

## Update from the Field: COVID-19 Booster Vaccination and the Prevention of Long COVID

### *A Series on Long COVID*

#### Introduction

COVID-19 vaccination has been shown to be safe and effective in preventing severe illness from SARS-CoV-2 infection, and COVID-19 booster vaccination remains an important tool for preventing severe illness. This update focuses on the efficacy of COVID-19 booster vaccination in preventing long COVID.

A literature search was conducted in January 2025 to identify studies on COVID-19 vaccination and long COVID outcomes. The literature search was updated in August 2025 using OpenEvidence, an AI-powered medical search platform, to identify any additional studies and narrow the focus to COVID-19 booster vaccination and the prevention of long COVID. Twelve published observational studies were identified and included in this review. For this review, booster vaccination was defined as receiving at least one dose of vaccine after completing the primary series. Some of the studies included in this review were conducted before the introduction of the bivalent vaccine formulation. Vaccine manufacturers and formulations differ by geographic location, availability, and the timing of the study.

#### Notable Findings

**Consistent Evidence of Benefit:** 10 of the 12 observational studies included in this review found a lower risk of long COVID among individuals who received a COVID-19 booster vaccination compared to the unboosted or with only the primary series.

**Common Limitations:** Most data were collected before bivalent vaccines became available, and booster formulations varied. All studies were observational, limiting causal inference.

**Overall, these findings support the continued use of booster vaccination as a strategy to reduce the burden of long COVID.**

#### Summary of literature

##### Prospective cohort studies

- Four studies found a lower risk of long COVID symptoms among participants who received booster vaccination compared with those who received only the primary series or were unvaccinated.
- One study found no significant difference in overall long COVID symptoms between boosted and unboosted cases (although it did find lower rates of mental health symptoms among boosted cases).
- Limitations:
  - Observational cohort study design cannot definitively establish causation.
  - Self-reported long COVID symptoms may be vulnerable to recall bias or subjective differences in reporting.

- Reinfections were excluded, limiting the ability to understand the impact multiple infections may have on results.
- Potential for misclassification: if individuals didn't seek testing, they would not be identified as COVID-19 cases.
- Participation bias may impact results if individuals who chose to participate differed from those who did not.

Study	Population	Outcomes
<a href="#"><u>Caspersen 2025</u></a>	<i>Norway, general population (11-80 years)</i>  January-February 2022 26,000 infected cases 31,000 uninfected controls Vaccination status documented in the immunization registry	Self-report at least one long COVID symptom at least 3 months after infection: <ul style="list-style-type: none"> <li>• Recent booster vaccination before infection substantially reduced neurocognitive and cardiorespiratory post-COVID symptoms, excess risk halved compared to cases with only two doses of vaccine</li> </ul>
<a href="#"><u>Di Fusco 2023 &amp; Di Fusco 2024</u></a>	<i>United States, adult general population</i>  January-April 2022 328 cases (260 with complete follow-up) Vaccination status self-reported	Self-report at least one long COVID symptom 4 weeks after infection: <ul style="list-style-type: none"> <li>• Boosted cases had significantly fewer long COVID symptoms compared to primed and unvaccinated cases</li> <li>• Symptoms improved over time for boosted cases and not for primed or unvaccinated</li> </ul>
<a href="#"><u>Rover 2024</u></a>	<i>Brazil, adult general population</i>  January 2022-June 2023 1,067 cases Vaccination status documented in medical record or self-reported	Self-report persistent symptoms 3 months after infection: <ul style="list-style-type: none"> <li>• Boosted cases had a lower occurrence of mental health symptoms than primed cases</li> <li>• No significant difference between primed and boosted cases regarding the occurrence of overall persistent symptoms</li> </ul>
<a href="#"><u>Spiliopoulos 2024</u></a>	<i>Denmark, general population (≥15 years)</i>  July 2021-January 2022 13,274 Omicron period cases 7,981 Delta period cases 14,854 uninfected controls Vaccination status documented in the immunization registry	Self-report long COVID symptoms 4 months after infection: <ul style="list-style-type: none"> <li>• Boosted Omicron cases had a significantly lower risk of developing 11 of 24 symptoms compared to primed cases. Risk was not significantly higher for any symptom.</li> </ul>

# Retrospective and population-based cohort studies

- Two studies found a lower risk of new diagnoses of conditions associated with long COVID among cases who received booster vaccination.
- One study found no association between vaccination status and the documentation of a long COVID diagnostic code in the medical record.
- Limitations:
  - Observational cohort study design cannot definitively establish causation.
  - Long COVID defined by diagnoses documented in medical record (Swift 2024 required a diagnostic code for long COVID specifically), potentially introducing bias due to healthcare access, healthcare-seeking behaviors, and severity of symptoms.
  - Potential for misclassification: if individuals didn't seek testing, they would not be identified as COVID-19 cases.

