Effectiveness of the Monovalent XBB.1.5 and of the 2024/2025 COVID-19 Vaccines
Living Evidence Synthesis #21
(Version 21.4: 21 October 2024)

Questions

What is the added protection (VE ≥7 days post vaccination and over time) conferred by any 2023/2024 monovalent XBB.1.5-containing vaccine or the 2024/2025 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;
- Individuals with immunocompromising conditions; 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 2023/2024 monovalent XBB.1.5 vaccine or the 2024/2025 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 2023/2024 monovalent XBB.1.5 vaccine or the 2024/2025 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 2024/2024 monovalent XBB.1.5 vaccine or the 2024/2025 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, and June 11th , 2024, a second and third round of searches were completed, respectively. By the fourth round (search date: October 1st, 2024) a total of 308 articles were title and abstract screened, 60 were full text appraised, with 23 initially included, 7 of these were excluded due to having a critical risk of bias (RoB; see **Appendix 1b)**, leaving 16 that were used to complete this summary. The reasons for excluding the 37 studies are reported in **Appendix 7b.** In addition, 172 records were identified through hand search, of which 88 were full text screened. Six studies were first included but one was later excluded due to having a critical risk of bias (RoB; see **Appendix 1b),** leaving 5 included studies through hand search. The reasons for excluding the 82 studies are reported in **Appendix 7b** as well. Therefore, a total of 21 studies are included in this summary, including an update of a previously included study.

High level summary for COVID-19 outcomes

COVID-19-related 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**, in the early (ca. 1-10 weeks) post vaccination period, overall incremental vaccine effectiveness [iVE] for **medically attended infections** is generally around 55%. In the mid (ca. 8-17 weeks) post vaccination period, iVE drops to around 48%. There is currently no consistent difference in protection between younger (<65 years) and older (≥ 65 years) adults.

- Four studies were included for **medically attended infections**.
    - 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 group (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%) while 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 with older adults (≥50 years = 46%).

- One test-negative case-control study (Tartof et al. (2023)*) of US adults found a moderate level of protection at a median of 30 days post vaccination (iVE = 58%) while 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 with younger adults (18-64 years = 32%).
- One test-negative case-control study from six university hospitals in South Korea (Lee et al. (2024)) found that adults aged ≥18 years who had received an mRNA 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 7-59 days post vaccination (iVE= 57.7%) while omicron sub variants were predominant (primarily XBB, EG.5.1, HK.3 and JN). The iVE was slightly higher in older adults (≥65 years = 60.2%).

Three studies were included for **any SARS-CoV-2 infection**.

- One study measured *self-reported symptomatic SARS-CoV-2 infection*.
  - A 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, iVE = 34.7%) than older adults (60-85 years, iVE = 55.0%) while XBB sublineages and JN.1 were predominant.
- Two studies measured *PCR confirmed SARS-CoV-2 infection*, with the majority, but not all, being symptomatic.
  - A prospective cohort study from the US (Shrestha et al. (2024)) found that the XBB.1.5 variant-adapted vaccine offered greater protection against infection before JN.1 became the dominant variant (iVE= 42%) than after it became dominant (iVE= 19%) when measured at least 7 days post vaccination.
  - A retrospective cohort study (Lin et al. (2024)) reported on individuals of all ages living in the US. Overall, the XBB.1.5 variant-adapted vaccine offered greater protection against the XBB.1.5 variant (iVE at 28-34 days = 64.4%) than the JN.1 variant (iVE at 28-34 days= 44.3%). The study also found that the iVE reached a peak at 4 weeks (iVE=52.2%) and waned after that (24-week iVE=16.4%).
- One study measured COVID-19 from any EHR or medical claim with either a COVID-19 diagnosis or positive laboratory test result
  - A retrospective cohort study from the US (Kopel et al. (2024)) found that the Moderna mRNA XBB.1.5 variant-adapted vaccine offered some protection against infections in adults (iVE=33.1%) and in adults with medical conditions (iVE=34.5%) when measured at least 7 days post vaccination while omicron sublineages were predominant (primarily XBB, EG.5.1 and JN). The protection offered by the vaccine did not differ with age (≥18 years, ≥50 years, and ≥65 years).

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

- Two studies were included for **medically attended infections**.
  - 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 iVE being around 55% with younger individuals (18-64 years) having less protection (iVE = 22-40%) than older adults (≥65 years: iVE = 65-71%) while omicron sublineages were predominant (primarily XBB, EG.5.1 and JN).

- One test-negative case-control study from six university hospitals in South Korea (Lee et al. (2024)) found that adults aged ≥18 years who had received an mRNA XBB.1.5 COVID-19 vaccine and at least one previous COVID-19 vaccine dose were less likely to have a medically attended infection compared with those who had not received the XBB.1.5 COVID-19 vaccine but had received at least one dose of a COVID-19 vaccine. The authors found a moderate level of protection 7-59 days post vaccination (iVE= 55.6%) while omicron sub variants were predominant (primarily XBB, EG.5.1, HK.3 and JN). The iVE was slightly higher in older adults (≥65 years = 57.6%). The protection was also higher in adults without immunocompromising conditions (iVE= 57.7%) than in adults with immunocompromising conditions (iVE= 47.6%).

