neutralisation was reduced by more than 10 times compared with the neutralisation of $B.1_{pp}$.

Finally, we assessed the sensitivity of $XBB.1_{pp}$ to neutralisation by antibodies induced by vaccination or vaccination plus breakthrough infection (figure B; appendix pp 1–2). Plasma of triple vaccinated individuals had almost no detectable neutralising activity against $XBB.1_{pp}$ (neutralising titre 50 [$NT_{50}$] 2), whereas the neutralising activity against $B.1_{pp}$ was high ($NT_{50}$ 1165) and against $BA.5_{pp}$ was moderate ($NT_{50}$ 127). Next, we measured the plasma of triple vaccinated individuals with breakthrough infection during the BA.5 wave in Germany (June to November, 2022). The plasma samples showed high neutralising activity against $B.1_{pp}$ ($NT_{50}$ 1779), moderate neutralising activity against $BA.5_{pp}$ ($NT_{50}$ 538), and low neutralising activity against $XBB.1_{pp}$ ($NT_{50}$ 14). Similar findings were made for plasma from triple vaccinated individuals who received either monovalent or bivalent (ie, B.1 or B.1 plus BA.5) booster vaccination: $B.1_{pp}$ $NT_{50}$ 1806 for B.1 or 1939 for B.1 plus BA.5; $BA.5_{pp}$ $NT_{50}$ 206 for B.1 or 525 for B.1 plus BA.5; and $XBB.1_{pp}$ $NT_{50}$ 8 for B.1 or 5 for B.1 plus BA.5.

Collectively, our data suggest that the SARS-CoV-2 XBB.1 lineage exhibits an extraordinarily strong ability for antibody evasion, which makes XBB.1 similar to BQ.1 and BQ.1.1;[9] two highly neutralisation-resistant sublineages of omicron that are currently increasing in incidence in several countries worldwide. The finding that most mAbs do not neutralise $XBB.1_{pp}$ highlights that novel mAbs are needed for the treatment of COVID-19 and that other or additional treatment options (eg, paxlovid, molnupiravir, or remdesivir) should be considered in areas with high incidence of the XBB sublineages. The observation that host-cell entry of $XBB.1_{pp}$ is reduced as compared with $BA.5_{pp}$ suggests that the increased ability of XBB.1 to evade antibody-mediated neutralisation might have come at the cost of a moderately reduced efficiency of host-cell entry.

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## Stability of hybrid versus vaccine immunity against BA.5 infection over 8 months

The coverage of SARS-CoV-2 vaccination in large parts of the world, together with the high number of breakthrough infections, especially following the emergence of Omicron subvariants, makes hybrid immunity (resulting from vaccine and infection) common. Hybrid immunity, particularly after BA.1 or BA.2 infection, confers substantial protection against the BA.5 infection.[1–3] However, although the waning of protection afforded by natural infection in non-vaccinated individuals or by vaccination has been well documented,[4,5] the stability of hybrid immunity, specifically against the BA.5 subvariant, now dominant in many countries, has not been thoroughly addressed.

We used the Portuguese COVID-19 registry (SINAVE), which includes all notified cases of infection in the

country on the basis of an official positive test and irrespective of clinical presentation, to investigate the risk of reinfection with BA.5 in a highly vaccinated population previously infected with BA.1 or BA.2 subvariants. We included the population aged 12 years or older, for whom the vaccination coverage was greater than 98% at the end of 2021 (appendix pp 4–5). The registry is very comprehensive due to legal requirements for compensation payment during mandatory isolation. We include infection data from the start of the pandemic until Sept 14, 2022.

We identified the periods of dominance (over 90% of the isolates) of BA.1 and BA.2 (Jan 1–Apr 17, 2022) and BA.5 infections (June 1–Sept 14, 2022) using the national SARS-CoV-2 genetic surveillance data and divided those periods into 15 day intervals (figure A). We then calculated the relative risk (RR) of BA.5 infection in each interval for individuals that had the first infection during each BA.1 and BA.2 dominance subinterval, compared with individuals also vaccinated but without any previous documented infection. Reinfection was defined as two positive tests in the same individual, at least 90 days apart. We found that the RR increased from around 0·06 to around 0·35 between 3 months and 8 months post BA.1 or BA.2 infection (figure B, appendix p 12). Indeed, the RR initially increases rapidly, then more slowly, stabilising at around 0·37.

