# Vaccination and protective immunity to SARS-CoV-2 omicron variants in people with immunodeficiencies

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Despite the success of COVID-19 vaccination programmes in reducing morbidity and mortality, a substantial number of individuals in the general population respond poorly to SARS-CoV-2 vaccination.[1,2] Furthermore, only about 20% of individuals throughout low-income countries have received their first dose of the SARS-CoV-2 vaccine.[3] Neutralising antibodies are a key correlate to protection from COVID-19, with booster vaccines offered to increase protection from new variants.[4,5] However, poor responsiveness to immunisation increases the risk of infection and disease.[6] The CDC[6] reported that patients with compromised immune systems accounted for about 12% of adult COVID-19 hospital admissions and had higher rates of intensive care admissions and in-hospital deaths compared with non-immunocompromised inpatients, in both vaccinated and unvaccinated populations. Although a heterogeneous group, the majority of patients with immunodeficiency show variable and weaker antibody-mediated responses post-vaccination to SARS-CoV-2 than individuals without immunodeficiency.[7] In March, 2022, a UK report revealed 45·5% of immunocompromised individuals received a booster vaccination dose.[8] However, without immune monitoring it remains unclear which individuals within this high-risk population have sufficient immunity.

Within the variants of concern, the omicron sublineages have represented the predominant variants of concern since December, 2021. Despite lower omicron-related fatality in the vaccinated population than in the unvaccinated population, there remains a significant risk of increased moderate-to-severe disease in individuals with partial or no immunity. WHO has recognised five different omicron lineages. Alongside mutations found in BA.1 and BA.2, the latest BA.4 and BA.5 variants have mutations that enhance antibody escape to the point of successful reinfection in immunocompetent, vaccinated individuals with previous BA.1 or BA.2 infection.[9,10]

Countries such as the UK offered an initial two-dose regimen of either ChAdOx nCoV-19 or BNT162b2 and a third mRNA-based SARS-CoV-2 booster dose, including Moderna's Spikevax. To determine the breadth of antibody-mediated neutralisation in serum samples from both healthy individuals (ie, health-care workers) and patients with immunodeficiencies in the UK after second-dose immunisation, we used pseudotyped virus incorporating either the BA.1, BA.2, or BA.2.12.1 spike, or the shared BA.4 and BA.5 spike. In the 4–6 weeks after the second dose of vaccination, neutralising immune responses to the ancestral (vaccine) strain were detected in 97% of the healthy cohort, with a median neutralising $IC_{50}$ titre of 956 (appendix p1). In comparison, detectable responses were found in only 44% of the healthy cohort after the first dose of vaccination, which we reported in 2021.[2] Compared to the ancestral strain, fewer health-care workers mounted a detectable neutralising response to any of the omicron strains after two doses and, of those who responded, neutralising $IC_{50}$ titres were significantly lower than titres against the ancestral strain (appendix p 1), although increased relative to responses following first vaccination doses (Wilcoxon matched-pairs test, p<0.0001; data not shown).

See Online for appendix

After a third vaccination dose (BNT162b2 or Spikevax) in health-care workers, the breadth of serum neutralising activity to omicron variants of concern was eight-times higher in median $IC_{50}$ against BA.2.12.1 and 14-times higher in median $IC_{50}$ against the shared BA.4 and BA.5 spike than after the second vaccination dose (Mann-Whitney, p<0·0001). After both second and third vaccination doses, healthy individuals show greater neutralisation of BA.2.12.1 than BA.4 and BA.5 (appendix p 1). However, there still remain healthy individuals with no or low detectable neutralising responses after the third vaccination dose (appendix p 1). Some individuals had a primary infection (presumed omicron BA.1 or BA.2 due to local temporal epidemiology) after receiving three doses of vaccination. Notably these individuals, infected during the BA.1 and BA.2 waves, had significantly higher neutralising titres against the currently circulating BA.2.12.1 and BA.4 and BA.5 omicron variants than individuals who were not infected after the third vaccination dose (Mann Whitney, p<0·0001; appendix p 1).

Although healthy individuals seem to show a neutralising capacity for omicron that progressively increases with subsequent booster immunisations

(and infection), individuals with immunodeficiencies responded quite differently. Whereas neutralising $IC_{50}$ in patients with immunodeficiencies was higher against the ancestral strain after second-dose vaccination than after first-dose vaccination,[2] the majority did not neutralise any of the omicron variants (appendix p 1). After two immunisations, only 18% of patients with immunodeficiencies neutralised BA.1, 22% neutralised BA.2, 17% neutralised BA.2.12.1, and 17% neutralised BA.4 and BA.5 (appendix p 1). Within the patients with immunodeficiencies who did respond to omicron, neutralising $IC_{50}$ titres increased between first-dose[2] and second-dose vaccination against both BA.1 and BA.2 (Wilcoxon matched-pairs test; p<0·0005 and p<0·0001, respectively; data not shown) and the increment was similar for health-care workers. After the third-dose vaccination, there was a significant increase in the percentage of patients with immunodeficiencies who had a detectable neutralisation against BA.2.12.1 (40% of patients) and BA.4 and BA.5 (30% of patients); however, in contrast to health-care workers, there was no significant difference in BA.2·12·1 or BA.4 and BA.5 $IC_{50}$ titres after the third vaccination dose (Mann-Whitney, p=0·07 and p=0·27, respectively).

In summary, healthy individuals in the UK benefited from boosting with a third ancestral-strain-based vaccine and it diversified their neutralising responses against BA.2·12·1 and BA.4 and BA.5. However, individuals with immunodeficiencies mounted weak responses against omicron, which were not significantly boosted. Individuals with different underlying immunodeficiencies will benefit from next-generation vaccines containing more antigenic targets with a broad variant-targeting capacity. This suggests that this group should be prioritised for the receipt of variant-informed SARS-CoV-2 vaccines containing relevant mutations specific to the variants of concern.

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