- One study measured **PCR confirmed SARS-CoV-2 infections**, with the majority, but not all, being symptomatic.
  - A retrospective cohort study (Chong et al. (2024)) from Singapore found an iVE of 41% against the JN.1 variant 8 to 120 days after the receival of an mRNA XBB.1.5 variant-adapted vaccine in individuals who received at least three previous mRNA doses when compared to individuals who had also received at least three mRNA vaccine doses but no XBB.1.5 variant-adapted vaccine.
- One study measured iVE against **PCR confirmed SARS-CoV-2 infection, including both symptomatic and mild/asymptomatic infections**.
  - A prospective cohort study (Kirwan et al. (2024)) found that in health care professionals (HCPs) the XBB.1.5 variant-adapted vaccine offered less protection against mild or asymptomatic infection (iVE= 12.0-17.8%) than symptomatic infection (iVE= 36.8-64.8%) in individuals who received at least three previous COVID-19 vaccine doses (but no more than five) when compared to individuals who have also received at least three COVID-19 vaccine doses (but no more than five) but not the XBB.1.5 variant-adapted vaccine while omicron sublineages were predominant (primarily XBB, JN, EG.5.1 and BA).

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

- Two test-negative case-control studies were included for **medically attended infections**.
  - The Tartof et al. (2023)* study in the US 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 aVE = 43%) while omicron sublineages were predominant (primarily XBB, EG.5.1 and JN). 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 finding was not statistically significant.
  - Another test-negative case-control study from six university hospitals in South Korea (Lee et al. (2024)) found that adults aged ≥18 years who had received an mRNA XBB.1.5 COVID-19 vaccine were less likely to have a medically attended infection compared with those who had not received any COVID-19 vaccine. The authors found a moderate level of protection 7-59 days post vaccination (aVE= 65.2%) while omicron sub variants were predominant (primarily XBB, EG.5.1, HK.3 and JN). The aVE was slightly higher in older adults (≥65 years = 67.2%). A median of 25.5 days post vaccination, the aVE was 71.0%.

* The Tartof et al. data reported here is from a pre-print that eventually became a published paper, but this data was not included in the final publication.

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

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

- Three test-negative case-control studies from the US were included.
    - One study (Caffrey et al. (2024)) found that 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 who had immunocompromising conditions had a lower iVE vs. those without immunocompromising conditions (34% vs. 42%). Older individuals had a lower iVE compared to young 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. (2024)) found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine had a 14-60 day iVE of 52% for COVID-19-related ED or UC visits during the JN.1 sublineage dominant period that dropped notably between 60 and 156 days (iVE = 34%), compared with those who had not received any XBB.1.5 vaccine (including unvaccinated individuals). During the XBB sublineage predominant period, the iVE was 59% 14-60 days post vaccination, dropping to an iVE of 39% at 60-128 days post vaccination.
    - 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%) while omicron sublineages were predominant (primarily XBB, EG.5.1 and JN). In general, there were no differences in iVE by age group (18-64 years vs. ≥65 years).

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

- One study from Singapore was included
    - The Chong et al. (2024) study, a retrospective cohort , found an iVE of 50% against the JN.1 variant 8 to 120 days after the receival of an mRNA XBB.1.5 variant-adapted vaccine in individuals who received at least three previous mRNA doses when compared to individuals who have also received at least three mRNA vaccine doses but no XBB.1.5 variant-adapted vaccine.

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

- No studies were included

COVID-19-related hospitalisations

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

As shown in **Figure 2**, overall, in the early (ca. 1-13 weeks) post vaccination period, incremental vaccine effectiveness [iVE] is generally between 50 and 60%. In the mid (ca. 8-26 weeks) post vaccination period, iVE drops slightly to between 45 and 55%. There is no consistent difference between younger (< 65 years) and older (≥ 65 years) adults, though it should be noted that there are limited studies that directly compare these groups and few studies that report on younger adults.

- Seven test-negative case-control studies (four from the US, one from England, one from South Korea and one multi-country study from Europe) and two retrospective study from the US were included.
    - One US study (Caffrey et al. (2024)) found that adults aged ≥18 years who had received the Pfizer-BioNTech 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). Individuals with immunocompromising conditions had a lower iVE vs. those who did not have immunocompromising conditions (33% vs. 49%). iVE was lower in older individuals 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. (2024)) found that adults aged ≥18 years who had received the Pfizer-BioNTech XBB.1.5 COVID-19 vaccine had a 14-60 day iVE of 50% for COVID-19-related hospitalisations during the JN.1 sublineage dominant period. Protection remained relatively stable between 60 and 156 days post vaccination (iVE = 57%) compared with those who had not received any XBB.1.5 vaccine (including unvaccinated individuals). During the XBB sublineage predominant period, the iVE was 74% 14-60 days post vaccination.
- One US study (DeCuir et al. (2024)) found that the mRNA and Novavax XBB.1.5 variant-adapted vaccines provided protection against COVID-19-related hospitalisation 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%) while omicron sublineages were predominant (primarily XBB, EG.5.1 and JN). In general, there were no differences in iVE 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 was 37%, increasing to around 55% 14-28 days post-vaccination, and then dropping to 42% at 64-98 days post-vaccination while omicron sublineages were predominant (primarily XBB, JN, EG.5.1 and BA).
- One US study (Link-Gelles et al. (2024)) found that the mRNA and Novavax XBB.1.5 variant-adapted vaccines provided some protection against COVID-related hospitalisations in adults aged ≥18 years with immunocompromising conditions 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) while the omicron XBB sublineages and JN.1 were predominant. 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%).
- One test-negative case-control study from six university hospitals in South Korea (Lee et al. (2024)) found that adults aged ≥18 years who had received an mRNA XBB.1.5 COVID-19 vaccine were less likely to be hospitalised because of COVID-19 compared with those who had not received the XBB.1.5 COVID-19 vaccine. The authors found a moderate level of protection 7-59 days post vaccination (iVE= 64.3%) while omicron sub variants were predominant (primarily XBB, EG.5.1, HK.3 and JN). The iVE was slightly higher in older adults (≥65 years = 66.5%)
- One test negative case-control study from Belgium, Germany, Italy, and Spain (Nguyen et al. (2024)) found that in adults aged ≥18 years old, the Pfizer-BioNTech XBB1.5-adapted vaccine offered moderate protection against COVID-19-related hospitalisations ≥14 days after vaccination (iVE= 54.8%) when compared to individuals who had not received an XBB.1.5 variant-adapted vaccine during the JN.1 predominance period. The iVE was similar in individuals who had immunocompromising conditions or had cancer (iVE= 56.0%) and varied slightly with age: 18 to <65 years (55.8%), 65 to 79 years (63.6%) and ≥80 years (49.8%). The protection was still moderate after 112-153 days in adults aged ≥18 years (iVE= 59.9%).
- One retrospective cohort study from the US (Kopel et al. (2024)) found that the Moderna mRNA XBB.1.5 variant-adapted vaccine offered a moderate level of protection against COVID-19 related hospitalisations in adults (iVE=60.2%) and in adults with medical

