Effectiveness of the Monovalent XBB.1.5 COVID-19 vaccines
Living Evidence Synthesis #21
(Version 21.3: 25 June 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 and medically attended 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
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 SARS-CoV-2 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, meaning that all articles mentioning the keywords of interest prior to our first round (January 30th, 2024) were captured. On March 19th, 2024, a second round of search was completed. By the third round (search date: June 11th, 2024) a total of 188 articles were title and abstract screened, 32 were full text appraised, with 12 initially included, 5 of these were excluded due to having a critical risk of bias (RoB; see **Appendix 1b)**, leaving 7 that were used to complete this summary. The reasons for excluding the 20 studies are reported in **Appendix 7b.** In addition, 94 records were identified through hand search, of which 64 were full text screened. Five studies were first included but one was later excluded due to having a critical risk of bias (RoB; see **Appendix 1b),** leaving 4 included studies through hand search. The reasons for excluding the 59 studies are reported in **Appendix 7b** as well. Therefore, a total of 11 studies are included in this summary.

High level summary for COVID-19 outcomes

Medically attended SARS-CoV-2 infections

*XBB.1.5 vaccination **vs.** no XBB.1.5 vaccination (including individuals who have not received any COVID-19 vaccine)*

As shown in **Figure 1**, overall, in the early (ca. 1-8 weeks) post vaccination period, incremental vaccine effectiveness [iVE] is around 55%. In the mid (ca. 8-17 weeks) post vaccination period, iVE drops to about 48%. These levels seemed to be consistent for younger (<65 years) and older (65+ years) adults.

- Three studies were included for medically attended infection.
    - One test-negative case control study (Skowronski et al. (2024)) found that Canadian individuals aged ≥12 years who had received the XBB.1.5 COVID-19 vaccine were less likely to have a medically-attended infection 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 (iVE = 44%) during the period where XBB EG.5.1, HV.1, BA.2.75, BA.2.86 and JN.1 sublineages were predominant, 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, the iVE increased to 72%.
    - One test-negative case-control study (Link-Gelles et al. (2024)) of US adults found a moderate level of protection ≥7 days post vaccination (iVE = 54%) whilst the XBB and JN.1 sublineages were predominant, compared with those who had not received any XBB.1.5 vaccine. When looking at specific periods of time, there was a drop in iVE from 58% at 7-59 days to 49% at 60-119 days. There was also a trend for the iVE to be higher in younger adults (18-49 years = 57%) compared to older adults (≥50 years = 46%).
    - Another test-negative case-control study (Tartof et al. (2023)) of US adults found a moderate level of protection a median of 30 days post vaccination (iVE = 58%) whilst the XBB sublineage was predominant, compared with those who had not received any XBB.1.5 vaccine. There was a trend for the iVE to be higher in older adults (≥65 years = 68%) compared to younger adults (18-64 years = 32%).

*One study was included for self-reported symptomatic SARS-CoV-2 infection (but not medically attended infections). This 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%).

*XBB.1.5 vaccination **vs.** variations in previous vaccination regimes*

- The Tartof et al. (2023) study explored a variety of vaccination comparator groups (adapted bivalent vaccine but no XBB1.5-adapted vaccine, ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind, and ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind). In general, the results were consistent with the median 30-day post-vaccination relative vaccine effectiveness (rVE) being around 55% with younger individuals (18-64 years) having less protection (rVE = 22-40%) than older adults (≥65 years: rVE = 65-71%).

*XBB.1.5 vaccination **vs.** no COVID-19 vaccination*

- In addition, Tartof et al. (2023) found that, compared to unvaccinated individuals, adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to have a medically attended COVID-19 infection (median 30 day rVE = 43%). What was notable, was a large absolute difference between younger individuals (18-64 years: aVE = 17%) and older adults (≥65 years: aVE = 60%); however, the overlapping confidence intervals meant that this was not statistically significant.

