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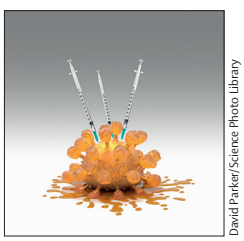
The elusive goal of COVID-19 vaccine immunity



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The immune evasiveness of SARS-CoV-2 omicron (B.1.1.529) subvariants resulted in large, global waves of infection and raised concerns about vaccine effectiveness against COVID-19-related hospitalisation and death. In *The Lancet Respiratory Medicine*, Sara Y Tartof and colleagues[1] assessed the effectiveness and duration of protection offered by two doses and three doses of BNT162b2 (Pfizer–BioNTech) against hospital and emergency department admission following infection with the omicron BA.1 or BA.2 subvariants.[1] Their study is timely, considering discussion about the effectiveness of the current generation of COVID-19 vaccines against infection and disease in the omicron era.

A key strength of Tartof and colleagues' study is that it was based on a large database containing the health records of more than 4·7 million patients from 15 hospitals in southern California, USA. Data were retrieved from an integrated electronic platform with nearly complete information on comorbidities, COVID-19 PCR testing, and COVID-19 vaccination. The authors analysed 16 994 adult hospital admissions for acute respiratory infection that occurred between Dec 27, 2021, and June 4, 2022, and involved RT-PCR COVID-19 testing. Using a test-negative design, Tartof and colleagues compared the vaccination status of 7435 admissions due to BA.1 infection and 1056 admissions due to BA.2 infection with that of 8503 SARS-CoV-2-negative admissions. The median age of the study population was 55 years (IQR 36–73), 9823 (57·8%) of 16 993 admissions were women and 7170 (42·2%) were men, and more than half of admissions were people with a Charlson Comorbidity Index of 1 or more.

Tartof and colleagues found that two-dose vaccination offered only partial, waning protection against hospital admission. Vaccine effectiveness against hospitalisation was 54% (95% CI 38 to 65) for BA.1 and 56% (–2 to 81) for BA.2 at less than 6 months after the second dose. Protection against BA.1-related hospitalisation waned to 32% (16 to 45) at 6 months or more after the second dose, but waning was not evident for BA.2. By contrast, three-dose vaccination induced high protection against hospital admission, with vaccine effectiveness equalling 80% (95% CI 74 to 84) for BA.1 and 74% (47 to 87) for BA.2 at less than 3 months after the third dose. Booster protection was relatively durable—vaccine effectiveness was 76% (69 to 82) against BA.1 and 70% (53 to 81) against BA.2 at 3 months or more after the third dose. Vaccine effectiveness against emergency department admission that did not require hospitalisation was lower than against hospitalisation and seemed to wane substantially for BA.2 compared with BA.1.

Suboptimal vaccine protection against severe omicron infections is of concern, but these estimates should probably be interpreted as representing minimal estimates of effectiveness. The authors defined COVID-19 severity using acute respiratory infection-related admissions with positive SARS-CoV-2 PCR test results. The massive BA.1 and BA.2 pandemic waves were associated with mild disease,[2] with many hospital or emergency department admissions related to acute respiratory infection being with COVID-19 rather than because of COVID-19. Hospitalisations with incidental COVID-19 have become common in the omicron era and can lead to serious underestimates of vaccine protection against severe COVID-19.[3,4] In Qatar[4] and the UK,[3] specific definitions of COVID-19 severity (ie, oxygen use, mechanical ventilation, or admission to intensive care), as opposed to just hospitalisation, resulted in higher estimates of effectiveness and durability than those reported by Tartof and colleagues. Studies, including that of Tartof and colleagues, have also shown a gradient in vaccine effectiveness against severe COVID-19, with higher and more durable protection against more versus less severe COVID-19.[1,3,4] This protection affirms the value of vaccination, despite the immune evasion of omicron subvariants. To further explore this severity gradient and produce more representative estimates, studies should use, whenever possible, specific definitions of severe COVID-19, such as WHO's definitions for severe and critical COVID-19.[5]

In the context of other evidence on COVID-19 vaccine effectiveness, the findings of Tartof and colleagues have important implications for the future shape of the pandemic. Strong and durable protection from the current generation of vaccines increasingly appears to be an elusive goal. Vaccine-derived immunity against infection with omicron subvariants wanes rapidly with time.[6] Viral evolution, leading to more immune evasion, will undermine vaccine protection and accelerate its

waning.[6] The same also applies to natural immunity induced by infection, although waning in this context appears slower than that of vaccine immunity.[7] These waning patterns suggest that the virus will probably cause repeated temporal and geographical waves. Immune imprinting might yet be another complication for vaccine and natural immunity.[8,9] This pandemic is not likely to end without considerable investment in developing a new generation of vaccines that offer effective, long-term protection against a broad spectrum of potential variants.

While we await such vaccines, booster vaccination, as shown in the study by Tartof and colleagues and elsewhere,[1,10] remains the best intervention to reduce the severity of this pandemic. Boosters might need to be given at shorter intervals, at least to those who are the most clinically vulnerable to severe COVID-19. Boosters restore vaccine protection to a high level for at least several months, even against the immune-evasive omicron subvariants.[1,6,10] The new omicron-specific boosters should also offer higher and more durable protection against currently circulating variants than will boosters based on the original virus.

We declare no competing interests.

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