conditions (iVE=58.7%) when measured at least 7 days post vaccination while omicron sublineages were predominant (primarily XBB, EG.5.1 and JN). The protection offered by the vaccine did not differ with age (≥18 years, ≥50 years, and ≥65 years).

- One retrospective cohort study (Lin et al. (2024)) reported on individuals of all ages living in the US. Overall, the XBB.1.5 variant-adapted vaccine offered greater protection against the XBB.1.5 variant (iVE at 28-34 days: 73.7%) than the JN.1 variant (iVE at 28-34 days: 60.1%) when compared to individuals who had not received the XBB.1.5 variant-adapted vaccine. The study also found that protection waned over time and that it took four weeks to reach peak protection.

*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 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 (iVE = 50.9-55.4%) when compared to individuals who had not received an XBB.1.5 variant-adapted vaccine but previously received at least one BA.1 bivalent dose .
  - One retrospective cohort study (Hansen et al. (2024)) of individuals aged ≥65 years in Denmark found a high level of protection ≥7 days post mRNA XBB.1.5 vaccination during XBB sublineage and EG.5.1 predominance (iVE = 76.1%) when compared to individuals who had not received an XBB.1.5 variant-adapted vaccine but previously received the seasonal booster the previous winter (2022/2023).
  - One test negative case-control study from Belgium, Germany, Italy, and Spain (Nguyen et al. (2024)) found that in adults aged ≥18 years old, the Pfizer-BioNTech XBB1.5-adapted vaccine offered moderate protection against COVID-19-related hospitalisations ≥14 days after (iVE= 61.0%) when compared to individuals who had not received an XBB.1.5 variant-adapted vaccine but received at least one BA.4/5 bivalent dose during the JN.1 predominance period.

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

- Five 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.
  - A multicounty European retrospective cohort study (Andersson et al. (2024)) of older individuals (≥65 years) found that the mRNA XBB.1.5 variant-adapted vaccines provided additional protection 8-91 days post-vaccination compared to having had four (rVE=65%), five (rVE=57%), or six (rVE=44%) prior doses of a non-XBB.1.5 variant-adapted vaccine while omicron sublineages were predominant (primarily XBB, EG.5.1, HK.3 and JN).
  - The Chong et al. (2024) study, a retrospective cohort from Singapore, found an iVE of 42% against the JN.1 variant 8 to 120 days after the receival of an mRNA XBB.1.5 variant-adapted vaccine in individuals who received at least two previous mRNA doses when compared to individuals who have also received at least three mRNA vaccine doses but no XBB.1.5 variant-adapted vaccine.
  - The Nunes et al. (2024) study, a multi-country European retrospective cohort, found an iVE of any XBB.1.5 vaccine (>95% Pfizer-BioNTech) of 50.2% in 65-79 year olds and 40.7% in ≥80-year-olds after at least 14 days when compared to individuals who had received at least two COVID-19 vaccine doses while BA.2.86 and JN.1 sublineages were predominant. The protection waned over time and was lower for older individuals.
  - One test-negative case-control study from six university hospitals in South Korea (Lee et al. (2024)) found that adults aged ≥18 years who had received an mRNA XBB.1.5 COVID-19 vaccine and at least one previous COVID-19 vaccine dose were less likely to have a medically

attended infection compared with those who had not received the XBB.1.5 COVID-19 vaccine but had received at least one dose of a COVID-19 vaccine. The authors found a moderate level of protection 7-59 days post vaccination (iVE= 61.2%) while omicron sub variants were predominant (primarily XBB, EG.5.1, HK.3 and JN). The iVE was slightly higher in older adults (≥65 years = 64.1%). The protection was also higher in individuals with immunocompromising conditions (iVE= 79.4%) than in those without (iVE= 56.4%).
    - One test negative case-control study from Belgium, Germany, Italy, and Spain (Nguyen et al. (2024)) found that in adults aged ≥18 years old the Pfizer-BioNTech XBB1.5-adapted vaccine offered moderate protection against COVID-19-related hospitalisations ≥14 days after vaccination (rVE= 48.8%) when compared to individuals who had not received an XBB.1.5 variant-adapted vaccine but received two mRNA wild-type doses only during the JN.1 predominance period.

