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SARS-CoV-2 delta variant neutralisation after heterologous ChAdOx1-S/BNT162b2 vaccination

Safety considerations associated with the Oxford–AstraZeneca COVID-19 ChAdOx1-S vaccine (AZD1222) have led many public health agencies to recommend a heterologous boost with an mRNA vaccine after prime vaccination with ChAdOx1-S instead of a homologous boost. The first results of a phase 2 trial from Spain[1] and additional reports from observational studies suggest robust immune responses accompanied by acceptable reactogenicity after ChAdOx1-S prime and BNT162b2[2,3] (Pfizer–BioNTech) or mRNA-1273[4] (Moderna) boost vaccination. Given the strong immune response after heterologous prime-boost vaccination, mixing of vaccines has been suggested as a suitable strategy to contain emerging SARS-CoV-2 variants.[5]

Heterologous boosting with BNT162b2 has been shown to induce higher counts of spike-specific CD4+ and CD8+ T cells and, in particular, high titres of neutralising antibodies in a surrogate test against the SARS-CoV-2 variants of concern (VOCs) alpha, beta, and gamma.[3] However, the rapid spread of the delta variant is a concern for both ChAdOx1-S-primed vaccinees who are expecting a boost vaccination and for individuals who have been fully vaccinated with ChAdOx1-S.

We analysed plasma from ChAdOx1-S-primed vaccinees at a mean 16·3 days (range 14–22 days) after homologous ChAdOx1-S (group 1; n=12, seven women) or heterologous BNT162b2 (group 2; n=11, eight women) boost[3] to compare neutralising activity against SARS-CoV-2 VOCs, including the delta variant. Detailed methodology is available in the appendix. The mean dose interval between prime and boost was 73·5 days (range 71–85 days) and did not differ between the groups (appendix p 1). We used a vesicular stomatitis virus-based pseudotyped virus assay to analyse neutralisation.[6] This study was approved by the Internal Review Board of Hannover Medical School. All participants gave written informed consent.

Mean anti-spike IgG (QuantiVac, Euroimmun, Lübeck, Germany) was 171·9 relative units (RU) per mL (SD 121·8 RU/mL) in group 1 and 611·0 RU/mL (SD 104·5 RU/mL) in group 2 (p<0·0001; appendix p 1). Plasma from individuals in group 1 had moderate 50% neutralisation titre (NT_{50}) against the wild type and alpha variant, and this activity was further diminished against beta, gamma, and delta variants (appendix p 2). In contrast, all heterologous ChAdOx1-S/BNT162b2 vaccinated individuals achieved at least NT_{50}=25 against all variants, including the delta variant (NT_{50}≥100 in 85% of vaccinees; appendix p 2). Mean anti-spike IgG correlated highly significantly to NT_{50} against the delta variant across both groups (r=0·901; p<0·0001, Pearson correlation; appendix p 3).

The statistical analysis in this small study does not account for potential confounding factors. However, the robust inhibition of variants including the delta variant further supports heterologous ChAdOx1-S/BNT162b2 vaccination. If confirmed in a large study, our data also support a heterologous boost vaccination of individuals with completed homologous ChAdOx1-S vaccination, once humoral immunity is declining and patients become susceptible to infection.

We declare no competing interests. The work presented in this Correspondence was supported by the German Center for Infection Research and the Federal Ministry of Education and Research, the Ministry for Science and Culture of Lower Saxony, and the German Research Foundation. The funders had no role in study design, data collection, data analysis, interpretation, writing, or submission of the Correspondence. Further details about contributors and acknowledgements are available in the appendix.

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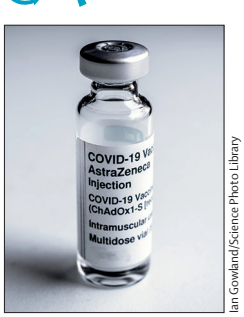
See **Online** for appendix



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Published **Online**
August 17, 2021
https://doi.org/10.1016/S0140-6736(21)01891-2

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Published **Online** August 16, 2021 https://doi.org/10.1016/S0140-6736(21)01604-4

40th anniversary of the WHO International Code of Marketing of Breastmilk Substitutes

The WHO International Code of Marketing of Breastmilk Substitutes is a seminal document, but to maintain this status it needs to be relevant to contemporary society; if not, there is the risk that it presents as a problem rather than a solution. A joint statement in 2021 by UNICEF and WHO on the 40th anniversary of the Code noted that, with regards to implementation during the 40-year period, only 25 countries (12·7% of the 197 countries worldwide) have implemented measures that are substantially, but not necessarily fully, aligned with the Code.[1]

The 40th anniversary was an opportunity to revisit the original concept, reflect on progress, and invite new thinking on how this document might be more effective for nations in the 21st century. The reluctance to independently review the Code after 40 years raises the suspicion that WHO is concerned that in its current form, under close examination, it would be found wanting. The current practice of clarifying aspects of the Code through random subsequent resolutions does not have credibility, and observers who are more sceptical might perceive this to be a tactic by WHO officials to change the meaning of the Code without resorting to an extensive consultation.[2] It might be that this bureaucratic approach is acceptable for minor adaptations relating to the Code, but when applied to something as fundamental as the definition of a breastmilk substitute, a term included in the title of the Code document, it is unsurprising that questions are being asked on matters of transparency, due diligence, and integrity.[3] Trust and respect are crucial commodities in partnership working, and these commodities will only be achieved if all partners listen, learn, and collectively reach the best nutrition solutions for all infants worldwide.

The webinar associated with the statement was sponsored by a Global Breastfeeding Collective, which includes UNICEF, WHO, and 25 international breastfeeding support agencies. It is perplexing that other key aspects of an infant diet, including complementary feeding where deficiency causes wasting, stunting, and death, are persistently overshadowed by breastfeeding. The health benefits from breastfeeding are undermined if the infant is subject to the negative effects of other nutritive and non-nutritive deficiencies, and therefore the best outcomes will be produced if these key interdependencies are simultaneously addressed. However, this approach can only be done if there is resolution of the stakeholder conflict that has dominated infant feeding policy and practice for more than 40 years.[2]

SF reports a consultancy contract with DSM Nutritional Products; consultancy fees from Danone, DSM Nutritional Products, and SciOpinion; received funding to attend scientific meetings from DSM Nutritional Products; and is a member of the Early Life Nutrition and Health Task Force at the International Life Sciences Institute (Brussels, Belgium).

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Published **Online** August 17, 2021 https://doi.org/10.1016/S0140-6736(21)01890-0

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Mendelow AD, Gregson BA, Rowan EN, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet *2013;* **382:** *397–408*—In this Article, M Javadpour (Walton Centre, Liverpool) should have been included in the STICH II Investigators list. This correction has been made to the online version as of Sept 16, 2021.

Carr EJ, Wu M, Harvey R, et al. Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients. Lancet *2021;* **398:** *1038–41*—In this Correspondence, author Matthew P M Graham-Brown's middle initial was incorrect, and reference 15 was incorrect and should have referred to Longlune N et al. *Nephrol Dial Transplant* 2021. These corrections have been made to the online version as of Aug 17, 2021, and the printed version is correct.