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

*XBB.1.5 vaccination **vs.** no XBB.1.5 vaccination (including individuals who have not received any COVID-19 vaccine)*

- Three test-negative case-control studies from the US were included.
    - One study (Caffrey et al. (2024)) found adults aged ≥18 years who had received the XBB.1.5 vaccine had a median 56-day iVE of 39% for COVID-19-related ED or UC visits, compared with those who had not received any XBB.1.5 vaccine (including unvaccinated individuals). Those with immunocompromising conditions had a lower iVE vs. those who were immunocompetent (34% vs. 42%) and older individuals had a lower iVE compared to younger individuals (18-64 years = 48% vs. ≥65 years = 35%). In addition, the vaccine seemed to provide better protection against XBB sublineages vs. JN.1 sublineages (14-60 day iVE = 52% vs. 41%).
    - One study (Tartof et al. (2023)) found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine had a median 30-day iVE of 58% for COVID-19-related ED or UC visits, compared with those who had not received any XBB.1.5 vaccine (including unvaccinated individuals), with a slight difference across age groups (18-64 years; iVE = 64% vs. ≥65 years: iVE = 55%). VE was estimated when the XBB sublineage was predominant.
    - One study (DeCuir et al. (2024)) found that XBB.1.5 variant-adapted vaccines provided some protection against COVID-related ED and UC visits in immunocompetent adults aged ≥18 years 7 to 119 days after receiving the vaccine, compared to those who did not receive the XBB.1.5 variant-adapted vaccine (including unvaccinated individuals), but that this protection diminished slightly over time (median 33 day iVE = 51% vs. median 74 day iVE = 39%). In general, there were no differences in the patterns by age group (18-64 years vs. ≥65 years).

*XBB.1.5 vaccination **vs.** variations in previous vaccination regimes*

- The Tartof et al. (2023) study explored a variety of vaccination comparator groups (adapted bivalent vaccine but no XBB1.5-adapted vaccine, ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind, and ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind). In general, the results were consistent with the median 30-day post-vaccination rVE being around 58% with younger individuals (18-64 years) having slightly higher protection (rVE = 60-66%) than older adults (≥65 years: rVE = 54-57%).

*XBB.1.5 vaccination **vs.** no COVID-19 vaccination*

- In addition, Tartof et al. (2023) found that, compared to unvaccinated individuals, adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to have a COVID-related ED or UC visit (median 30 day aVE = 60%), with comparable levels of protection for younger individuals (18-64 years: aVE = 63%) and older adults (≥65 years: aVE = 67%).

COVID-19-related hospitalisations

*XBB.1.5 vaccination **vs.** no XBB.1.5 vaccination (including individuals who have not received any COVID-19 vaccine)*

As can be seen in **Figure 2**, overall, in the early (ca. 1-8 weeks) post vaccination incremental vaccine effectiveness [iVE] is around 60%. In the mid (ca. 8-17 weeks) post vaccination period iVE drops a little but stays relatively consistent at around 55%. These levels seemed to be consistent for younger (< 65 years) and older (≥65 years) adults.

- Five test-negative case-control studies were included (four from the US and one from England).
    - One US study (Caffrey et al. (2024)) found adults aged ≥18 years who had received the XBB.1.5 vaccine had a median 53-day iVE of 43% for COVID-19-related hospitalisations, compared with those who had not received any XBB.1.5 vaccine (including unvaccinated individuals). Those who were immunocompromised had a lower iVE vs. those who were immunocompetent (33% vs. 49%) and older individuals had a lower iVE compared to young individuals (18-64 years = 58% vs. ≥65 years = 41%). In addition, the vaccine seemed to provide notably better protection against XBB sublineages vs. JN.1 sublineages (14-60 day iVE = 62% vs. 32%).
    - One US study (Tartof et al. (2023)) found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine had a median 30-day iVE of 63% for COVID-19-related hospitalisations, compared with those who had not received any XBB.1.5 vaccine (including unvaccinated individuals), with a slight difference across age groups (18-64 years; iVE = 68% vs. ≥65 years: iVE = 63%). These data were when the XBB sublineage was predominant.
    - One US study (DeCuir et al. (2024)) found that XBB.1.5 variant adapted vaccines provided protection against COVID-19-related hospitalisations in immunocompetent adults aged ≥18 years after receiving the vaccine, compared to those who did not receive the XBB.1.5 variant adapted vaccine (including unvaccinated individuals), but that this protection diminished slightly over time (median 32 day iVE = 53% vs. median 73 day iVE = 50%). In general, there were no differences in the patterns by age group (18-64 years vs. ≥65 years), though older adults had a 5-12% greater iVE than younger adults.
    - One study from England (Kirsebom et al. (2024)) found that XBB.1.5 variant adapted vaccines provided protection against COVID related hospitalisations in adults aged ≥65 years, compared to those who did not receive the XBB.1.5 variant adapted vaccine (including unvaccinated individuals). The 9-13 day post-vaccination iVE = 37%, rising to around 55% 14-28 days post-vaccination, and then dropping to 42% 64-98 days post-vaccination.
    - One US study (Link-Gelles et al. (2024)) found that XBB.1.5 variant adapted vaccines provided some protection against COVID related hospitalisations in adults with immunocompromising conditions aged ≥18 years 7+ days after receiving the vaccine (iVE=36%), compared to those who did not receive the XBB.1.5 variant adapted vaccine (including unvaccinated individuals). The level of iVE seemed to be stable up to 119 days post-vaccination (7–59-day iVE = 38% and 60-119 days iVE = 34%).

