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including through cell-mediated immunity. Even full-dose repeat boosted regimens have not provided prolonged protection.⁸ Follow-up of this cohort to report relative incidence of clinical outcomes, although underpowered, will be useful. Specific examination of potentially immune senescent older adults, or of children would also be useful, and of course the findings will need replication in the omicron era. Second-generation vaccines are in development that aim to broaden protection in variant-independent ways, or to target mucosal immunity and hopefully reduce transmission (although the methodological challenges are far from trivial), and that provide sustained defence against severe disease and prolonged protection from infection. These vaccines will also need to be subjected to pragmatic trials in immunologically experienced populations. These are precisely the kinds of trials we need, cross-platform, pragmatic, and policy minded. The foresight of the Indonesian Ministry of Health who sponsored the trial is to be applauded.

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*Naor Bar-Zeev, Latif Ndeketa

nbarzee1@jhu.edu

International Vaccine Access Center, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, MD, USA (NB-Z); Malaria Epidemiology Research Group, Malawi Liverpool Wellcome Research Programme, Blantyre, Malawi (LN); Department of Clinical Infection, Microbiology & Immunology, Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool, UK (LN); Department of Public Health, School of Global and Public Health, Kamuzu University of Health Sciences, Blantyre, Malawi (LN)

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The benefit of vaccination after previous SARS-CoV-2 infection in the omicron era

Understanding the durability of the protection conferred by SARS-CoV-2 infection and vaccination is of utmost importance to guide COVID-19 mitigation policies worldwide. In November, 2021, before the emergence of the omicron (B.1.1.529) variant, an estimated 3.8 billion people (44% of the global population) had been infected by SARS-CoV-2.¹ This number is likely to have exponentially increased with the spread of the omicron variant, the most transmissible SARS-CoV-2 variant to date, suggesting that most of the global population has now already experienced SARS-CoV-2 infection at least once. As with previous infections, vaccines induce a memory response and protection against COVID-19, and the combination of SARS-CoV-2 infection and vaccination (hybrid immunity) offers the highest rate of protection.² However, the durability of this protection

against reinfection and severe disease remains undefined.

In *The Lancet Infectious Diseases*, Niklas Bobrovitz and colleagues³ present the results of a well-conducted systematic review and meta-analysis investigating the long-term benefit of SARS-CoV-2 vaccines in individuals who have developed hybrid immunity. The authors observed ephemeral protection against reinfection after booster vaccination (46.5% [36.0-57.3] at 6 months) or previous infection (24.7% [95% CI 16.4-35.5] at 12 months) but sustained high levels of protection against hospital admission or severe disease 6-12 months after the last exposure to SARS-CoV-2 antigens (97.4% [95% CI 91.4-99.2] with primary series vaccination at 12 months and 95.3% [81.9-98.9] with the first booster vaccination at 6 months). The magnitude and durability of protection



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See [Articles](#) page 556

was particularly high for those with hybrid immunity compared to those with previous infection alone, reinforcing the importance of vaccination despite previous infection in protecting against severe disease due to the omicron variant. There were two important findings about the primary series versus the booster dose in cases of previous infection: the primary series offered a high rate of protection (>90%) against severe disease, without imparting additional protection after booster vaccination; and both the primary series and booster vaccination offered short-term protection against reinfection. These findings align with the preserved cellular immune response despite the decrease in the humoral response to omicron subvariants.^{4,5} Nonetheless, these findings should be interpreted with caution since the conclusions cannot be extrapolated to specific groups at increased risk of developing severe disease, such as older and immunosuppressed people, who were not analysed in this study.

Despite this limitation, these findings have important implications for public health policies. Reducing infection has been the focus of first-generation vaccines against SARS-CoV-2 and has been investigated from the first clinical trials to most effectiveness studies. After the first 2 years of massive vaccination campaigns worldwide and almost 1 year of omicron subvariants causing high rates of infection worldwide, Bobrovitz and colleagues³ clearly demonstrate that the focus of first-generation vaccines should be prevention of severe disease. For this purpose, a first-generation vaccine is still an excellent option when offered as a primary series in areas with a high rate of previous infection, or with boosters, if a low infection rate has been observed.

Several countries still face vaccine shortages, and the benefit of offering multiple booster doses should be discussed in light of the findings of the present study.³ Even though nearly 70% of the world's population has received at least one SARS-CoV-2 vaccine dose, the distribution of vaccine coverage remains unequal. North America has vaccinated approximately 76% of its population with one dose, while Africa has only

vaccinated 32%.⁶ High-income countries administered almost five times more doses than low-income countries for the primary series and more than 20 times more booster doses.⁶ Coverage can be improved even in countries with high availability of vaccines. For example, in the USA only 69% of the population has completed the primary series vaccination.⁶ This inequality of distribution between low-income and high-income countries and the relatively high refusal to receive vaccines in high-income countries still need to be addressed to achieve higher protection against hospital admission and death due to COVID-19. These strategies could include more equitable distribution of vaccines within countries and improved communication about the protection offered by hybrid immunity.

We are currently facing a new wave of omicron subvariants. While waiting for data about the effectiveness of bivalent and other next-generation vaccines, the gold standards against COVID-19 remain both non-pharmacological strategies to prevent SARS-CoV-2 infection and vaccination to avoid severe disease.

VSB and MB-N are employees of Fiocruz, a federal public institution that manufactures the ChAdOx1 (Oxford-AstraZeneca) vaccine in Brazil, through a full technology transfer agreement with AstraZeneca. Fiocruz allocates all its manufactured products to the Ministry of Health in Brazil for public health use. TC-S declares no competing interests.

*Viviane S Boaventura, Thiago Cerqueira-Silva, Manoel Barral-Netto
viviane.boaventura@fiocruz.br

LIB and LEITV Laboratories, Instituto Gonçalo Moniz, Fiocruz, Salvador, Bahia, Brazil; Universidade Federal da Bahia, Salvador, Bahia, Brazil

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