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## Dawn of the hybrid immunity era in long-term care facilities



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COVID-19 vaccines have saved numerous lives in long-term care facilities around the world by diminishing disease severity. These vaccines have also reduced the risk of COVID-19 outbreaks by decreasing SARS-CoV-2 transmission among residents and staff of long-term care facilities,<sup>1</sup> although the protective effect has been shown to wane over time in the general population and has probably become less clinically significant after the emergence of the omicron (B.1.1.529) variant.<sup>2</sup>

The omicron variant has substantially changed the course of the COVID-19 pandemic. It has led to unprecedented numbers of SARS-CoV-2 infections in various populations, including residents of long-term care facilities. Consequently, many people who had been vaccinated before infection, now have hybrid immunity, a mix of vaccine-induced and infection-induced immunity. Still, the evolution of SARS-CoV-2 is ongoing. The phylogenetic tree of omicron is branching into new subvariants, some of which hide better from our bodies' defence systems than earlier SARS-CoV-2 variants. Therefore, SARS-CoV-2 is not going to disappear in the coming years.<sup>3</sup> The attention of policy makers is, therefore, on identifying the most advantageous COVID-19 vaccination strategy, which is why they need high-quality studies focusing not only on vaccine-induced immunity, but also on hybrid immunity.

What is known about hybrid immunity? A few studies have shown that hybrid immunity was superior to vaccine-induced and infection-induced immunity in protecting against SARS-CoV-2 infection before and after the emergence of omicron in general populations. Similar to vaccine-induced and infection-induced immunity, hybrid immunity also wanes over time.<sup>4-7</sup> Unsurprisingly, omicron can evade hybrid immunity acquired in the pre-omicron era.<sup>5,6</sup> Nevertheless, hybrid immunity seems to protect well against severe COVID-19 caused by omicron, at least in young populations.<sup>7</sup> However, the understanding of hybrid immunity in residents of long-term care facilities is still very limited.

In *The Lancet Healthy Longevity*, Madhumita Shrotri and colleagues<sup>8</sup> estimated COVID-19 vaccine effectiveness among 15 518 residents and 19 515 staff in long-term care facilities, distinguishing between those who had a SARS-CoV-2 infection in the past and those who had

not. A limitation of the study is that it was conducted before the omicron variant was predominant. However, a strength of the study is the meticulous design based on routine testing of residents and staff of long-term care facilities from all regions in England.

In Shrotri and colleagues' study,<sup>8</sup> previous SARS-CoV-2 infection reduced the risk of COVID-19-related hospitalisation by 62.0% (95% CI 34.1–78.1) among unvaccinated residents of long-term care facilities. Three COVID-19 vaccine doses reduced the risk of COVID-19 hospitalisation by 90.1% (80.6–95.0) among residents without previous infection. Thus, infection-induced immunity was inferior to vaccine-induced immunity. Unfortunately, Shrotri and colleagues could not estimate the benefit of vaccination among those with previous infection precisely due to the small number of previously infected study participants. However, the estimates, although not statistically significant, suggest that infection-induced immunity might be inferior to hybrid immunity.<sup>8</sup>

Similar results were shown in staff of long-term care facilities. Although four unvaccinated staff members with infection-induced immunity needed to be hospitalised due to re-infection, there were no hospitalisations among those with hybrid immunity.<sup>8</sup>

Shrotri and colleagues' study<sup>8</sup> also showed that vaccine effectiveness against COVID-19-related hospitalisation in residents with no previous exposure to SARS-CoV-2 decreased over time: from 89.0% (95% CI 70.6–95.9) at 14–83 days after dose two to 56.3% (30.1–72.6) at 84 days or longer after dose two. This decrease in vaccine effectiveness seems to be larger than the decrease observed in a similar study of community-dwelling older people aged 65 years and older after receipt of the ChAdOx1-S or BNT162b2 vaccine.<sup>9</sup> Therefore, it might be assumed that any immunity (ie, infection-induced, vaccine-induced, or hybrid immunity) wanes more rapidly in the highly susceptible group of residents of long-term care facilities than in the rest of the population. These residents are thus likely to benefit from additional vaccine booster doses sooner. Some residents of long-term care facilities have already benefitted from a fourth dose.<sup>10</sup> To date it remains unclear at which timepoint additional booster doses should be offered to residents of long-term care

facilities and whether residents with pure vaccine-induced immunity should be boosted differently than those with hybrid immunity.

We declare no competing interests.

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