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

- Three studies 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)) in adults ≥18 years, 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 vaccines, 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.*** *variations in previous vaccination regimes*

- The Tartof et al. (2023) study explored a variety of vaccination comparator groups (i.e., ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind and ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind). In general, the results were consistent with the median 30-day post-vaccination rVE being around 65% with younger individuals (18-64 years) having slightly higher protection (rVE = 70-73%) than older adults (≥65 years: rVE = 63-64%).
- A multicounty European retrospective cohort study (Andersson et al. (2024)) of older individuals (≥65 years) found that the XBB.1.5 variant-adapted vaccine provided additional protection 8-91 days post-vaccination compared to having had 4 (rVE=65%), 5 (rVE=57%), or 6 (rVE=44%) prior doses of a non-XBB.1.5 variant adapted vaccine.

XBB.1.5 vaccination ***vs.*** *no COVID-19 vaccination*

- In addition, Tartof et al. (2023) found that, compared to unvaccinated individuals, adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine were less likely to have a COVID-19-related hospitalisation (median 30 day rVE = 68%), with younger individuals having slightly lower protection (18-64 years: aVE = 63%) compared to older adults (≥65 years: aVE = 71%).

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

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

COVID-19-related deaths

XBB.1.5 vaccination ***vs.*** *at least 4 prior doses*

- A multicounty European retrospective cohort study (Andersson et al. (2024)) of older individuals (≥65 years) found that the XBB.1.5 variant adapted vaccine provided additional protection against COVID-19-related mortality 8-91 days post-vaccination compared to having received at least 4 prior doses of COVID-19 vaccine (rVE=78%). The level of rVE seemed to slowly decline across the post-vaccination period (8–28-day rVE = 83% and 71-91 day rVE = 72%).

XBB.1.5 vaccination ***vs.*** *variations in previous vaccination regimes*

- The European retrospective cohort study (Andersson et al. (2024)) also found that the XBB.1.5 variant-adapted vaccine provided additional protection against COVID-19-related mortality 8-91 days post-vaccination compared to having had 4 (rVE = 78%), 5 (rVE = 77%), or 6 (rVE = 82%) prior doses of a non-XBB.1.5 variant-adapted vaccine.

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 evidence from three studies from different countries, including one study from Canada, suggests a **moderate benefit of the XBB.1.5 vaccine** against COVID-19-related **medically attended infections**, which may last up to 119 days post-vaccination. The raw average iVE was around 55%, and there was a general waning of effectiveness over time (ca. iVE=47%). iVE was consistent between age groups.

The initial evidence from eight studies from a variety of different countries (though there was no Canadian data) suggests a **moderate benefit of the XBB.1.5 vaccine** against COVID-19-related **hospitalisations**, which may last up to 98 days post-vaccination. Initial iVE was consistently around 60% (8-54 days post-vaccination) which only dropped to about 55% (64-98 days).

Both of these fundings were relatively consistent no matter what the comparator group where, meaning that the XBB.1.5 vaccines seem to provide notable benefit no matter what individuals previous vaccination or infection pattern is. Unsurprisingly, there may be additional benefit of the XBB.1.5 vaccines for those who are immunocompetent (vs. immunocompromised) and against XBB sublineages vs. JN.1 sublineages, though this comparative data only comes from study and needs to be replicated.

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

Though positive, it should be noted that this data is drawn from only a small number of studies, all with slightly different methodologies, and most of which were not conducted in Canada. Also, these were not randomised controlled studies, so individuals chose to get vaccinated. 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 and medically attended COVID-19 infections

Table 1: VE of the XBB.1.5 variant-adapted COVID-19 vaccine against symptomatic and medically attended COVID-19 infections compared with those who have not received the XBB.1.5 variant-adapted COVID-19 vaccine (n=4).

