Effectiveness of the Monovalent XBB.1.5 COVID-19 vaccines
Living Evidence Synthesis #21
(Version 21.1: 16 February 2024)

Questions

What is the added protection (VE ≥7 days post vaccination and over time) conferred by any monovalent XBB.1.5-containing COVID-19 vaccines authorised in Canada against the following Omicron-related outcomes during XBB subvariant (and any future variant) predominance:

1. Symptomatic COVID-19 infections;
2. COVID-19-related emergency department (ED) visits;
3. COVID-19-related hospitalisations;
4. COVID-19-related intensive care unit (ICU) admissions;
5. COVID-19-related deaths;
6. Multisystem inflammatory syndrome in children (MIS-C); and
7. Post-COVID Conditions

compared with:

- Previous COVID-19 vaccines:
  - Previous mRNA COVID-19 bivalent boosters;
  - Previous original monovalent COVID-19 vaccines
- No COVID-19 vaccination; and
- Hybrid immunity.

This question is being explored in the following populations (where possible):

- General population;
- Healthcare workers;
- Older adults (≥65 years);
- Infants, children, and adolescents;
- Immunocompromised individuals; and
- Pregnant people and their newborns.

Box 1: Our approach

We retrieved candidate studies and updates to living evidence syntheses on vaccine effectiveness using the following mechanisms: 1) search on the National Institute of Health (NIH) iSearch COVID-19 portfolio, EMBASE and Medline; 2) systematic scanning of the Research Analysis (EXTRA) COVID-19 Titles from NACI / CCNI (PHAC/ASPC) and WHO weekly COVID-19 newsletter; and 3) exploration of citations of systematic reviews on this topic. We included studies and updates to living evidence syntheses identified up to seven days before the version release date. We did not include press releases unless a preprint was available. *A full list of included and excluded studies is provided in **Appendix 1 and 7**, respectively.*

Outcome measures: Symptomatic SARS-CoV-2 infections, COVID-19-related ED visits; hospitalisation due to COVID-19, ICU admission due to COVID-19, death due to COVID-19, MIS-C, and post-COVID conditions. Other outcomes (e.g., COVID-19 related outpatient visits)

Data extraction: We prioritised total population data over sub-groups. We extracted data from each study using a standard template with peer-review to confirm information (see ***Appendix 6***).

Critical appraisal: We assessed risk of bias in duplicate for individual outcomes using an adapted version of ROBINS-I (***Appendix 5***).

Summaries: Where data was insufficient to undertake meta-analyses, we provide an average (and range) of the available data or (point estimates and 95% CIs). Where there is enough data, we summarise the evidence by presenting meta-analysed pooled estimates with 95% CIs (see **Appendix 3** for details).

*A glossary of terms is provided in **Appendix 4**.*

This living systematic review was designed and executed by the Montreal Behavioural Medicine Centre, a joint Concordia University, Université du Québec à Montréal, and CIUSSS-NIM centre, and in collaboration with a network of evidence-support units supported by a secretariat housed at the McMaster health forum.

Visual representation of findings

1. The impact of any prior COVID-19 vaccination plus a monovalent XBB.1.5 COVID-19 vaccine vs. any prior COVID-19 vaccination against COVID-19-related ED visits is presented in Table 1.
2. The impact of any prior COVID-19 vaccination plus a monovalent XBB.1.5 COVID-19 vaccine vs. any prior COVID-19 vaccination against COVID-19 related hospitalisations is presented in Table 2.

Flow of included studies

Overall, 98 studies were title and abstract screened, 8 were full text appraised, with 3 initially included, 1 study was excluded (RoB; see **Appendix 1b)**, leaving 2 that were used to complete this summary. The reasons for excluding the 5 studies are reported in **Appendix 7b.** In addition, 4 records were identified through hand search, of which, 1 was included, the reason for excluding the 3 studies are reported in **Appendix 7b** as well. This leads to a total of 3 included studies in this summary.

High level summary for COVID-19 outcomes

Symptomatic COVID-19 infections

- There were no studies which reported data for this outcome.

COVID-19-related emergency department (ED) or urgent care (UC) visits

*XBB.1.5 vaccination **vs.** no XBB.1.5 vaccination*

- One study (Tartof et al. (2023), a test-negative case-control study from the United States) was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to visit the ED or UC for COVID-19 a median of 30 days after receiving the vaccine, compared with those who had not received any XBB.1.5 vaccine, with no difference across age groups (relative vaccine effectiveness [VE] ranged from 55-64% during an XBB sub lineages dominant period).

