matched unvaccinated contacts. Although we discussed the confounding effect of age on our results as a limitation of the study, we acknowledge that this could have been more clearly and explicitly elaborated in the Discussion. However, stratifying the household contacts by age, we found no significant difference in the SAR between unvaccinated contacts younger than 20 years versus those aged 20 years and older (p=0·749), nor between vaccinated contacts younger than 20 years versus those aged 20 years and older (p=0·594). Similarly, there was no significant difference in the SAR between contacts exposed to unvaccinated index cases younger than 20 years versus those aged 20 years and older (p=0·151), nor between contacts exposed to vaccinated index cases younger than 20 years versus those aged 20 years and older (p=0·311). Knol and colleagues' study in the Netherlands using routine contact-tracing data,[3] which had a larger sample size than our study and adjusted for age, showed significantly reduced infectiousness in vaccinated breakthrough cases compared with unvaccinated cases. However, test-and-trace-based surveillance data are biased towards symptomatic cases, so the estimated vaccine effectiveness against transmission might also include some protection against symptomatic disease (rather than just infection). Ultimately, one has to consider the totality of data on SAR estimates, which are generated using different methods and populations, each with their own particular strengths and limitations. The public health messages of our paper and media briefing (Science Media Centre, London, Oct 28, 2021) are thus complementary to the findings of Knol and colleagues. First, despite vaccination, the delta variant readily transmits in households, and unvaccinated people cannot therefore rely on the immunity of the vaccinated population for protection as they remain susceptible to infection, severe illness, and death. Second, increasing population immunity via booster programmes and vaccination of teenagers will help to increase the population-level protective effect of vaccination on delta-variant transmission. Third, direct protection of those at risk of severe outcomes, via vaccination and non-pharmacological interventions, remain necessary to contain the burden of disease. Fortunately, the vast majority of media coverage of our paper, comprising over 360 news stories to date, has conveyed these important messages without misinterpretation.

Although our findings support Franco-Peredes' conclusion that vaccination status should not replace social and physical public health mitigation practices, the above clarifications explain why our findings do not support his assertion that mandatory vaccination of health-care workers would not reduce nosocomial SARS-CoV-2 transmission.

We thank Ko for his cogent recommendations for future SARS-CoV-2 genomic research. We are pleased to report that sequencing of isolates from index cases and their respective household contacts in one of our related cohorts is underway to verify transmission chains, identify evolutionary transmission bottlenecks, and longitudinally

quantify acquisition of mutations over the time course of infection. We will also stratify the number of mutations observed by vaccination status to test Ko's compelling hypothesis, although our modest sample size will likely limit our power to detect vaccine-induced selective pressure, which requires larger, national datasets.

NMF reports grants from UK Medical Research Council (MRC), UK National Institute of Health Research (NIHR), UK Research and Innovation, Community Jameel, Janssen Pharmaceuticals, the Bill & Melinda Gates Foundation, and Gavi, the Vaccine Alliance; consulting fees from the World Bank; payment or honoraria from the Wellcome Trust; travel expenses from WHO; advisory board participation for Takeda; and is a senior editor of the *eLife* journal. All other authors declare no competing interests.

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Anti-SARS-CoV-2 antibodies in healthy donor plasma pools and IVIG products—an update

In a previous Correspondence,[1] we demonstrated the appearance of antibodies to SARS-CoV-2 in pooled donor plasma and intravenous immunoglobulin (IVIG) products from these pools over the period of May–December, 2020. In this update, we describe increasing levels of anti-SARS-CoV-2 antibodies in pooled plasma and IVIG products up to September, 2021, and neutralising activity of these antibodies against wild-type virus and variants of concern (VOC).

Since May, 2020, we have measured SARS-CoV-2 antibodies (by ELISA[2]) in healthy donor plasma pools collected in Spain, Germany, Czech Republic, Slovakia, and the USA, and the products made from this plasma.[1] Plasma and products from Hungary and Italy have been included since May, 2021. Concentrated immunoglobulins have been, and are currently being, investigated as a potential treatment for COVID-19 (NCT04480424).[3] Anti-SARS-CoV-2 antibody levels in these products could have bearing on their effectiveness. These plasma pools also reflect the antibody contributions of over 1000 donors and are a indirect measure of the epidemiology of COVID-19 at that time.

We previously showed early appearance of anti-SARS-CoV-2 antibodies in Spain and the USA and later appearance in central European countries.[1] Subsequent data show that anti-SARS-CoV-2 antibodies dramatically increased (ten to 50 times) in all plasma pools and IVIG products, regardless of geographic origin (appendix pp 1–3). The highest titres and the greatest increases in titres of anti-SARS-CoV-2 antibodies were seen in the regions where antibodies first appeared (Spain and the USA). The titres of anti-SARS-CoV-2 antibodies in the final products showed similar changes over time as those seen in pooled plasma (appendix p 3). All products showed upwards trends in their titres except those from Slovakia.

Neutralisation studies were conducted with wild-type SARS-CoV-2 virus and psueudoviruses representing the native strain and several VOC. These studies showed neutralisation potency of several batches of IVIG (Gamunex-C and Flebogamma DIF) from plasma of different origins (appendix p 4). Importantly, IVIG products (from the USA and Germany) showed neutralisation activity against psuedoviruses representing the wild-type virus and alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and delta (B.1.617.2) VOC (appendix p 4).

This follow-up provides even stronger evidence that anti-SARS-CoV-2 antibodies in pooled plasma and IVIG products mirror exposure in the general population. IVIG products are indicated for immunodeficient patients and for other prophylactic or therapeutic aproaches. Continued monitoring of these antibodies and assessment of their functionality (eg, neutralisation capacity, effectiveness against VOC) is recommended.

CR, J-MD, and RG are full-time employees of Grifols, a manufacturer of IVIG products and other blood plasma derivatives.

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See **Online** for appendix