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 mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech or Novavax)	Did not receive the XBB.1.5 vaccine (includes unvaccinated individuals)	≥7	**Medically attended infections:** • ≥18 years: 54 (46-60) • 18-49 years: 57 (48-65) • ≥50 years: 46 (31-58)
					7-59	**Medically attended infections:** • ≥18 years: 58 (48-65) • 18-49 years: 64 (53-73) • ≥50 years: 45 (26-60)
					60-119	**Medically attended infections:** • ≥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 (includes unvaccinated individuals)	Median (IQR): 35 (21-49)	**Medically attended infections:** ≥12 years: 44 (14-63)
					Median (IQR): 42 (21-56)	**Medically attended infections:** 12-64 years: 46 (2-70)
					Median (IQR): 35 (21-56)	**Medically attended infections:** ≥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)	**Medically attended infections:** ≥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)	**Medically attended infections:** ≥12 years: 47 (21-65)
			Received an mRNA XBB.1.5 variant-adapted vaccine (Moderna, Pfizer-BioNTech) – Excluding influenza positive cases from the	Did not receive the XBB.1.5 vaccine – Excluding influenza positive cases from the COVID-19 control group	Median (IQR): 35 (21-56)	**Medically attended infections:** ≥12 years: 54 (31-70)

			COVID-19 control group	(includes unvaccinated individuals)		
			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 (includes unvaccinated individuals)	Median (IQR): 42 (21-56)	**Medically attended infections:** ≥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 (includes unvaccinated individuals)	Median (IQR): 42 (21-56)	**Medically attended infections:** ≥12 years: 72 (39-87)
*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)	Omicron	Received a BNT162b2 XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine (includes unvaccinated individuals)	Median (range): 30 (14 to 73)	**Medically attended infections:** • ≥18 years: 58 (34 to 73) • 18-64 years: 32 (-1 to 54) • ≥65 years: 68 (49 to 79)
				Received BA.4/5-adapted bivalent vaccine but no XBB1.5-adapted vaccine		**Medically attended infections:** • ≥18 years: 51 (32 to 65) • 18-64 years: 22 (-21 to 50)

