# Long-term booster effectiveness and immune imprinting

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## BACKGROUND

Long-term effectiveness of coronavirus disease 2019 (COVID-19) mRNA boosters against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe COVID-19 is inadequately understood, including in populations with different prior infection histories and clinical vulnerability profiles.

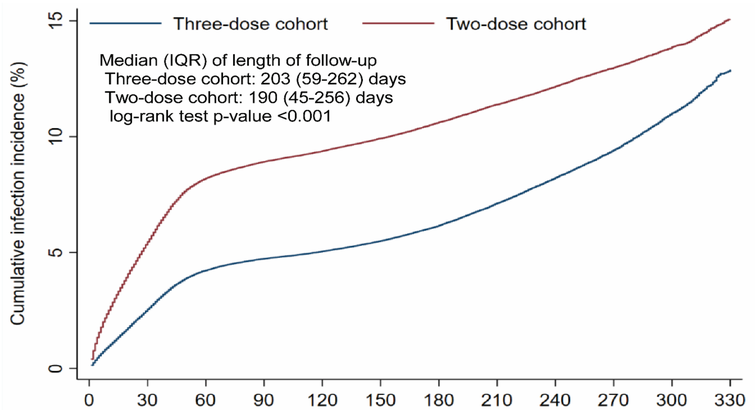
**Boosters reduced infection and severe COVID-19, particularly among those clinically vulnerable to severe COVID-19.**

**Protection against infection waned after the booster, and eventually suggested a negative imprinting effect relative to primary series.**

## METHODS

- A national, matched, retrospective, target trial cohort study was conducted in Qatar during January 5, 2021-October 12, 2022.
- We estimated effectiveness of a third mRNA (booster) dose, relative to two-dose primary series, against omicron infection and against severe COVID-19.
- Associations were estimated using inverse-probability-weighted Cox proportional-hazards regression models.

**Figure 1. Cumulative incidence of SARS-CoV-2 infection in the matched three-dose and two-dose vaccination cohorts.**




| Time (days) | 0 | 30 | 60 | 90 | 120 | 150 | 180 | 210 | 240 | 270 | 300 | 330 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No. at risk** | | | | | | | | | | | | |
| Three-dose cohort | 304,091 | 254,314 | 227,650 | 212,711 | 199,880 | 182,862 | 168,544 | 146,233 | 108,728 | 64,463 | 22,278 | 2,377 |
| Two-dose cohort | 304,091 | 245,772 | 216,168 | 201,153 | 188,586 | 171,931 | 158,144 | 136,657 | 100,213 | 57,231 | 19,486 | 2,014 |

IQR denotes interquartile range.

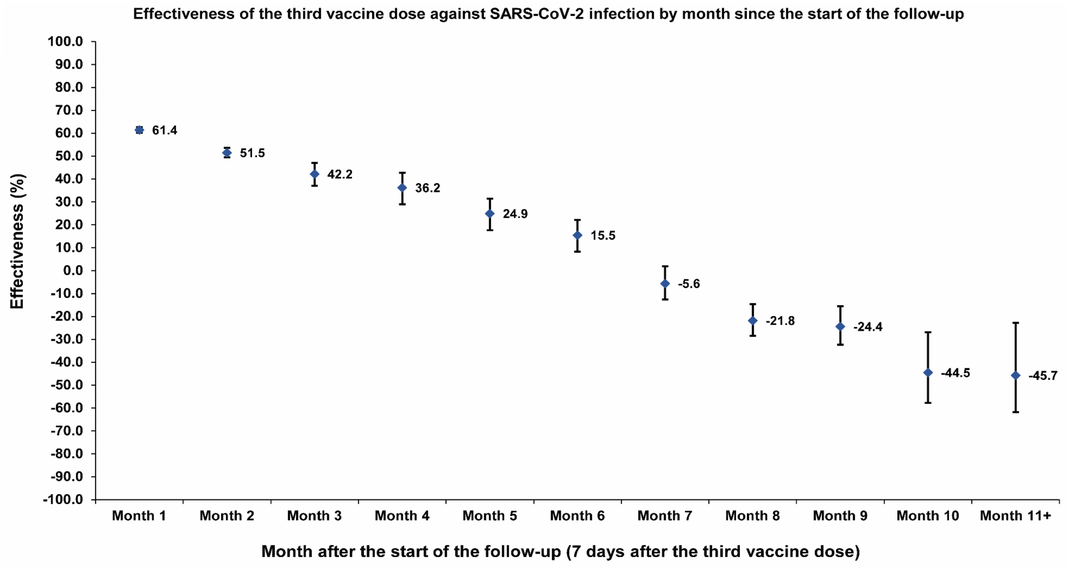
## RESULTS

- There were 20,528 incident infections in the three-dose cohort and 30,771 infections in the two-dose cohort (Figure 1).
- Table 1 shows booster effectiveness estimates.
- Effectiveness against infection was 61.4% (95% CI: 60.2-62.6%) in the 1st month after the booster but waned thereafter.
- From the 7th month, coincident with BA.4/BA.5 and BA.2.75* incidence, effectiveness was progressively negative.
- Patterns of protection were similar irrespective of prior infection status, clinical vulnerability, or type of mRNA vaccine.

**Table 1. Effectiveness of booster relative to primary-series against SARS-CoV-2 infection and against severe, critical, or fatal COVID-19 in the matched cohorts.**

| Analysis type | Effectiveness against SARS-CoV-2 infection in % (95% CI)† | Effectiveness against severe COVID-19 in % (95% CI)† |
|---|---|---|
| **Overall booster effectiveness** | 26.2 (23.6 to 28.6) | 75.1 (40.2 to 89.6) |
| **Booster effectiveness by prior infection status** | | |
| No prior infection | 26.3 (23.6 to 28.8) | 74.4 (38.3 to 89.4) |
| Prior pre-omicron infection | 24.9 (17.4 to 31.6) | --‡ |
| Prior omicron infection | 21.9 (-8.7 to 44.3) | --‡ |
| Prior pre-omicron & omicron infections | 62.8 (-52.3 to 93.4) | --‡ |
| **Booster effectiveness by clinical vulnerability to severe COVID-19** | | |
| Persons less clinically vulnerable to severe COVID-19 | 23.4 (21.1 to 25.7) | 57.9 (-55.6 to 92.1) |
| Persons more clinically vulnerable to severe COVID-19 | 34.2 (27.0 to 40.6) | 76.6 (34.5 to 91.7) |
| **Booster effectiveness by vaccine type** | | |
| Vaccinated with BNT162b2 | 30.4 (27.5 to 33.3) | 74.0 (37.2 to 89.2) |
| Vaccinated with mRNA-1273 | 9.1 (5.0 to 13.0) | --‡ |

**Figure 2. Booster effectiveness relative to primary series against SARS-CoV-2 infection by month since the start of the follow-up.**




## CONCLUSIONS

- Protection against omicron infection waned after the booster, and eventually suggested a possibility for negative immune imprinting.
- However, boosters substantially reduced severe COVID-19, particularly among those clinically vulnerable, affirming the public health value of booster vaccination.
- There was no evidence for negative imprinting against severe COVID-19.

### Funding

The authors are grateful for support from the Biomedical Research Program and the Biostatistics, Epidemiology, and Biomathematics Research Core at Weill Cornell Medicine–Qatar; the Qatar Ministry of Public Health; Hamad Medical Corporation; and Sidra Medicine. The authors are also grateful for the Qatar Genome Programme and Qatar University Biomedical Research Center for institutional support for the reagents needed for the viral genome sequencing.