Effectiveness of the Monovalent XBB.1.5 COVID-19 vaccines
Living Evidence Synthesis #21
(Version 21.2: 22 April 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 sublineage (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-realted deaths;
6. Multisystem inflammatory syndrome in children (MIS-C); and
7. Post-COVID Conditions
8. Other outcomes: e.g., COVID-19 related outpatient visits

compared with:

- Previous COVID-19 vaccines:
  - No COVID-19 vaccination and previous COVID-19 bivalent or monovalent 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 infections is presented in Table 1 and Figure 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 ED visits is presented in Table 2.
3. 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 3.

Flow of included studies

In order to capture as many articles as possible, our initial search did not include date limits, starting from the beginning, until our first round (January 30th, 2024) to capture all articles that mentioned the keywords of interest. By the second round (search date: March 19th, 2024), a total of 117 studies were title and abstract screened, 12 were full text appraised, with 4 initially included, 1 study was excluded (RoB; see **Appendix 1b)**, leaving 3 that were used to complete this summary. The reasons for excluding the 8 studies are reported in **Appendix 7b.** In addition, 15 records were identified through hand search, of which 3 were included. The reason for excluding the 12 studies are reported in **Appendix 7b** as well. Therefore, a total of 6 studies are included in this summary.

High level summary for COVID-19 outcomes

Symptomatic SARS-CoV-2 infection

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

- Three studies were included for symptomatic SARS-CoV-2 infection.
    - Two of these studies found that adults aged ≥18 years who had received the XBB.1.5 COVID-19 vaccine were less likely to be infected compared with those who had not received the XBB.1.5 COVID-19 vaccine.
        - One test-negative case-control study (Link-Gelles et al. (2024)) of US adults found a moderate level of protection ≥7 days post vaccination (relative vaccine effectiveness [rVE] = 54%) while XBB and JN.1 sublineages were predominant, compared with those who had not received any XBB.1.5 vaccine. When the looking at specific periods of time, there was a drop in rVE from 58% at 7-59 days to 49% at 60-119 days. There was also a trend for the rVE to be higher in younger adults (18-49 years = 57%) compared to older adults (≥50 years = 46%).
        - In contrast to the Link-Gelles et al. study, one prospective cohort study from the Netherlands (Huiberts et al. (2024)) found a lower level of protection ≥7 days post vaccination in younger adults (18-59 years = 34.7%) than older adults (60-85 years = 55.0%).
    - The third study (Skowronski et al. (2024)) used a test-negative case-control design and found that Canadian individuals aged ≥12 years who had received the XBB.1.5 COVID-19 vaccine were less likely to be infected compared with those who had not received the XBB.1.5 COVID-19 vaccine. The authors found a moderate level of protection approximately 35 days post vaccination (rVE = 44%) during XBB EG.5.1, HV.1, BA.2.75, BA.2.86 and JN.1 sublineage predominance, compared with those who had not received any XBB.1.5 vaccine. This level of protection did not differ by age (12-64 years = 46%; ≥65 years = 46%). When restricting the analysis to those who reported a prior NAAT- or RAT-confirmed SARS-CoV-2 infection and when excluding influenza cases from controls, there was a relatively higher level of protection for individuals who received the XBB.1.5 COVID-19 vaccine compared with individuals who had not received the XBB.1.5 COVID-19 vaccine (including unvaccinated individuals) (rVE = 72%).

Of note, the Huiberts et al. (2024) study also reported general infection data (symptomatic and asymptomatic combined). As with the Link-Gelles et al (2024) study, there was a trend for a reduction in VE over time for older adults (7-42 days = 52.1% vs. 49-84 days = 40.6%), which was not seen in the younger adults (7-42 days = 40.2% vs. 49-84 days = 46.7%).

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

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

- One test-negative case-control study from the United States (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 not received any XBB.1.5 vaccine (including unvaccinated individuals), with no difference across age groups. rVE ranged from 55% to 64% when XBB sublineages were predominant.

*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. rVE ranged from 57% to 60% while XBB sublineages were predominant.

*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. rVE ranged from 55% to 66% while XBB sublineages were predominant.

*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. rVE ranged from 54% to 65% while XBB sublineages were predominant.

*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 (aVE) ranged from 60% to 67% while XBB sublineages were predominant.

COVID-19-related hospitalisations

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

- One test-negative case-control study from the United States (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 those who had not received the XBB.1.5 vaccine (including unvaccinated individuals), with no difference across age groups. rVE ranged from 63% to 68% while XBB sublineages were predominant.

