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Severe breakthrough COVID-19 cases in the SARS-CoV-2 delta (B.1.617.2) variant era



Despite compelling evidence that SARS-CoV-2 vaccines are highly effective in preventing COVID-19 infections, breakthrough cases have been emerging at an increasing rate.¹ A retrospective cohort study by Tartof and colleagues² found that vaccine effectiveness against COVID-19 decreased over time; however, its effectiveness against hospitalisation associated with COVID-19 remained robust, with no apparent reduction in vaccine effectiveness between 1 month (87%) and 5 months (88%) after vaccination with the BNT162b2 vaccine. Although most breakthrough COVID-19 cases are mild or moderate in severity,³ severe cases and deaths have been reported. In this Comment, we describe the shift in the landscape of severe COVID-19 requiring hospitalisation in a health system with high regional vaccination rates, whereby 90.9% of individuals aged 65–74 years and 85.6% of those aged 75 years and older are fully vaccinated as of Oct 17, 2021.⁴

We conducted a systematic review of patients with SARS-CoV-2 infection confirmed by PCR test, who were hospitalised at the Yale New Haven Health System (New Haven, CT, USA) between Aug 4 and Oct 12, 2021, during which time the SARS-CoV-2 delta (B.1.617.2) variant accounted for over 95% of COVID-19 cases in the region.⁵ Among 371 patients admitted with a positive SARS-CoV-2 PCR test, 129 (35%) were fully vaccinated at the time of hospitalisation. 222 (60%) patients met the criteria for being severely or critically ill with COVID-19 during their hospitalisation, among whom 82 (37%) were fully vaccinated. Overall, a much larger proportion of patients hospitalised with a positive SARS-CoV-2 test had severe or critical breakthrough COVID-19 during this period (82 [22%] of 371 patients) than was reported in the same health-care system between March 23 to July 1, 2021 (14 [1%] of 969 patients), when the delta variant accounted for less than 20% of COVID-19 cases in the region.^{5,6} Additionally, evaluation of time to COVID-19 from the date of final vaccine dose showed a marked rise in the frequency of severe breakthrough cases with an increasing number of days since completed vaccination (appendix p 1).

Among the patients with severe or critical COVID-19, the age distribution of patients with breakthrough

infections was skewed towards older age groups (mean age 71.5 years) compared with those who were unvaccinated (55.2 years; appendix p 2). Furthermore, underlying comorbidities—including cardiovascular and lung disease, type 2 diabetes, history of malignancy, and baseline use of immunosuppressive medications—were more prevalent in patients with breakthrough infections than in those who were unvaccinated (appendix p 3). Despite these differences, which could potentially portend worse clinical outcomes for the patients with severe breakthrough COVID-19, we observed a shorter mean duration of hospitalisation (10.8 days vs 13.1 days), lower risk of advanced oxygen or ventilatory support (26 [32%] of 82 vs 72 [51%] of 140 patients), and lower in-hospital mortality (eight [10%] vs 17 [12%] patients) among patients with breakthrough COVID-19 than among those who were unvaccinated.

The shifting landscape of breakthrough COVID-19 cases is likely to involve multiple factors, including demonstrated waning of antibody response after full vaccination^{7,8} and emergence of variant strains of SARS-CoV-2. The differences in the incidence of breakthrough cases based on vaccine type is of interest and will need further investigation. The accelerating trend of breakthrough COVID-19 cases with time since vaccination highlight the important need for booster vaccinations, especially given emerging data supporting their efficacy,⁹ in particular for older populations and for individuals with underlying comorbidities who face an increased risk of developing severe breakthrough infections.

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See Online for appendix

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