*XBB.1.5 vaccination **vs.** Unvaccinated*

- Two test-negative 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 test-negative case-control study from six university hospitals in South Korea (Lee et al. (2024)) found that adults aged ≥18 years who had received an mRNA XBB.1.5 COVID-19 vaccine were less likely to be hospitalised due to COVID-19 compared with those who never received a COVID-19 vaccine. The authors found a good level of protection 7-59 days post vaccination (aVE= 77.3%) while omicron sub variants were predominant (primarily XBB, EG.5.1, HK.3 and JN). The aVE was slightly lower in older adults (≥65 years = 72.8%).
    - One test negative case-control study from Belgium, Germany, Italy, and Spain (Nguyen et al. (2024)) found that in adults aged ≥18 years, the Pfizer-BioNTech XBB1.5-adapted vaccine offered some protection against COVID-19-related hospitalisations after ≥14 days (aVE= 51.1%) when compared to individuals who never received a COVID-19 vaccine during the JN.1 predominance period.

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

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

COVID-19-related deaths

As shown in **Figure 3**, in the early (ca. 1-13 weeks) post vaccination period, overall incremental vaccine effectiveness [iVE] is generally between 70 and 75%. In the mid (ca. 10-20 weeks) post vaccination period, there is a slight drop in iVE in older adults (≥ 65 years) to 63%. In contrast, there is a notable drop in protection in the general adult population (≥ 18 years) to 38%. There were no available data for a younger population (18-64 years). These patterns need to be interpreted with caution given the limited available data (e.g., there is only one study in the general population).

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

- One retrospective cohort study in the US reported on this outcome.
    - (Lin et al. (2024)) reported on individuals of all ages living in the US. Overall, the mRNA XBB.1.5 variant-adapted vaccines offered greater protection against the XBB.1.5 variant (iVE at 28-34 days = 86.2%) than the JN.1 variant (iVE at 28-34 days = 59.8%) when compared to individuals who had not received the XBB.1.5 variant-adapted vaccine. The study also found that the iVE waned overtime and took a few weeks before reaching peak protection at week 4.

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

- One retrospective cohort study from Europe reported on this outcome.
    - A multicountry 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 four prior doses of COVID-19 vaccine (iVE = 78%). iVE slowly declined across the post-vaccination period (8–28-day iVE = 83% and 71-91 days iVE = 72%) while omicron sublineages were predominant (primarily XBB, EG.5.1, HK.3 and JN).

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

- Three retrospective studies (two European and one from Australia) reported on this outcome.
    - A European retrospective cohort study (Andersson et al. (2024)) 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 four (rVE=78%), five (rVE=77%), or six (rVE=82%) prior doses of a non-XBB.1.5 variant-adapted vaccine while omicron sublineages were predominant (primarily XBB, EG.5.1, HK.3 and JN).
    - An Australian retrospective cohort study (Liu et al. (2024)) found that in individuals aged ≥65 years who received at least one COVID-19 vaccine booster dose, an mRNA XBB.1.5 variant-adapted vaccine offered additional protection against COVID-19-related mortality 8-90 days post vaccination (iVE= 74.7%) compared to having received a booster vaccine at least one year earlier and no XBB.1.5 vaccine. The protection offered did not differ during the JN.1 period (iVE= 74.6%) and was slightly higher in older individuals ≥75 years (iVE= 76.7%).
    - A multi-country European retrospective cohort study by Nunes et al. (2024) found an iVE of 57.5% in individuals 65-79 years old and 48.4% in individuals ≥80 years old after at least 14 days when compared to individuals who had received at least two COVID-19 vaccine doses while BA.2.86 and JN.1 sublineages were predominant. This protection waned over three to six months and was lower for older individuals.

Multisystem inflammatory syndrome in children (MIS-C)

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

Post-COVID Conditions

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

Potential implications for health systems decision-making

The limited initial evidence from four 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 crude early phase (1-10 weeks post-vaccination) iVE average was around 55%, and there was a general waning of effectiveness over time (ca. iVE=48% 11-17 weeks post-vaccination). iVE was consistent between age groups.

The initial evidence from eleven studies from a variety of different countries (though there were no Canadian data) suggests a **moderate benefit of the XBB.1.5 vaccine** against COVID-19-related **hospitalisations**. Initial iVE was around 50-60% (8-90 days post-vaccination) which dropped to about 45-55% (64-179 days).

The limited initial evidence from four studies from a variety of different countries (though there were no Canadian data) suggests a **relatively strong benefit of the XBB.1.5 vaccine** against COVID-19-related

deaths, especially in older adults (≥ 65 years). Initial iVE was around 70-75% (8-90 days post-vaccination) which dropped to about 65% (71-179 days) in older adults and to 38% (133-139 days) in the general population (≥ 18 years). However, it should be noted that the general population data are from only one study.

These findings were relatively consistent no matter what the comparator group was, meaning that the XBB.1.5 vaccines seem to provide notable benefit no matter what an individual's previous vaccination or infection pattern was. Unsurprisingly, the 2023/2024 COVID-19 vaccines may offer additional benefit against XBB sublineages vs. JN.1 sublineages, though there are limited comparative data to confirm this observation.

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, hospitalisations, and deaths**.