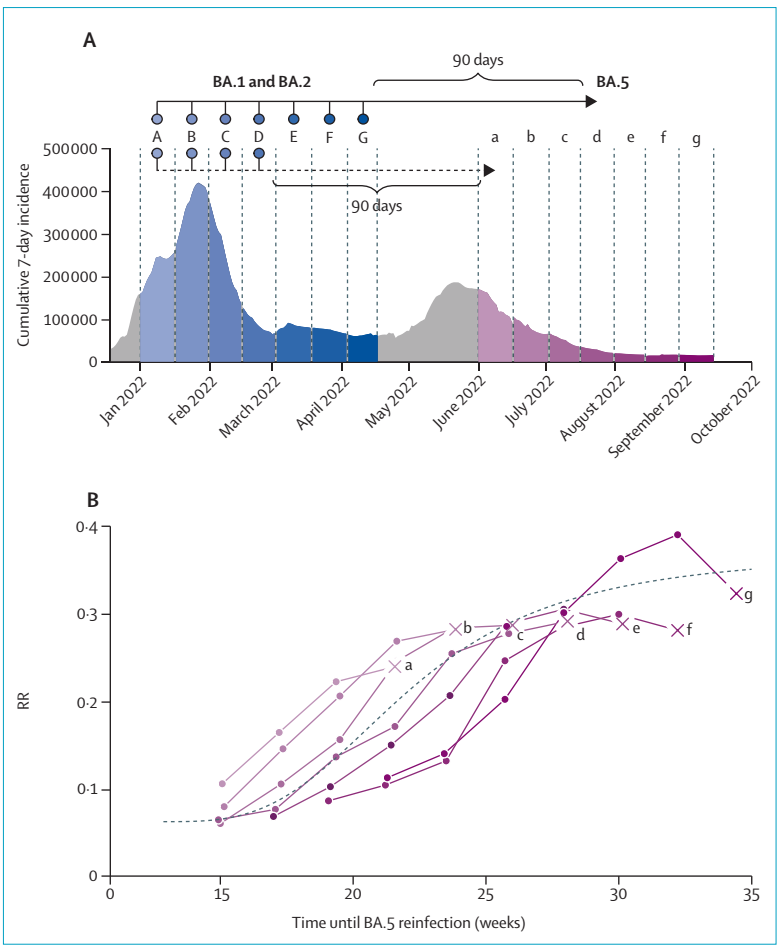


***Figure:*** **Stability of hybrid immunity protection against BA.5 infection following infection with BA.1 or BA.2 subvariants**

(A) Incidence of documented SARS-CoV-2 infection overlaid with the period of dominance of the BA.1 and BA.2 variants, Jan 1–Apr 14, 2022, divided into 15-day sub-intervals (shades of blue), and the period of dominance of the BA.5 variant, Jun 1–Sep 14, 2022, also divided into 15-day sub-intervals (shades of purple). Two illustrative comparisons are represented. In period d (BA.5 dominance), the risk of infection was compared between individuals with a first documented infection in one of the seven subintervals of BA.1 and BA.2 dominance (A–G), represented with the solid arrow. In the second example with the dashed arrow, in period a of BA.5 dominance, the risk of infection was compared between individuals with a first documented infection in the first four periods of BA.1 and BA.2 dominance (A–D), as reinfections were only considered 90 days following the first infection. (B) RR of reinfection versus first infection in each subinterval of the period of BA.5 dominance (curves a–g, corresponding with the periods of the same letter as in (A) over time since the first infection. The increase in risk is well described by a saturating function (appendix pp 5, 9) as represented by the fitted line (dashed, black). RR=relative risk.