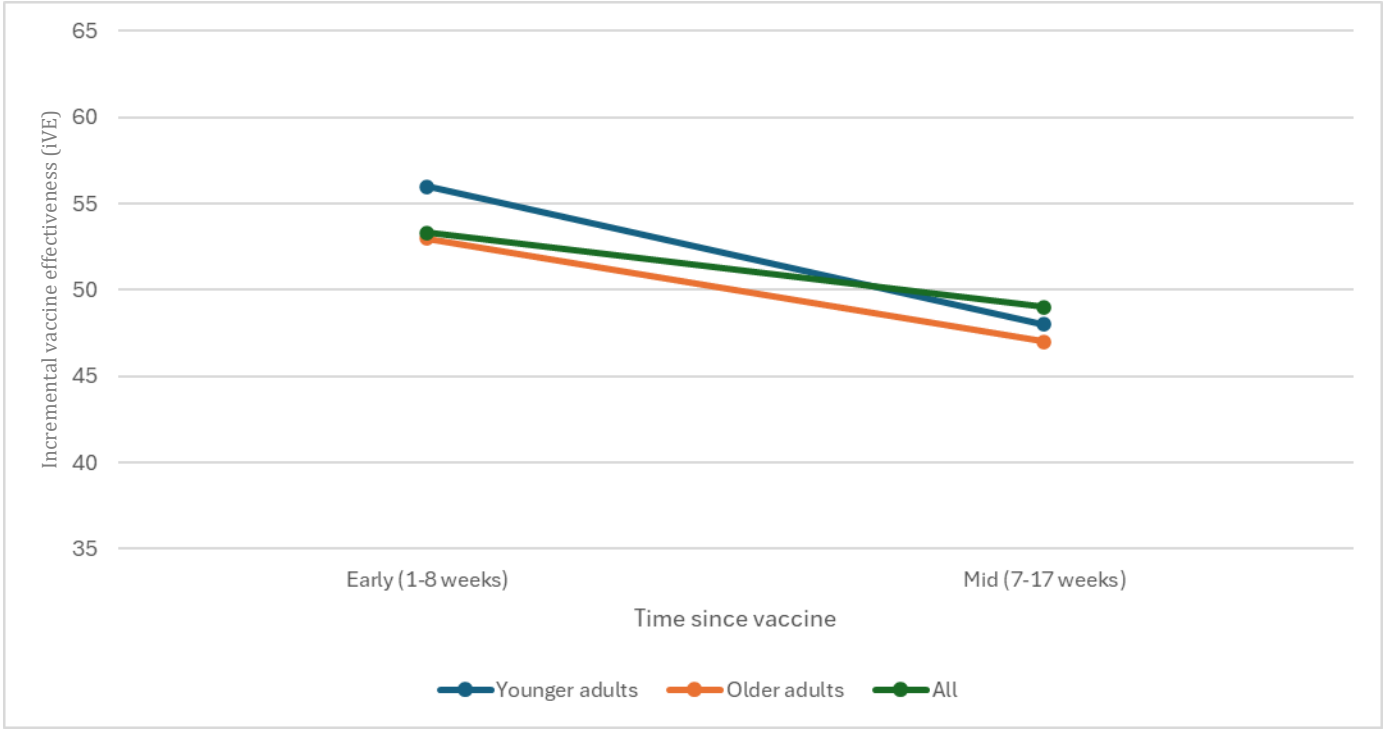
						• ≥65 years:71 (53 to 82)
				≥3 doses of wild-type vaccine but no variant- adapted vaccines of any kind		**Medically attended infections:** • ≥18 years: 56 (40 to 67) • 18-64 years: 40 (10 to 60) • ≥65 years:65 (45 to 78)
				≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind		**Medically attended infections:** • ≥18 years: 54 (38 to 66) • 18-64 years: 35 (3 to 57) • ≥65 years: 67 (47 to 79)
				Unvaccinated		**Medically attended infections:** • ≥18 years: 43 (16 to 61) • 18-64 years: 17 (-33 to 48) • ≥65 years: 60 (13 to 82)
Prospective cohort						
Huiberts et al. (2024) – Netherlands	18- to 85-year-old community dwelling Dutch participating to the	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	≥7	**Self-reported infections** • 18 to 59 years: 41.3 (22.6-55.5)

Peer-reviewed	VAccine Study COvid-19 (VASCO) (N=23,895)			variant adapted vaccine		• 60 to 85 years: 50.3 (43.8-56.1) **Self-reported symptomatic infections** • 18 to 59 years: 34.7 (10.4-52.4) • 60 to 85 years: 55.0 (47.6-61.4)
					7-42	**Self-reported infections** • 18 to 59 years: 40.2 (19.6-55.5) • 60 to 85 years: 52.1 (45.4-57.9)
					49-84	**Self-reported infections** • 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	Did not have any prior infection and received a booster dose but did not receive an XBB.1.5 variant adapted vaccine	≥7	**Self-reported infections** • 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 infections** • 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			**Self-reported infections**

			Pfizer-BioNTech XBB.1.5 variant-adapted vaccine			• 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 infections** • 18 to 59 years: 44.6 (25.0-59.1) • 60 to 85 years: 51.4 (44.3-57.6)

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

Figure 1: A visual representation of the trend in incremental vaccine effectiveness (iVE) for **medically attended infections** of the XBB.1.5 adapted COVID-19 vaccine over time (comparator = those who did not receive the XBB.1.5 vaccine, including unvaccinated individuals).



* The following categories consist of the data from the 3 included studies: The early time period covers the 7-59 days and medians of 30-42 days; the mid time period covers 60-119 days (there is only 1 study that is providing mid-time data); the younger adults include those who are 18-49, 12-64, and 18-64; and the older adults include those who are ≥50 and ≥65. A simple averaging of data was applied across studies.

Question 2: Impact of the XBB.1.5 COVID-19 vaccine on COVID-related ED or UC 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 (n = 3).