*XBB.1.5 vaccination **vs.** bivalent vaccine but no XBB.1.5 vaccination*

- One study, Tartof et al. (2023), was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to visit the ED or UC for COVID-19 a median of 30 days after receiving the vaccine, compared with those who had received an mRNA bivalent BA.4/BA.5 vaccine but no XBB.1.5 vaccine, with no difference across age groups (relative VE ranged from 57-60% during an XBB sub lineages dominant period).

*XBB.1.5 vaccination **vs.** ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind*

- One study, Tartof et al. (2023), was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to visit the ED or UC for COVID-19 a median of 30 days after receiving the vaccine, compared with those who had received at least three doses of the original wild-type vaccines but had not received the XBB.1.5 vaccine, with no difference across age groups (relative VE ranged from 55-66% during an XBB sub lineages dominant period).

*XBB.1.5 vaccination **vs.** ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind*

- One study, Tartof et al. (2023), was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to visit the ED or UC for COVID-19 a median of 30 days after receiving the vaccine, compared with those who had received at least two doses of the original wild-type vaccines but had not received the XBB.1.5 vaccine, with no difference across age groups (relative VE ranged from 54-65% during an XBB sub lineages dominant period).

*XBB.1.5 vaccination **vs.** unvaccinated*

- One study, Tartof et al. (2023), was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to visit the ED or UC for COVID-19 a median of 30 days after receiving the vaccine, compared with those who were unvaccinated, with no difference across age groups (absolute VE ranged from 60-67% during an XBB sub lineages dominant period).

COVID-19-related hospitalisations

*XBB.1.5 vaccination **vs.** no XBB.1.5 vaccination*

- One study (Tartof et al. (2023), a test-negative case-control study from the United States) was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to be hospitalised for COVID-19 a median of 30 days after receiving the vaccine, compared with those who had not received the XBB.1.5 vaccine, with no difference across age groups (relative VE ranged from 63-68% during an XBB sub lineages dominant period).

*XBB.1.5 vaccination **vs.** bivalent vaccine but no XBB.1.5 vaccination*

- Three studies were included and found that individuals who had received the XBB.1.5 COVID-19 vaccine were less likely to be hospitalised for COVID-19 compared with those who had not received the XBB.1.5 vaccine. One US study (Tartof et al. (2023)), found that at a median of 30 days post vaccination, relative VE of the Pfizer-BioNTech XBB.1.5 vaccine, compared with bivalent BA.4/BA.5 vaccination, ranged from 60-65% during an XBB sub lineages dominant period, and was not different across age groups. One UK population study (UK Health Security Agency (2024)) conducted among individuals aged ≥65 years, found consistent levels of protection between 14-63 days post Pfizer-BioNTech XBB.1.5 vaccination (50.9-55.4%). One population study from Denmark (Hansen et al. (2024)) of individuals aged ≥65 years found a high level of protection 7+ days post vaccination (76.1%).

*XBB.1.5 vaccination **vs.** ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind*

- One study from the US (Tartof et al. (2023)), was included and found individuals who had received the XBB.1.5 COVID-19 vaccine were less likely to be hospitalised for COVID-19 compared with those who had not received the XBB.1.5 vaccine. It found that at a median of 30 days post vaccination, relative VE of the Pfizer-BioNTech XBB.1.5 vaccine, compared with at least three doses of the original wild-type vaccines, ranged from 64-73% among adults aged ≥18 years during an XBB sub lineages dominant period, and was not different across age groups.

*XBB.1.5 vaccination **vs.** ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind*

- One study (Tartof et al. (2023)) was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to be hospitalised for COVID-19 at a median of 30 days after receiving the vaccine, compared with those who had received at least two doses of the original wild-type vaccines, with no difference across age groups (relative VE ranged from 63-70% during an XBB sub lineages dominant period).

*XBB.1.5 vaccination **vs.** unvaccinated*

- One study (Tartof et al. (2023)) was included and found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to be hospitalised for COVID-19 a median of 30 days after receiving the vaccine, compared with unvaccinated individuals, with no difference across age groups (absolute VE ranged from 63-71% during an XBB sub lineages dominant period).

COVID-19-related intensive care unit (ICU) admissions

- There were no studies which reported data for this outcome.

COVID-19-related deaths

- There were no studies which reported data for this outcome.

Multisystem inflammatory syndrome in children (MIS-C)

- There were no studies which reported data for this outcome.