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. It should also be noted that it is not possible to get a 'pure' VE measure as most included individuals had previous vaccinations as well as there being high rates of infection-induced immunity in most populations. Additionally, these were not randomised controlled studies as individuals chose to get vaccinated. It is possible that those individuals who willingly got vaccinated 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						
Lee et al. (2024) – South Korea Peer-reviewed	Adults aged ≥18 year who underwent PCR testing or rapid antigen testing in the emergency department, outpatient clinics, general wards, or intensive care units of each hospital were included in the study. (N=5,516)	Omicron (primarily XBB, EG.5.1, HK.3 and JN sub variants)	Received an mRNA XBB.1.5 variant-adapted vaccine	Unvaccinated individuals	7 to 59	**Medically attended infections:** • ≥18 years: 65.2 (36.1-81.0) • ≥ 65 years: 67.2 (34.3-83.6)
					Median of 25.5	**Medically attended infections** • ≥18 years: 71.0 (44.6-84.8)
				Did not receive the XBB.1.5 vaccine (includes unvaccinated individuals)	7 to 59	**Medically attended infections** • ≥18 years: 57.7 (34.7-72.6) • ≥ 65 years: 60.2 (35.6-75.4)
				Did not receive the XBB.1.5 vaccine but have received at least one dose of COVID-19 vaccine	7 to 59	**Medically attended infections** • ≥18 years: 55.6 (31.2-71.3) • Immunocompromised: 47.6 (-43.6-80.9) • Immunocompetent: 57.7 (31.0-74.1)

						• ≥ 65 years: 57.6 (30.9-74.0)
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 COVID-19 control group	Did not receive the XBB.1.5 vaccine – Excluding influenza positive cases from the COVID-19 control group (includes unvaccinated individuals)	Median (IQR): 35 (21-56)	**Medically attended infections:** ≥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 (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 This outcome was not reported in the updated article Tartof et al. (2024)	≥18 years who have been at Kaiser Permanente Southern California (KPSC) for at least a year (N=24,007)	Omicron (primarily XBB, EG.5.1 and JN)	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)

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

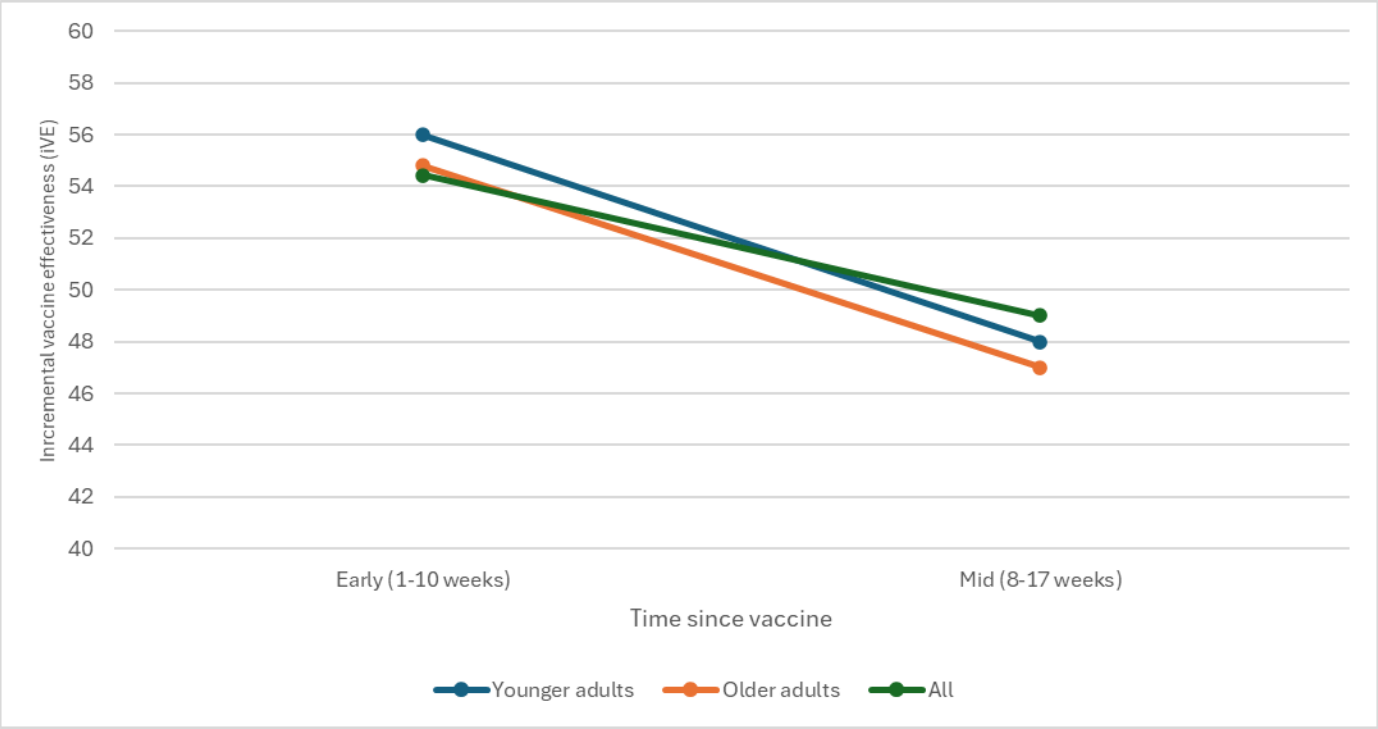

Figure 1: A visual representation of the trend in incremental vaccine effectiveness (iVE) for **medically attended infections** of the XBB.1.5 adapted COVID-19 vaccine over time (comparator = those who did not receive the XBB.1.5 vaccine, including unvaccinated individuals).

* The following categories consist of the data from the 4 included studies: The early time period covers the 7-73 days and medians of 30-42 days; the mid time period covers 60-119 days (there is only 1 study that provides 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.

Table 2: VE of the XBB.1.5 variant-adapted COVID-19 vaccine against COVID-19 infections compared with those who have not received the XBB.1.5 variant-adapted COVID-19 vaccine (n=6).