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						
Caffrey et al. (2024) – United States Preprint	113,174 respiratory infection episodes in adults aged 18+ and diagnosed with an acute respiratory infection in hospital, emergency department, urgent care or outpatient setting from the US Veterans Affairs Healthcare system	Omicron	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive the XBB.1.5 variant adapted vaccine (includes unvaccinated individuals)	Median (IQR): 56 (36-76)	≥18 years: 39 (33-45)
					Median (IQR): 55 (35-74)	Immunocompromised: 34 (22-45)
					Median (IQR): 56 (36-77)	Immunocompetent: 42 (34-49)
					Median (IQR): 54 (35-74)	18 to 64 years: 48 (37-57)
					Median (IQR): 56 (36-77)	≥65 years: 35 (27-43)
		XBB sublineages and JN.1			Median (IQR): 53 (38-67)	≥18 years: 43 (33-52)
		XBB sublineages			Median (IQR): 31 (22-40)	≥18 years: 50 (35-61)
					14 to 60	≥18 years: 52 (37-63)
		JN.1			14 to 60	≥18 years: 41 (23-54)
					61 to 133 days	≥18 years: 30 (16-41)

					Median (IQR): 75 (55-90)	≥18 years: 33 (22-43)
DeCuir et al. (2024) – United States Report	128,825 immunocompetent adults aged ≥18 years from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)	Omicron	Received an XBB.1.5 variant-adapted vaccine	Did not receive the XBB.1.5 variant adapted vaccine (includes unvaccinated individuals)	Median (IQR): 33 (20-46)	≥18 years: 51 (47-54)
					Median (IQR): 44 (26-64)	≥18 years: 47 (44-50)
					Median (IQR): 74 (66-83)	≥18 years: 39 (33-45)
					Median (IQR): 33 (21-46)	18 to 64 years: 52 (45-58)
					Median (IQR): 46 (27-66)	18 to 64 years: 50 (44-55)
					Median (IQR): 74 (66-83)	18 to 64 years: 45 (34-55)
					Median (IQR): 33 (21-46)	≥65 years: 49 (44-54)
					Median (IQR): 46 (27-66)	≥65 years: 45 (41-49)
					Median (IQR): 74 (66-83)	≥65 years: 37 (29-44)
*Tartof et al. (2023) – United States Preprint	≥18 years who have been at Kaiser Permanente Southern California (KPSC)	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)

	for at least a year (N=24,007)			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)
				Received ≥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)
				Received ≥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 effectiveness (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 (n = 8).

Author (date) - Country Type of publication	Population	Predominant variant	Intervention	Comparator group (reference)	Time since last dose (days)	VE (%) (95% CI)
Retrospective cohort						
Andersson et al. (2024) – Denmark, Sweden and Finland Preprint	≥65 years living in Denmark, Sweden or Finland (N=3,734,896)	Omicron	Received the XBB.1.5 variant adapted vaccine as their 5th dose	Received at least 4 prior doses of COVID-19 vaccine but not an XBB.1.5 variant adapted vaccine	8 to 91	64.6 (51.0-78.1)
			Received the XBB.1.5 variant adapted vaccine as their 6th dose			57.0 (41.6-72.4)
			Received the XBB.1.5 variant adapted vaccine as their 7th dose			44.4 (20.2-68.7)
			Received at least 4 prior doses of COVID-19 vaccine and received an XBB.1.5 variant adapted vaccine			• ≥65 years: 60.6 (46.1-75.1) • 65-74 years: 58.3 (42.1-74.6) • ≥75 years: 62.0 (47.5-76.4)
					8 to 28	65.2 (50.6-79.8)
					29 to 49	63.4 (47.1-79.6)
					50 to 70	35.6 (-15.9-87.0)
					71 to 91	60.2 (45.3-75.0)
					21 to 91	Finland and Denmark: 57.6 (29.8-85.5)
		XBB sublineages			8 to 49	**Hospital admission and death** 73.6 (60.4-86.7)

		BA.2.86 sublineages			8 to 49	**Hospital admission and death** 56.6 (42.8-70.4)
*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						
Caffrey et al. (2024) – United States Preprint	113,174 respiratory infection episodes in adults aged 18+ and diagnosed with an acute respiratory infection in hospital, emergency department, urgent care or outpatient setting from the US Veterans Affairs Healthcare system	Omicron	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive the XBB.1.5 variant adapted vaccine (includes unvaccinated individuals)	Median (IQR): 53 (34-74)	≥18 years: 43 (34-51)
					Median (IQR): 52 (33-73)	Immunocompromised: 33 (16-47)
					Median (IQR): 54 (34-74)	Immunocompetent: 49 (38-58)
					Median (IQR): 50 (34-67)	18 to <65 years: 58 (33-73)
					Median (IQR): 54 (33-74)	≥65 years: 41 (32-50)
		XBB sublineages and JN.1			Median (IQR): 50 (37-65)	≥18 years: 46 (32-58)
		XBB sublineages			Median (IQR): 30 (21-38)	≥18 years: 61 (44-73)
					14 to 60	≥18 years: 62 (44-74)
		JN.1			14 to 60	≥18 years: 32 (3-52)