Post-COVID Conditions

- There were no studies which reported data for this outcome.

Potential implications for health systems decision-making

The initial evidence from three studies from different countries suggest a *short-term (up to 30 days post vaccination) benefit of the XBB.1.5 vaccine* for COVID-19-related hospitalisations. The relative VE was consistently between 50 and 70%, irrespective of the comparator vaccine regimen, meaning that previous COVID-19 vaccination (i.e., those who had more vaccines before the XBB.1.5 vaccine) might not account for the benefits seen. There also did not seem to be major differences in VE between age groups. As such, **the initial evidence supports the use of the *XBB.1.5 vaccine* for COVID-19-related hospitalisations** across all ages of individuals.

Though positive, it should be noted that this data is drawn from only three studies, all with slightly different methodologies. Also, these were not randomised controlled studies, so individuals chose to get the vaccine. It is possible that those individuals might have engaged in more COVID-19 preventative behaviours, so we can't be sure that the benefits of the XBB1.5 vaccine were totally due to the vaccine and not these other factors.

Visual representation of data

- For Table 1 and 2, **the number** indicates the *level of effectiveness* of the XBB.1.5 COVID-19 vaccine compared to individuals who did not receive the vaccine. A value of 0% indicates no protection and a value of 100% indicates that the vaccine maximally prevents COVID-19 outcomes (e.g., hospitalisations).
- **Colour** indicates **Level of Certainty** based on the evidence (see note after the table about colourations of previous versions).
- In all tables, **days** refers to time since the administration of the vaccine.

High certainty evidence	Moderate certainty evidence	Low certainty evidence	Not enough evidence
Pooling of sufficient observational studies (including RCTs with follow-up data) with consistent findings	Pooling of sufficient observational studies (including RCTs with follow-up data) with some consistency in findings	Pooling of sufficient observational studies (including RCTs with follow-up data) but *inconsistent* findings	Pooling of insufficient observational studies (including RCTs with follow-up data) to be able to draw conclusions
At least 10 cohorts represented with at least one CI within 10% of the point estimate	At least 4 cohorts represented with at least one CI within 15% of the point estimate	At least 4 cohorts represented	Less than 4 cohorts reported

Question 1: Impact of the XBB.1.5 COVID-19 vaccine on symptomatic COVID-19 infections

No data to report

Question 2: Impact of the XBB.1.5 COVID-19 vaccine on COVID related ED visits

Table 1: VE against COVID related ED or UC visits of the XBB.1.5 adapted COVID-19 vaccine compared to those who have not received the XBB.1.5 adapted COVID-19 vaccine

Author (date) - Country Type of publication	Population	Dominant variant	Intervention (XBB.1.5 vaccine)	Comparator (reference)	Days since last dose	(Relative) VE% (95% CI)
Case-control						
*Tartof et al. (2023) – United States Preprint	≥18 years who have been at Kaiser Permanente Southern California (KPSC) for at least a year (N=24,007)	XBB sub-lineages	Received a BNT162b2 XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine	Median (range): 30 (14 to 73)	• ≥18 years: 58 (47 to 66) • 18-64 years: 64 (46 to 76) • ≥65 years: 55 (41 to 66)
				Received BA.4/5-adapted bivalent vaccine but no XBB1.5-adapted vaccine		• ≥18 years: 57 (45 to 66) • 18-64 years: 60 (38 to 74) • ≥65 years: 57 (42 to 69)
				≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind		• ≥18 years: 59 (49 to 67) • 18-64 years: 66 (49 to 77) • ≥65 years: 55 (40 to 66)
				≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind		• ≥18 years: 58 (48 to 67) • 18-64 years: 65 (48 to 77) • ≥65 years: 54 (39 to 65)

				Unvaccinated		• ≥18 years: 60 (48 to 69) • 18-64 years: 63 (44 to 76) • ≥65 years: 67 (51 to 78)

* The primary article presented outcomes in the form of odds ratio (OR) data, subsequently translated into vaccine effects (VE).