Author (date) - Country **Type of publication**	**Population**	**Predominant variant**	**Intervention**	**Comparator group (reference)**	**Time since last dose (days)**	**VE (%) (95% CI)**
Prospective cohort						
Huiberts et al. (2024) – Netherlands Peer-reviewed This study was not included in the figure above as it reports on self-reported infections.	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 infections** • 18 to 59 years: 41.3 (22.6-55.5) • 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	Did not have any prior infection and received a booster	≥7	**Self-reported infections**

			Pfizer-BioNTech XBB.1.5 variant-adapted vaccine	dose but did not receive an XBB.1.5 variant-adapted vaccine		• 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 Pfizer-BioNTech XBB.1.5 variant-adapted vaccine			**Self-reported infections** • 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)
Kirwan et al. (2024) - United Kingdom Peer-reviewed This study was not included in the figure above as it reported on positive PCR test regardless of the presence of symptoms or the	Health care workers of the NHS, part of the SIREN study, who received their last COVID-19 booster more than 6 months ago, contributed at least 2 PCR tests to the study and did not receive more than 5 COVID-19 doses.	Omicron (primarily XBB, JN, EG.5.1 and BA)	Received the XBB.1.5 variant-adapted vaccine and at least one previous booster (maximum of 5 previous COVID-19 vaccine doses)	Received at least one booster (maximum of 5 COVID-19 vaccine doses) and did not receive the XBB.1.5 variant-adapted vaccine	61 to 122	**Positive PCR test:** 24.1 (-0.7-42.9) • Symptomatic: 36.8 (6.3-57.4) • Mild/asymptomatic: 12 (-26.4-38.8)
					123 to 183	**Positive PCR test:** 26.7 (-27.5-57.9) • Symptomatic: 64.8 (8.5-86.5) • Mild/asymptomatic: -17.8 (-122.1-37.5)

receival of medical attention.	(N=2,867)					
Shrestha et al. (2024)– USA (Ohio) Peer-reviewed This study was not included in the figure above as it reported on positive NAAT that were performed routinely as part of the study.	Cleveland Clinic Health System (CCHS) employees in employment at any Cleveland Clinic location in Ohio on 10 October 2023, the day the 2023–2024 formulation of the COVID-19 vaccine was available to employees at Cleveland Clinic, were included in the study. (N=48,210)	Omicron (before JN.1 lineages become pre-dominant)	Received an mRNA XBB.1.5 variant-adapted vaccine	Did not receive the XBB.1.5 variant-adapted vaccine (include unvaccinated individuals)	≥7	**Positive NAAT for SARS-CoV-2 any time after the study start date**: 42 (32-51)
		Omicron (after JN.1 lineages become pre-dominant)				**Positive NAAT for SARS-CoV-2 any time after the study start date:** 19 (-1-35)
Retrospective cohort						
*Chong et al. (2024) – Singapore Peer-reviewed This study was not included in the figure above as it reported on positive PCR or rapid antigen test regardless of the presence of symptoms or receival of medical attention.	Adult aged ≥18 years who did not receive non-mRNA COVID-19 vaccines, and who were boosted (received ≥3 mRNA COVID-19 vaccine doses) before study start date (N=3,086,562)	JN.1	Received an mRNA XBB.1.5 variant-adapted vaccine and at least one previous mRNA booster	Received at least one mRNA booster and did not receive the XBB.1.5 variant-adapted vaccine	8 to 120	**Positive PCR or rapid antigen test:** 41 (34-48) • Previous COVID-19 infection: 44 (33-53)

Kopel et al. (2024) – US Pre-print This study was not included in the figure above as it included laboratory results in its definition regardless of the presence of symptoms	Adult aged ≥18 years from the Veradigm Network (EHR linked to healthcare claims sourced from Komodo Health). Individuals were required to have continuous enrollment in medical and pharmacy claims from September 12, 2022, through 7 days after the index date. (N=1,718,670)	Omicron (primarily XBB, EG.5.1 and JN)	Received a dose of the Moderna mRNA XBB.1.5 variant adapted vaccine	Did not receive an XBB.1.5 variant adapted vaccine	Median (IQR): 63 (44-78)	Any COVID-19 infections • ≥18 years: 33.1 (30.2-35.9)
					Median (IQR): 64 (45-78)	Any COVID-19 infections • ≥18 years with medical conditions: 34.5 (31.2-37.6)
					Median (IQR): 64 (45-78)	Any COVID-19 infections • ≥50 years: 35.3 (32.2-38.2)
					Median (IQR): 65 (46-79)	Any COVID-19 infections • ≥65 years: 38.7 (35.4-41.9)
Lin et al. (2024) – United states (Nebraska) Peer-reviewed This study was not included in the figure above as it reported on positive PCR test regardless of the presence of symptoms (even though most were symptomatic)or the receival of medical attention.	Individuals of all ages whose information is available in the Nebraska Electronic Disease Surveillance System and the Nebraska State Immunization Information System (NESIIS) (N=1,830,088)	XBB.1.5 or JN.1	Received an XBB.1.5 variant-adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (include unvaccinated individuals)	**Positive PCR test. Individuals were generally symptomatic, but not all.**	
					7 to 13	16.8 (13.7-19.8)
					14 to 20	30.8 (25.6-35.7)
					21 to 27	42.5 (35.8-48.5)
					28 to 34	52.2 (44.6-58.7)
					35 to 41	45.0 (40.2-49.5)
					42 to 48	36.9 (30.2-42.9)
					49 to 55	35.8 (29.9-41.3)
					56 to 62	34.7 (29.5-39.6)
					63 to 69	33.7 (28.9-38.1)
					70 to 76	32.6 (28.1-36.8)
					77 to 83	31.4 (27.0-35.6)
					84 to 90	30.3 (25.5-34.8)
					91 to 97	29.1 (23.8-34.1)
					98 to 104	28.0 (21.8-33.7)