Study	Population	Outcomes
<a href="#"><u>Swift 2024</u></a>	<i>United States</i>  February 2021-December 2022  41,652 patients (≥5 years) with medically attended post-acute sequelae of COVID-19 (PASC)  Vaccination status documented in medical record and/or immunization registry	PASC diagnostic code documented in a clinical encounter 30 days – 6 months after infection: <ul style="list-style-type: none"><li>• No association between vaccination status at the time of infection and documentation of PASC in medical record</li></ul>
<a href="#"><u>Huh 2024</u></a>	<i>South Korea, adult general population</i>  January-March 2022  394,773 unvaccinated cases  2,604,042 primed cases  5,001,039 boosted cases  Vaccination status documented in medical record	New diagnosis of 26 conditions associated with long COVID within 30-120 days after infection: <ul style="list-style-type: none"><li>• Boosted cases had a lower risk of cardiovascular and thromboembolic events after infection</li><li>• Slight increased risk of hospitalization due to diabetes among boosted cases</li></ul>
<a href="#"><u>Wee 2025</u></a>	<i>Singapore, adult general population</i>  January 2022-December 2023  1,080,348 primed cases  9,824 boosted cases  Vaccination status documented in medical record	New diagnosis of condition associated with long COVID within 31-365 days after infection: <ul style="list-style-type: none"><li>• Bivalent boosted cases had a lower risk of any post-acute sequelae, any neurological sequelae, episodic neurological disorders, and movement disorders compared with monovalent boosted cases</li></ul>

# Cross-sectional surveys

- All four surveys found a lower risk of long COVID with booster vaccination.
- Limitations:
  - Observational cross-sectional study design means that causality cannot be assessed.
  - Self-reported long COVID symptoms and vaccination status may be vulnerable to recall bias or subjective differences in reporting.
  - Participation bias may affect results if participants differed from non-participants.

Study	Population	Outcomes
<a href="#">Nguyen 2024</a>	<i>United States, general adult population</i> December 2022-February 2023 214,768 respondents Vaccination status self-reported	Self-report of long COVID symptoms lasting 3 months or longer: <ul style="list-style-type: none"><li>• Boosted respondents were less likely to have long COVID</li></ul>
<a href="#">Zheng 2024</a>	<i>Hong Kong, general adult population</i> December 2021-April 2022 1,542 respondents Vaccination status self-reported	Self-report of 14 symptoms associated with long COVID at least 2 months after infection: <ul style="list-style-type: none"><li>• Boosted cases were less likely to report any long COVID symptoms compared to primed cases</li></ul>
<a href="#">Woldegiorgis 2024</a>	<i>Australia, general adult population</i> July-August 2022 11,697 respondents Vaccination status documented in the immunization registry	Self-report of new or ongoing symptoms 90 days after infection: <ul style="list-style-type: none"><li>• Cases with 4 or more vaccine doses (i.e., 2 or more booster doses) had a lower risk of long COVID</li></ul>
<a href="#">Romeiser 2024</a>	<i>United States, general adult population</i> January-December 2022 9,521 respondents Vaccination status self-reported	Self-report of any symptoms lasting 3 months or longer that were not present before COVID-19 infection: <ul style="list-style-type: none"><li>• Boosted cases had lower odds of reporting long COVID symptoms</li></ul>

# Literature Search Description

The literature search for articles was conducted using OpenEvidence (an AI-powered medical search platform) which identified 40 articles relevant to the question of “how COVID-19 booster vaccination influences acute COVID-19 outcomes and post-COVID-19 symptoms”. The types of studies included in the search included systematic reviews/meta-analyses, cohort studies, and case control. Articles were reviewed and narrowed down to a list of 14 articles that met the following inclusion criteria: included COVID-19 infections since Omicron

emergence (November 2021), addressed the impact of booster vaccination on long COVID outcomes, and were published between January 2022-June 2025. Furthermore, two systematic reviews and meta-analyses were excluded from the review because the studies those included didn't consistently meet this inclusion criteria.

## Acknowledgment:

Thank you to our Long COVID Guiding Council and MDH Infectious Disease Epidemiology, Prevention and Control colleagues for their expertise, feedback, and review of this update.

Document produced in November 2025. Updates to this document may be made as new significant evidence becomes available.

*This project is funded through the State of Minnesota.*