Question 3: Impact of the XBB.1.5 COVID-19 vaccine on hospitalisations related to COVID-19

Table 2: VE against hospitalisations related to COVID-19 of the XBB.1.5 adapted COVID-19 vaccine compared to those who have not received the XBB.1.5 adapted COVID-19 vaccine

Author (date) - Country Type of publication	Population	Dominant variant	Intervention (XBB.1.5 vaccine)	Comparator (reference)	Days since last dose	(Relative) VE% (95% CI)
Retrospective cohort						
*Hansen et al. (2024) – Denmark Peer-reviewed	> 65 years living in Denmark (N=1,037,479)	Omicron	At least one booster dose plus a mRNA XBB.1.5 adapted vaccine	At least one booster dose but not the XBB.1.5 vaccine	7+	76.1 (62.3 to 84.8)
Test-negative case-control						
UK Health Security Agency (2024) – England Report	≥ 65 years (N=16,549)	Omicron	Received a bivalent BA.1 booster vaccine as part of the autumn 2022 booster programme plus a BNT162b2 XBB1.5-adapted vaccine	Received a bivalent BA.1 booster vaccine as part of the autumn 2022 booster programme	9 to 13	42.3 (20.5 to 58.2)
					14 to 28	55.4 (45 to 63.8)
					29 to 63	50.9 (37.5 to 61.5)
**Tartof et al. (2023) – United States Preprint	≥18 years who have been at Kaiser Permanente Southern California (KPSC) for at least a year (N=24,007)	XBB sub-lineages	Received a BNT162b2 XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine	Median (range): 30 (14 to 73)	• ≥18 years: 63 (33 to 80) • 18-64 years: 68 (-148 to 96) • ≥65 years: 63 (31 to 80)
				Received BA.4/5-adapted bivalent vaccine but no XBB1.5-adapted vaccine		• ≥18 years: 60 (25 to 79) • 18-64 years: 65 (-199 to 96) • ≥65 years: 61 (24 to 80)
				≥3 doses of wild-type vaccine but no variant-		• ≥18 years: 64 (35 to 80)

				adapted vaccines of any kind		• 18-64 years: 73 (-114 to 97) • ≥65 years: 64 (32 to 81)
				≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind		• ≥18 years: 63 (33 to 80) • 18-64 years: 70 (-132 to 96) • ≥65 years: 63 (30 to 80)
				Unvaccinated		• ≥18 years: 68 (36 to 84) • 18-64 years: 63 (-222 to 96) • ≥65 years: 71 (39 to 86)

*The primary article presented outcomes in the form of hazard ratio (HR) data, subsequently translated into vaccine effects (VE);

**The primary article presented outcomes in the form of odds ratio (OR) data, subsequently translated into vaccine effects (VE).

Question 4: Impact of the XBB.1.5 COVID-19 vaccine on COVID related intensive care unit (ICU) admissions

No data to report

Question 5: Impact of the XBB.1.5 COVID-19 vaccine on COVID related deaths

No data to report

Question 6: Impact of the XBB.1.5 COVID-19 vaccine on multisystem inflammatory syndrome in children (MIS-C)

No data to report

Question 7: Impact of the XBB.1.5 COVID-19 vaccine on post-COVID conditions

No data to report

Definitions for vaccine effectiveness (VE)

- The WHO defines preferred levels of initial VE as:
  - VE against symptomatic disease ≥ 70%, with the lower 95% CI ≥ 50%; or
  - VE against severe disease ≥ 90%, with the lower 95% CI ≥ 70%
  - https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines

Risk of bias (RoB) assessment

The risk of bias data for each individual study is provided in the Supplementary File (les21.1_vaccine_effectiveness_XBB15_3_RoB_2024-01-14.xlsx).

Strengths and Limitations

Key strengths of the present review include the broad search terms that were included during the initial screening phase, the rigorous methodologies that were employed throughout the review, and validation processes that were included to ensure consistency. In spite of these strengths, there were several limitations that need to be noted. As with any rapid review process, there is a slightly increased possibility that studies might be missed when compared to a full systematic review. However, this was potentially mitigated as we validated our study inclusions against another evidence synthesis team. Due to the turnaround time for the review, we weren't able to contact authors for studies that could have potentially provided data, which means that some studies which had the potential to be included, were excluded (e.g., those that graphed data but did not provide explicit data within the manuscript).

Land Acknowledgements

The Montreal Behavioural Medicine Centre, Concordia University, UQAM, and the CIUSSS-NIM are located on unceded Indigenous lands. The Kanien'kehá:ka Nation is recognized as the custodians of the lands and waters on which these institutions stand today. Tiohtiá:ke commonly known as Montreal is historically known as a gathering place for many First Nations. Today, it is home to a diverse population of Indigenous and other peoples. We respect the continued connections with the past, present, and future in our ongoing relationships with Indigenous and other peoples within the Montreal community.

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