					61 to 133 days	≥18 years:
					Median (IQR): 73 (53-89)	≥18 years: 35 (20-48)
DeCuir et al. (2024) – United States Report	37,503 immunocompetent adults aged ≥18 years from the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)	Omicron	Receive an XBB.1.5 variant-adapted vaccine	Did not receive the XBB.1.5 variant adapted vaccine (includes unvaccinated individuals)	Median (IQR): 32 (19-45)	≥18 years: 53 (46-59)
					Median (IQR): 42 (24-62)	≥18 years: 52 (47-57)
					Median (IQR): 73 (66-81)	≥18 years: 50 (40-59)
					Median (IQR): 30 (19-44)	18 to <65 years: 42 (14-61)
					Median (IQR): 38 (22-58)	18 to <65 years: 43 (20-59)
					Median (IQR): 74 (67-81)	18 to <65 years: 45 (-6-71)
					Median (IQR): 32 (19-46)	≥65 years: 54 (47-60)
					Median (IQR): 43 (25-62)	≥65 years: 53 (47-58)
					Median (IQR): 73 (66-81)	≥65 years: 50 (39-59)
Link-Gelles et al. (2024) – United States	Immunocompromised adults aged ≥18 years	Omicron	Received an XBB.1.5 variant adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (includes	≥7	36 (25-46)
					7 to 59	38 (23-50)

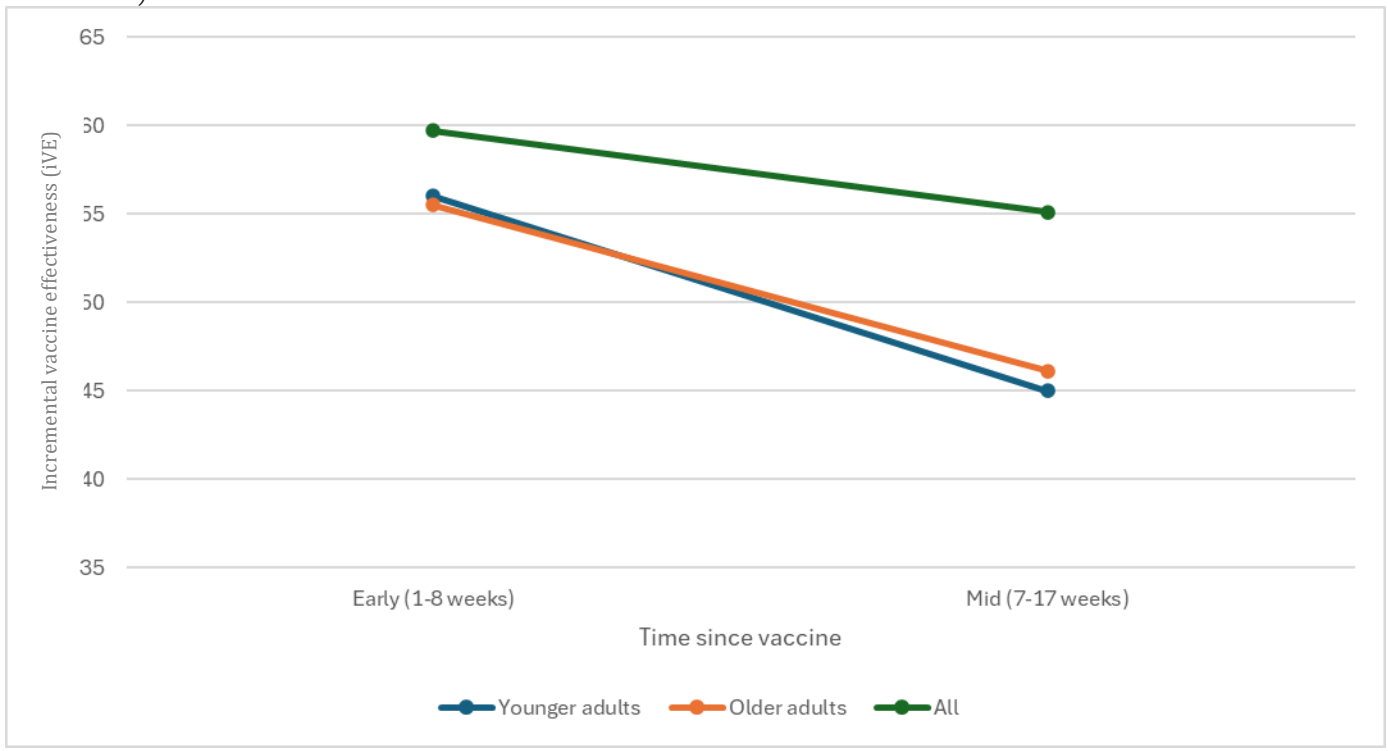
Report	from the VISION Network (N=14,586)			unvaccinated individuals)	60 to 119	34 (16-47)
Kirsebom et al. (2024) – England Peer-review	≥65 years (N=28,916)	Omicron	Received an XBB.1.5 variant adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (includes unvaccinated individuals)	9 to 13	37.4 (17.8-52.3)
					14 to 28	54.8 (46.8-61.6)
					29 to 63	48.3 (41.0-54.7)
					64 to 98	42.2 (32.3-50.6)
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)
				Received ≥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)