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

- Three studies were included and they 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, rVE of the Pfizer-BioNTech XBB.1.5 vaccine, compared with Pfizer-BioNTech or Moderna bivalent BA.4/BA.5 vaccination, ranged from 60% to 65% while XBB sublineages were predominant. rVE was consistent across age groups.
    - One test-negative case-control study (UK Health Security Agency (2024)) conducted among individuals aged ≥65 years in England found consistent levels of protection between 14 and 63 days post Pfizer-BioNTech XBB.1.5 vaccination during XBB sublineage predominance (rVE = 50.9-55.4%).
    - One retrospective cohort study (Hansen et al. (2024)) of individuals aged ≥65 years in Denmark found a high level of protection ≥7 days post vaccination during XBB sublineage and EG.5.1 predominance (rVE = 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. The authors found that at a median of 30 days post vaccination, rVE of the Pfizer-BioNTech XBB.1.5 vaccine, compared with at least three doses of the original wild-type vaccines, ranged from 64% to 73% among adults aged ≥18 years during XBB sublineage predominance, and was consistent 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. rVE ranged from 63% to 70% during XBB sublineage predominance.

*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. aVE ranged from 63% to 71% during XBB sublineage predominance.

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 two studies from different countries suggest a **moderate benefit of the XBB.1.5 vaccine** against COVID-19-related **infections**, which may last up to 119 days post infection. rVE was consistently between 40% and 60%, and there was a general waning of effectiveness over time. rVE was consistent between age groups.

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**. rVE was consistently between 50% and 70%, irrespective of the comparator vaccine regimen. This finding means that previous COVID-19 vaccination (i.e., those who had vaccines before the XBB.1.5 vaccine) may not contribute to the observed protection. There also did not seem to be major differences in rVE between age groups.

As such, **this initial evidence supports the use of the XBB.1.5 vaccine** to protect all age groups against **COVID-19-related infections and hospitalisations**.

Though positive, it should be noted that this data is drawn from only six 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 may have engaged in more COVID-19 preventative behaviours (e.g., wearing masks, physical distancing, hand washing, etc.), so we can't be sure that the benefits of the XBB.1.5 vaccine were totally due to the vaccine and not these other factors.

Visual representation of data

- For Table 1, 2 and 3, **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

Table 1: VE of the XBB.1.5 variant-adapted COVID-19 vaccine against COVID infection compared with those who have not received the XBB.1.5 variant-adapted COVID-19 vaccine.

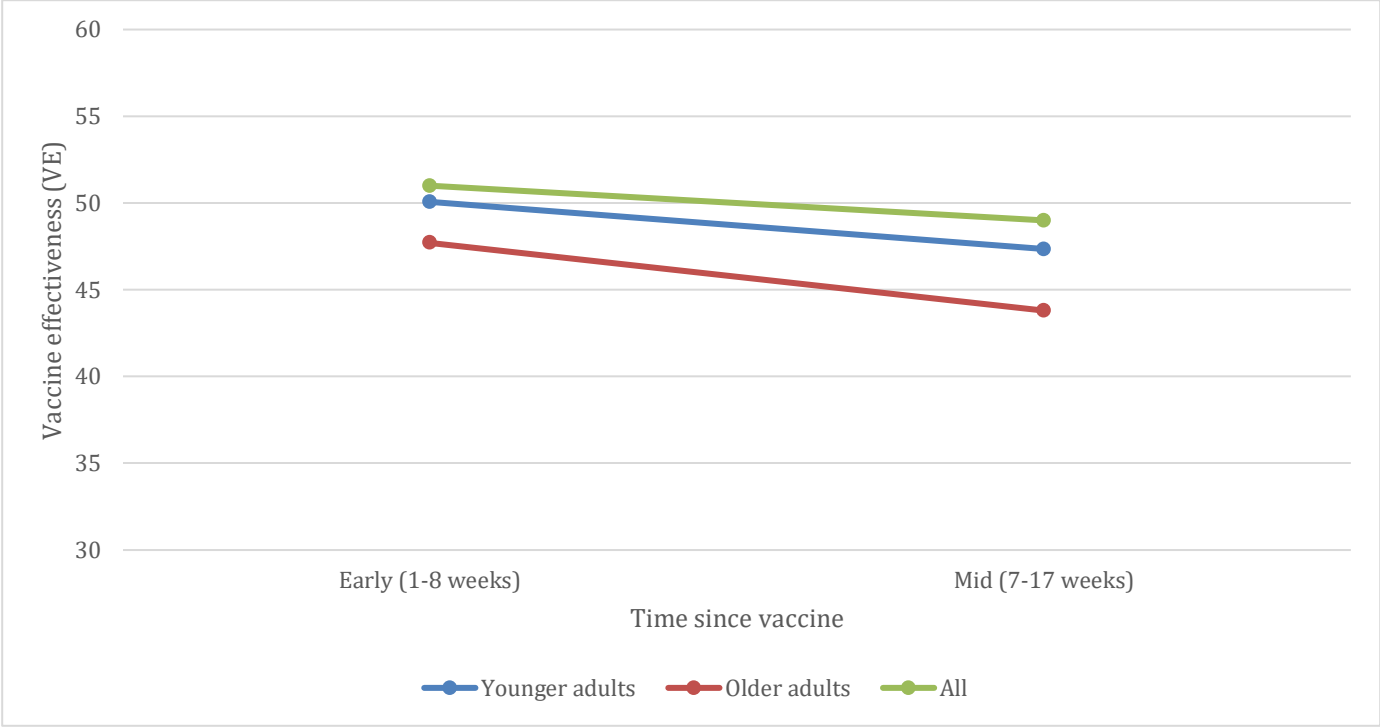
Author (date) - Country Type of publication	Population	Predominant variant	Intervention	Comparator group (reference)	Time since last dose (days)	VE (%) (95% CI)
Test-negative case control						
Link-Gelles et al (2024) - US Peer-reviewed	≥18 years who had at least one symptom and had a COVID-19 test conducted at a participating CVS Pharmacy or Walgreens (N=9,222)	Omicron XBB sublineages and JN.1	Received an XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech or Novavax)	Did not receive the XBB.1.5 vaccine	≥7	**Symptomatic infection** • ≥18 years: 54 (46-60) • 18-49 years: 57 (48-65) • ≥50 years: 46 (31-58)
					7-59	**Symptomatic infection** • ≥18 years: 58 (48-65) • 18-49 years: (64 (53-73) • ≥50 years: 45 (26-60)
					60-119	**Symptomatic infection** • ≥18 years: 49 (36-58) • 18-49 years: 48 (31-60) • ≥50 years: 47 (24-62)