The present authors previously assessed the effect of unreported infections in the calculation of RR.[1] Here, we mitigate this effect by calculating the RR for the same interval of BA.5 infection for individuals infected by BA.1 or BA.2 in distinct periods, thus with a constant frequency of unreported infections. In any case, our findings are consistent throughout the entire dataset (appendix p 12). Our registry-based dataset includes data on essentially the whole population, but only includes data on positive tests. This feature precludes using a test-negative study design, which has been successfully used in other studies of RR.[2,6] However, previous reports indicate that the estimates of protection efficacy using the national registry are well aligned with studies that used a test-negative design, albeit in a different population.[1,2] Studies since 2021 have made clear the potential for immune imprinting, with one study[7] suggesting that protection against infection waned after the booster (relative to primary series). In our study, essentially the whole population is vaccinated with the booster dose, and therefore we cannot distinguish effects of booster versus primary series. However, our results of increased protection with hybrid immunity versus vaccine

See **Online** for appendix

For **how reinfection was defined** see https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance Guidance-2022.2

immunity, agrees with the overall conclusion of that study that "imprinting effects are unlikely to negate the overall public health value of booster vaccinations".[7]

This study shows that hybrid immunity following infection with Omicron BA.1 or BA.2 when compared with vaccine-only immunity leads to substantially increased protection against BA.5 reinfection for up to 8 months.

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See Online for appendix

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## 7-month duration of SARS-CoV-2 mucosal immunoglobulin-A responses and protection

Mucosal immunity has a pivotal role in protection from respiratory viral infections.[1] The current authors have showed substantial protection from omicron infection by high concentrations of nasal mucosal SARS-CoV-2 WT spike immunoglobulin-A (M-IgA) over a 4-week screening period.[2] A sharp increase in M-IgA concentrations following BA.1 or BA.2 breakthrough infection in triple vaccinated health-care workers was also observed.[2] Here, we present follow-up data with prospectively collected omicron infection rates and systemic and mucosal antibody concentrations from the same cohort (appendix pp 7–9, 12–14).

The association between M-IgA concentrations at the 75th percentile or higher at enrolment and a reduced risk of symptomatic BA.1, BA.2, or BA.5 breakthrough infection remained over an 8-month follow-up period, with a hazard ratio (HR) of 0·55 (95% CI 0·35–0·87), much due to the initial risk difference (figure A). Serum WT spike-specific IgG (S-IgG) concentrations waned over 8 months following a third vaccine dose in all study participants (appendix p 10), concurrent with previous data.[3] However, concentrations of nasal M-IgA in participants with previous SARS-CoV-2 infection, but without omicron breakthrough infection, remained above the amount associated to 65% protection[2] over the 8-month study period (figure C). This finding suggests a long-lasting mucosal immunity evoked by SARS-CoV-2 infection.

We next followed systemic and mucosal immune responses in participants that had a BA.1 or BA.2 breakthrough infection during the screening study. 7 months following breakthrough infection, S-IgG concentrations waned to be lower than at baseline (appendix p 10). As previously shown,[4] serological responses were lower among participants with a history of SARS-CoV-2 infection before breakthrough infection compared with those without and the difference remained over the 7-months follow-up (appendix p 10). Whether these findings reflect immune imprinting after previous infection[5] or a hampered systemic viral replication due to stronger and more rapid mucosal immune responses[2] needs further investigation. Interestingly, although nasal M-IgA concentrations waned, they remained above the protective threshold[2] in 94% of participants with previous SARS-CoV-2 WT or delta infection and in 58% of previously SARS-CoV-2-naive participants (figure B). In line with this, and in agreement with recent population-based data,[6,7] BA.1 and BA.2 infections were strongly protective against subsequent BA.5 infection in this cohort, with a HR of 0·13 (95% CI 0·04–0·44; figure D).

To assess whether M-IgA in nasal samples originated in the mucosa, we correlated M-IgA to mucosal spike-specific secretory IgA in nasal samples, and M-IgA to spike-specific IgA in serum. Concentrations of M-IgA correlated stronger to mucosal