				Received ≥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 effectiveness (VE);

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

Figure 2: A visual representation of the trend in incremental vaccine effectiveness (iVE) for **COVID-19-related hospitalisations** of the XBB.1.5 adapted COVID-19 vaccine over time (comparator = those who did not receive the XBB.1.5 vaccine, including unvaccinated individuals).



* The following categories consist of the data from 8 included studies: The early time period covers 7-91 days and includes ranges and median times; the mid time period covers 64-98 days and includes ranges and median times; the younger adults include those who are 18-64; and the older adults include those who are ≥65. A simple averaging of data was applied across studies.

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

Table 4: VE of the XBB.1.5 variant-adapted COVID-19 vaccine against death related to COVID-19 compared with those who did not receive the XBB.1.5 variant-adapted COVID-19 vaccine (n = 1).

Author (date) - Country Type of publication	Population	Predominant variant	Intervention	Comparator group (reference)	Time since last dose (days)	VE (%) (95% CI)
Retrospective cohort						
Andersson et al. (2024) – Denmark, Sweden and Finland Preprint	≥65 years living in Denmark, Sweden or Finland (N=3,734,896)	Omicron	Received the XBB.1.5 variant adapted vaccine as their 5th dose	Received at least 4 prior doses of COVID-19 vaccine but not an XBB.1.5 variant adapted vaccine	8 to 91	77.7(67.5-87.9)
			Received the XBB.1.5 variant adapted vaccine as their 6th dose			76.9 (66.4-87.4)
			Received the XBB.1.5 variant adapted vaccine as their 7th dose			82.1 (68.8-95.5)
			Received at least 4 prior doses of COVID-19 vaccine and received an XBB.1.5 variant adapted vaccine			• ≥65 years: 77.9 (69.2-86.7) • 65-74 years: 77.5 (65.6-89.5) • ≥75 years: 78.0 (69.3-86.8)
					8 to 28	82.7 (79.2-86.2)
					29 to 49	81.3 (67.1-95.4)
					50 to 70	68.8 (39.9-93.8)
					71 to 91	72.3 (60.8-83.8)
					21 to 91	76.2 (64.2-88.2)
		XBB sublineages			8 to 49	**Hospital admission and death** 87.5 (80.3-94.6)
		BA.2.86 sublineages			8 to 49	**Hospital admission and death**

						77.5 (71.4-83.6)

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 the different terms for VE as follows:
  - Absolute VE (aVE) refers to vaccine protection that is estimated by comparing vaccinated individuals with unvaccinated individuals.
  - Relative VE (rVE) refers to vaccine protection that is estimated by comparing individuals who received the vaccine or regimen of interest with those who received a different vaccine or a different vaccine schedule.
  - Incremental VE (iVE) refers to vaccine protection that is estimated by comparing individuals who received more doses with those who received fewer doses.

Risk of bias (RoB) assessment

The risk of bias data for each individual study is provided in the Supplementary File (les21.3_vaccine_effectiveness_XBB15_3_RoB_2024-06-14.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.

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

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