					105 to 111	26.8 (19.5-33.3)
					112 to 118	25.5 (17.1-33.1)
					119 to 125	24.3 (14.6-32.9)
					126 to 132	23.0 (11.9-32.7)
					133 to 139	21.8 (9.1-32.6)
					140 to 146	20.4 (6.2-32.5)
					147 to 153	19.1 (3.2-32.4)
					154 to 160	17.8 (0.1-32.4)
					161 to 167	16.4 (-3.2-32.3)
		XBB.1.5			**Positive PCR test. Individuals were generally symptomatic, but not all.**	
					7 to 13	22.7 (17.6-27.5)
					14 to 20	40.3 (32.2-47.5)
					21 to 27	53.9 (44.1-61.9)
					28 to 34	64.4 (54.0-72.4)
					35 to 41	57.1 (50.7-62.7)
					42 to 48	48.5 (40.7-55.2)
					49 to 55	46.7 (39.6-52.9)
					56 to 62	44.8 (38.5-50.5)
					63 to 69	42.9 (37.1-48.2)
					70 to 76	40.9 (35.6-45.8)
					77 to 83	38.9 (33.8-43.6)
					84 to 90	36.8 (31.6-41.6)
					91 to 97	34.6 (29.0-39.8)
					98 to 104	32.3 (25.9-38.2)
					105 to 111	30.0 (22.5-36.7)
					112 to 118	27.6 (18.7-35.4)
					119 to 125	25.0 (14.6-34.2)
					126 to 132	22.4 (10.2-33.1)
		JN.1			**Positive PCR test. Individuals were generally symptomatic, but not all.**	

					7 to 13	13.6 (9.7- 17.4)
					14 to 20	25.4 (18.4-31.7)
					21 to 27	35.5 (26.3-43.6)
					28 to 34	44.3 (33.5-53.4)
					35 to 41	34.8 (27.3-41.6)
					42 to 48	23.8 (11.4-34.4)
					49 to 55	22.2 (11.8-31.4)
					56 to 62	20.6 (11.6-28.7)
					63 to 69	19.0 (10.6-26.6)
					70 to 76	17.4 (8.5-25.4)
					77 to 83	15.7 (5.3-24.9)
					84 to 90	13.9 (1.3-25.0)

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

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

Table 3: 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 = 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						
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 (primarily XBB, EG.5.1 and JN)	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. (2024) – United States Peer-reviewed	≥18 years who have been at Kaiser Permanente Southern California (KPSC)	Omicron	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine (including unvaccinated individuals)	Median of 59	≥18 years: 40 (34-45)
		JN.1 sublineages			Median of 59	≥18 years: 41 (32-49)
					14 to <60	≥18 years: 52 (39-61)
					60 to 156	≥18 years: 34 (22-44)
		XBB sublineages			Median of 52	≥18 years: 55 (45-64)

	for at least a year (N=52,036)				14 to <60	≥18 years: 59 (48-68)
					60 to 128	≥18 years: 39 (10-59)
Retrospective cohort						
**Chong et al. (2024) – Singapore Peer-reviewed	Adult aged ≥18 years who did not receive non-mRNA COVID-19 vaccines, and who were boosted (received ≥3 mRNA COVID-19 vaccine doses) before study start date (N=3,086,562)	JN.1	Received an mRNA XBB.1.5 variant-adapted vaccine and at least one previous mRNA booster	Received at least one mRNA booster and did not receive the XBB.1.5 variant-adapted vaccine	8 to 120	• Overall: 50 (27-66) • Previous COVID-19 infection: 22 (-43-57)

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

** The primary article presented outcomes in the form of hazard ratio (HR) 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 4: 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 = 14).

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 (XBB, EG.5.1, HK.3 and JN)	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)
*Chong et al. (2024) – Singapore Peer-reviewed This study was not included in the figure below as it reported for the VE after 8 to 120 days, which included both early and mid-times	Adult aged ≥18 years who did not receive non-mRNA COVID-19 vaccines, and who were boosted (received ≥3 mRNA COVID-19 vaccine doses) before study start date (N=3,086,562)	JN.1	Received an mRNA XBB.1.5 variant-adapted vaccine and at least one previous mRNA booster	Received at least one mRNA booster and did not receive the XBB.1.5 variant-adapted vaccine	8 to 120	• Overall: 42 (9-63) • Previous COVID-19 infection: 43 (3-67)
*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)
Kopel et al. (2024) – US Pre-print	Adult aged ≥18 years from the Veradigm Network EHR linked to healthcare claims sourced from Komodo Health. Individuals were required to have continuous enrollment in medical and pharmacy claims from September 12, 2022, through 7 days after the index date. (N=1,718,670)	Omicron (primarily XBB, EG.5.1 and JN)	Received a dose of the Moderna mRNA XBB.1.5 variant adapted vaccine	Did not receive an XBB.1.5 variant adapted vaccine	Median (IQR): 63 (44-78)	≥18 years: 60.2 (53.4-66.0)
					Median (IQR): 64 (45-78)	≥18 years with medical conditions: 58.7 (51.3-65.0)
					Median (IQR): 64 (45-78)	≥50 years: 61.1 (54.3-66.9)
					Median (IQR): 65 (46-79)	≥65 years: 60.5 (53.3-66.6)
					7 to 13	24.1 (16.7-30.9)

