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## Immunocompromise and durability of BNT162b2 vaccine against severe outcomes due to omicron and delta variants

Our previous data showed early signs of waning effectiveness of the BNT162b2 (Pfizer–BioNTech) mRNA COVID-19 vaccine against omicron (B.1.1.529) variant-related hospital and emergency department admission 3 months or longer after receipt of a third dose in US adults aged 18 years and older.<sup>1</sup> The omicron-specific data in that report were from Dec 1, 2021, through to Feb 6, 2022—a period that included the first half of the omicron wave.

Given that the US Food and Drug Administration initially authorised a third dose of the vaccine for individuals aged 65 years and older and individuals at high risk of severe COVID-19 on Sept 22, 2021, initial study estimates of vaccine effectiveness at 3 months or longer after a third dose were enriched for high-risk

populations, including patients who are immunocompromised and have suppressed response to vaccination due to their conditions.

To provide additional context, we have updated our analysis with data up to March 18, 2022, and stratified our findings by immunocompromised status. Briefly, immunocompromised status, defined using previously published criteria,<sup>2</sup> included diagnosis of leukaemia, lymphoma, congenital immunodeficiencies, asplenia or hyposplenia, HIV/AIDS, history of haematopoietic stem cell or solid organ transplantation, or receipt of immunosuppressive medication. Our updated findings primarily show two things. First, that the waning effectiveness against omicron-related hospitalisation noted at 3 months or longer after a third dose of vaccine during the initial study period (data cutoff of Feb 6, 2022) was not as pronounced after excluding individuals who were immunocompromised (original vaccine effectiveness  $\geq 3$  months after a third dose of 55% [95% CI 28–71] against omicron-related hospitalisation vs 74% [52–86] after excluding individuals who were immunocompromised). Second,

extending the analysis period up to March 18, 2022 (after more of the general population became eligible for booster doses on Nov 29, 2021) further attenuated evidence of waning vaccine effectiveness after a third dose. Specifically, after extending the analysis period, waning of effectiveness against omicron-related outcomes was no longer apparent, particularly in the immunocompetent population. Among immunocompetent individuals, effectiveness at 3 months or longer after a third dose of BNT162b2 against omicron-related hospital admission was 86% (95% CI 81–90) and against emergency department admission was 76 (70–81) from Dec 1, 2021, to March 18, 2022 (table).

High-risk patients, particularly those who are immunocompromised, have weaker initial immune responses to vaccination and have more pronounced waning of vaccine-induced immunity against severe outcomes than do other patients.<sup>2</sup> In initial analyses (data cutoff of Feb 6, 2022), patients who were immunocompromised comprised 48% of the study population who were analysed at 3 months or longer



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	Initial analysis period (Dec 1, 2021, to Feb 6, 2022)			Updated analysis period (Dec 1, 2021, to March 18, 2022)		
	Overall cohort (n=32 445)	Immunocompetent patients (n=27 080)	Immunocompromised patients (n=16 49)	Overall cohort (n=47 794)	Immunocompetent patients (n=39 852)	Immunocompromised patients (n=2457)
Hospital admission	15 150	12 488	912	23 751	19 557	1440
<3 months since third dose	85 (80 to 89)	87 (82 to 91)	49 (–15 to 77)	83 (79 to 86)	86 (83 to 89)	55 (17 to 75)
$\geq 3$ months since third dose	55 (28 to 71)	74 (52 to 86)	–28 (–207 to 46)	79 (73 to 84)	86 (81 to 90)	25 (–40 to 60)
Emergency department admission	17 295	14 592	737	24 043	20 295	1017
<3 months since third dose	77 (72 to 81)	77 (72 to 81)	54 (–12 to 81)	76 (72 to 79)	78 (74 to 81)	52 (1 to 76)
$\geq 3$ months since third dose	53 (36 to 66)	56 (37 to 69)	12 (–130 to 66)	74 (67 to 79)	76 (70 to 81)	47 (–11 to 75)

Data are n or adjusted vaccine effectiveness, with 95% CIs in parentheses. Number of immunocompetent and immunocompromised patients might not add up to total because some patients had unknown status. Estimates are adjusted for age (45–64 and  $\geq 65$  years vs 18–44 years), sex (male vs female), race or ethnicity (Black, Hispanic, Asian or Pacific Islander and other or unknown vs White), body-mass index (<18.5, 25–29.9, 30–34.9,  $\geq 35$  kg/m<sup>2</sup>, and unknown vs 18.5–24.9 kg/m<sup>2</sup>), Charlson comorbidity index (1, 2–3, and  $\geq 4$  vs 0), previous SARS-CoV-2 infection (yes vs no), previous influenza vaccination (yes vs no), and previous pneumococcal vaccination (yes vs no).

**Table:** Adjusted vaccine effectiveness of three doses of mRNA COVID-19 vaccine BNT162b2 (Pfizer–BioNTech) against hospital and emergency department admission for omicron (B.1.1.529) infection among individuals diagnosed with acute respiratory infection, by time since vaccination and immunocompromised status

after their third dose compared with only 23% in the updated analysis (data cutoff of Mar 18, 2022). Thus, patients who were immunocompromised probably drove much of the observed waning seen in our initial report. Other explanations are possible. For example, waning of vaccine effectiveness might have been more likely during the initial study period, when rates of omicron infection and transmission were highest. Furthermore, the background rates of the BA.2 sublineage of the omicron variant were higher (40%) during our updated analysis period than during our initial study period (<5%), and the vaccine might perform better against the BA.2 sublineage. However, the paucity of data available thus far suggest that effectiveness of the BNT162b2 vaccine against BA.1 and BA.2 are similar.<sup>3,4</sup> Differences in severity of illness among patients admitted to the hospital or emergency department over time, possibly associated with increasing levels of immunity due to natural infection, might have contributed to the observed differences in effectiveness. Additionally, at-home testing became more readily available during our updated study period and might have led to a decrease in the number of patients with mild illness presenting to the emergency department for testing.

However, we saw no notable changes in hospital admission criteria at the study centre during the study period (data not shown).

In summary, our updated findings suggest that waning effectiveness against hospital and emergency department admission after receiving a third dose of BNT162b2 vaccine is likely nuanced; that it is likely occurring for some high-risk individuals and in some settings (as was initially identified), but not in others. Despite emerging evidence from Israel showing that a fourth dose improves protection against severe outcomes, including hospitalisation and death, in the general older adult population,<sup>5-7</sup> more data are needed to fully understand long-term protection against omicron after a third dose and to inform recommendations for fourth doses (ie, second boosters) in those who are not high risk.

The declaration of interests remains the same as in the original Article.<sup>1</sup>

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