Skowronski et al. (2024) – Canada Peer-reviewed	2,176 individuals with respiratory infection symptoms, aged 12+ and recruited from community-based sentinel practitioners (Canadian Sentinel Surveillance Network) in British Columbia, Ontario and Quebec	XBB sublineages, EG.5.1, HV.1, BA.2.75, BA.2.86 and JN.1	Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech)	Did not receive the XBB.1.5 vaccine	Median (IQR): 35 (21-49)	**Laboratory confirmed symptomatic infection:** • ≥12 years: 44 (14-63)
					Median (IQR): 42 (21-56)	**Laboratory confirmed symptomatic infection:** • 12-64 years: 46 (2-70)
					Median (IQR): 35 (21-56)	**Laboratory confirmed symptomatic infection:** • ≥65 years: 46 (-3-72)
			Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech) and received their previous dose (non-XBB.1.5) more than 12 weeks ago	Did not receive the XBB.1.5 vaccine and received their last dose more than 12 weeks ago	Median (IQR): 35 (21-56)	**Laboratory confirmed symptomatic infection:** • ≥12 years: 41 (13-60)
			Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech) and received their previous dose (non-XBB.1.5) more than 24 weeks ago	Did not receive the XBB.1.5 vaccine and received their last dose more than 24 weeks ago	Median (IQR): 35 (21-56)	**Laboratory confirmed symptomatic infection:** • ≥12 years: 47 (21-65)
			Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech) – Excluding influenza	Did not receive the XBB.1.5 vaccine – Excluding influenza positive cases from	Median (IQR): 35 (21-56)	**Laboratory confirmed symptomatic infection:**

			positive cases from the COVID-19 control group	the COVID-19 control group		• ≥12 years: 54 (31-70)
			Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech) and had a previous COVID-19 infection	Did not receive the XBB.1.5 vaccine and had a previous COVID-19 infection	Median (IQR): 42 (21-56)	**Laboratory confirmed symptomatic infection:** • ≥12 years: 67 (28-85)
			Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech) and had a previous COVID-19 infection – Excluding influenza positive cases from the COVID-19 control group	Did not receive the XBB.1.5 vaccine and had a previous COVID-19 infection – Excluding influenza positive cases from the COVID-19 control group	Median (IQR): 42 (21-56)	**Laboratory confirmed symptomatic infection:** • ≥12 years: 72 (39-87)
Prospective cohort						
Huiberts et al. (2024) – Netherlands Peer-reviewed	18- to 85-year-old community dwelling Dutch participating to the VAccine Study COvid-19 (VASCO) (N=23,895)	XBB sublineages and JN.1	Received a booster dose and a dose of the Pfizer-BioNTech XBB.1.5 variant-adapted vaccine	Received a booster dose but did not receive an XBB.1.5 variant adapted vaccine	≥7	**Self-reported infection** • 18 to 59 years: 41.3 (22.6-55.5) • 60 to 85 years: 50.3 (43.8-56.1) **Self-reported symptomatic infection** • 18 to 59 years: 34.7 (10.4-52.4) • 60 to 85 years: 55.0 (47.6-61.4)
					7-42	**Self-reported infection**

