Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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.

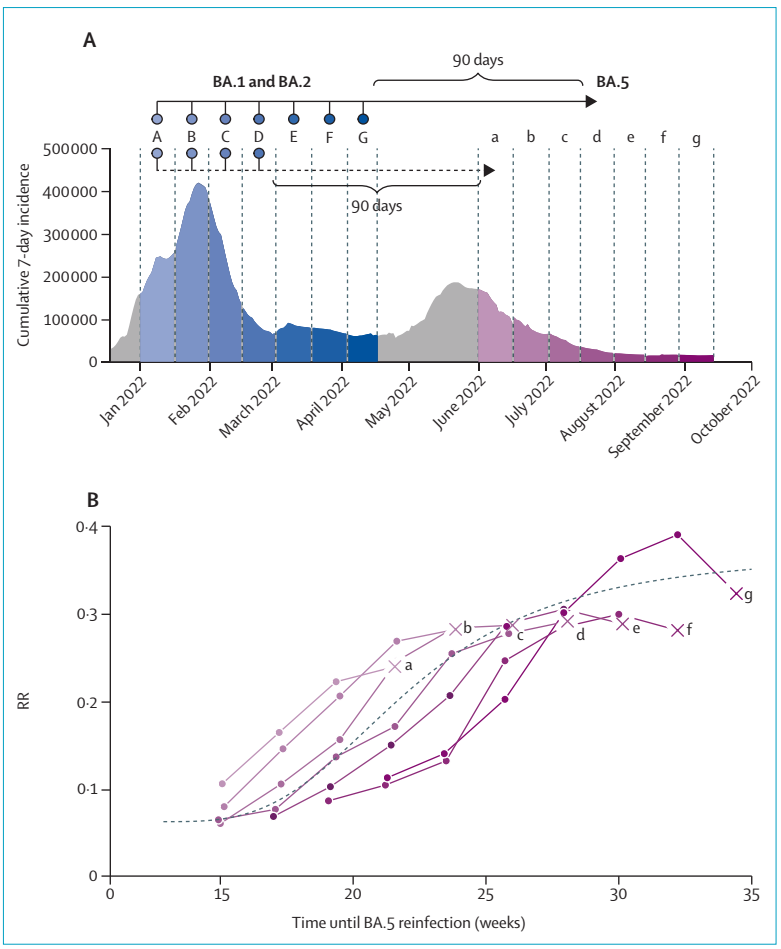

Figure: **Stability of hybrid immunity protection against BA.5 infection following infection with BA.1 or BA.2 subvariants**

(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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1 Malato J, Ribeiro RM, Leite PP, et al. Risk of BA.5 Infection among persons exposed to previous SARS-CoV-2 Variants. *N Engl J Med* 2022; **387:** 953–54.
2 Altarawneh HN, Chemaitelly H, Ayoub HH, et al. Protective effect of previous SARS-CoV-2 infection against omicron BA.4 and BA.5 subvariants. *N Engl J Med* 2022; **387:** 1620–22.
3 Hansen CH, Friis NU, Bager P, et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a nation-wide population-based study in Denmark. *Lancet Infect Dis* 2022; published online Oct 18. https://doi.org/10.1016/S1473-3099(22)00595-3.
4 Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med* 2021; **385:** e83.
5 Goldberg Y, Mandel M, Bar-On YM, et al. Protection and waning of natural and hybrid immunity to SARS-CoV-2. *N Engl J Med* 2022; **386:** 2201–12.
6 Ayoub HH, Tomy M, Chemaitelly H, et al. Estimating protection afforded by prior infection in preventing reinfection: applying the test-negative study design. *Epidemiology* 2022; published online Jan 3. https://doi.org/10.1101/2022.01.02.22268622 (preprint).
7 Chemaitelly H, Tang P, Coyle P, et al. Protection against reinfection with SARS-CoV-2 omicron BA.2.75* sublineage. *Epidemiology* 2022; published online Oct 30. https://doi.org/10.1101/2022.10.29.22281606 (preprint).