						• 18 to 59 years: 40.2 (19.6-55.5) • 60 to 85 years: 52.1 (45.4-57.9)
					49-84	**Self-reported infection** • 18 to 59 years: 46.7 (-5.7-73.1) • 60 to 85 years: 40.6 (25.7-52.4)
			Didn't have any prior infection and received a booster dose and the Pfizer-BioNTech XBB.1.5 variant-adapted vaccine	Didn't have any prior infection and received a booster dose but did not receive an XBB.1.5 variant adapted vaccine	≥7	**Self-reported infection** • 18 to 59 years: 11.7 (-60.9-51.6) • 60 to 85 years: 48.8 (36.4-58.8)
			Had prior infection <1 year ago, received a booster dose and the Pfizer-BioNTech XBB.1.5 variant-adapted vaccine			**Self-reported infection** • 18 to 59 years 49.7 (22.8-67.2) • 60 to 85 years: 67.7 (61.2-73.1)
			Had prior infection > 1 year ago, received a booster dose and the Pfizer-BioNTech XBB.1.5 variant-adapted vaccine			**Self-reported infection** • 18 to 59 years: 86.7 (68.7 (94.3) • 60 to 85 years: 85.3 (80.6-88.9)
			Received an mRNA booster dose and a dose of the Pfizer-BioNTech XBB.1.5 variant-adapted vaccine	Received an mRNA booster dose but did not receive an XBB.1.5 variant adapted vaccine		**Self-reported infection** • 18 to 59 years: 44.6 (25.0-59.1) • 60 to 85 years: 51.4 (44.3-57.6)

Figure 1: A visual representation of the trend in vaccine effectiveness (VE) for infections (including symptomatic and asymptomatic) of the XBB.1.5 adapted COVID-19 vaccine over time.



* The following categories consist of the data from the 3 included studies: The early time period covers the 7-42 days, 35-42 days, and 7-59 days; the mid time period covers the 49-60 days and 60-119 days; the younger adults include those who are 18-49, 12-64, and 18-59; and the older adults include those who are ≥50, ≥65, and 60-85 years. A simple averaging of data was applied across studies.

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

Table 2: VE of the XBB.1.5 variant-adapted COVID-19 vaccine against COVID related ED or UC visits compared with those who have not received the XBB.1.5 variant-adapted COVID-19 vaccine.

Author (date) - Country Type of publication	Population	Predominant variant	Intervention	Comparator group (reference)	Time since last dose (days)	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 sublineages	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine (including unvaccinated individuals)	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 a Pfizer-BioNTech or Moderna 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 3: VE of the XBB.1.5 variant-adapted COVID-19 vaccine against hospitalisations related to COVID-19 compared with those who have not received the XBB.1.5 variant-adapted COVID-19 vaccine.

Author (date) - Country Type of publication	Population	Predominant variant	Intervention	Comparator group (reference)	Time since last dose (days)	VE (%) (95% CI)
Retrospective cohort						
*Hansen et al. (2024) – Denmark Peer-reviewed	≥65 years living in Denmark (N=1,037,479)	Omicron EG.5.1, XBB sublineages	At least one Pfizer-BioNTech or Moderna bivalent BA.4/BA.5 or BA.1 booster dose plus an mRNA XBB.1.5-adapted vaccine	At least one Pfizer-BioNTech or Moderna bivalent BA.4/BA.5 or BA.1 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 BA.5, BA.2.75, BQ.1, EG.5.1, XBB sublineages	Received a Pfizer-BioNTech or Moderna bivalent BA.1 booster vaccine as part of the autumn 2022 booster programme plus a Pfizer-BioNTech XBB1.5-adapted vaccine	Received a Pfizer-BioNTech or Moderna 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 sublineages	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine (including unvaccinated individuals)	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 Pfizer-BioNTech or Moderna 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-adapted vaccines of any kind		• ≥18 years: 64 (35 to 80) • 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%
- The CDC defines absolute and relative VE as:
  - Absolute VE refers to study that determine the VE by comparing vaccinated individuals with unvaccinated individuals
  - Relative VE (rVE) refers to study that determine the VE by comparing individuals who have received the vaccine or regimen of interest with people who have received a different vaccine or a different regimen.

Risk of bias (RoB) assessment

The risk of bias data for each individual study is provided in the Supplementary File (les21.2_vaccine_effectiveness_XBB15_3_RoB_2024-05-24.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.

We are grateful to have the opportunity to work on these lands.

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