Lin et al. (2024) – United states (Nebraska) Published	Individuals of all ages whose information is available in the Nebraska Electronic Disease Surveillance System and the Nebraska State Immunization Information System (NESIIS) (N=1,830,088)	XBB.1.5 or JN.1	Received an XBB.1.5 variant-adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (includes unvaccinated individuals)	14 to 20	42.4 (30.5-52.2)
					21 to 27	56.3 (42.1-66.9)
					28 to 34	66.8 (51.7-77.1)
					35 to 41	65.3 (52.5-74.7)
					42 to 48	63.8 (52.6-72.4)
					49 to 55	62.3 (51.7-70.6)
					56 to 62	60.6 (49.4-69.4)
					63 to 69	58.9 (45.6-69.0)
					70 to 76	57.1 (40.4-69.2)
					77 to 83	55.3 (34.0-69.7)
					84 to 90	53.3 (26.3-70.5)
					91 to 97	51.3 (17.3-71.3)
					98 to 104	49.2 (7.0-72,2)
					105 to 111	47.0 (-4.8-73.2)
					112 to 118	44.7 (-18.3-74.1)
					119 to 125	42.3 (-33.6-75.1)
					126 to 132	39.8 (-51.0-76.0)
					133 to 139	37.1 (-70.8-76.9)
		XBB.1.5			7 to 13	28.4 (18.3-37.3)
					14 to 20	48.7 (33.2-60.7)
					21 to 27	63.3 (45.4-75.3)
					28 to 34	73.7 (55.4-84.5)
					35 to 41	71.7 (55.7-81.9)
					42 to 48	69.6 (55.5-79.2)
					49 to 55	67.2 (54.6-76.3)
					56 to 62	64.7 (52.4-73.8)
					63 to 69	62.0 (48.5-72.0)
					70 to 76	59.1 (42.4-71.0)
					77 to 83	56.0 (34.2-70.6)
					84 to 90	52.7 (23.7-70.6)
					91 to 97	49.0 (10.7-70.9)

					98 to 104	45.1 (-5.0-71.3)
					105 to 111	40.9 (-23.8-71.8)
		JN.1			7 to 13	20.5 (8.8-30.7)
					14 to 20	36.9 (16.9-52.0)
					21 to 27	49.8 (24.2-66.8)
					28 to 34	60.1 (30.9-77.0)
					35 to 41	56.8 (33.5-71.9)
					42 to 48	53.1 (28.6-69.2)
					49 to 55	49.2 (14.0-70.0)
					56 to 62	44.9 (-10.4-72.5)
					63 to 69	40.3 (-45.9-75.6)
Nunes et al. (2024) - Belgium, Denmark, Italy, Navarre (Spain), Norway, Portugal and Sweden Preprint	≥65 years residing in one of the regions, included in and eligible to receive the autumnal 2023 vaccine dose at the start of the country-specific vaccination campaign and part of the VEBIS-HER study (N=20,440,689)	BA.2.86 and JN.1	Received the XBB.1.5 vaccine and at least 2 previous COVID-19 vaccine doses	Received at least 2 COVID-19 vaccine doses but have not received the XBB.1.5 vaccine	≥14	• 65-79 years: 50.2 (44.6-55.2) • ≥80 years: 40.7 (35.0-45.8)
					14 to 89	• 65-79 years: 50.9 (45.1-56.1) • ≥80 years: 42.0 (36.3-47.1)
					90 to 179	• 65-79 years: 47.3 (32.0-59.1) • ≥80 years: 35.9 (11.2-53.7)
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	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)

	setting from the US Veterans Affairs Healthcare system				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 (primarily XBB, EG.5.1 and JN)	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)
Lee et al. (2024) – South Korea Peer-reviewed	Adults aged ≥18 year who underwent PCR testing or rapid antigen testing in the emergency department, outpatient clinics, general wards, or intensive care units of each hospital were included in the study. (N=5,516)	Omicron (primarily XBB, EG.5.1, HK.3 and JN sub variants)	Received an mRNA XBB.1.5 variant-adapted vaccine	Unvaccinated individuals	7 to 59	• ≥18 years: 77.3 (51.1-89.5) • ≥ 65 years: 72.8 (37.3-88.2)
				Did not receive the XBB.1.5 vaccine (includes unvaccinated individuals)	7 to 59	• ≥18 years: 64.3 (35.9-80.2) • ≥ 65 years: 66.5 (38.1-81.8)
				Did not receive the XBB.1.5 vaccine but have received at least one dose of COVID-19 vaccine	7 to 59	• ≥18 years: 61.2 (29.7-78.6) • Immunocompromised: 79.4 (7.4-95.4) • Immunocompetent: 56.4 (16.2-77.3) • ≥ 65 years: 64.1 (33.2-80.7)
Link-Gelles et al. (2024) – United States Report This study was not included in the figure	Immunocompromised adults aged ≥18 years from the VISION Network (N=14,586)	Omicron XBB sublineages and JN.1	Received an XBB.1.5 variant-adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (includes unvaccinated individuals)	≥7	36 (25-46)
					7 to 59	38 (23-50)
					60 to 119	34 (16-47)

below as it reported on immunocompromised individuals						
Kirsebom et al. (2024) – England Peer-review	≥65 years (N=28,916)	Omicron (primarily XBB, JN, EG.5.1 and BA)	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)
Nguyen et al. (2024) - Belgium, Germany, Italy, Spain Preprint	≥18 years individuals eligible for COVID-19 vaccination and admitted at one of the study centers (hospitals) of the id.Drive study for at least one overnight stay with a severe acute respiratory infection (SARI). Symptom onset must have occurred within 1 days prior to admission. Patients who were infected with the JN.1 variant or experienced symptom onset during the JN.1 prevalent period were included. (N=1,445)	JN.1	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (includes unvaccinated individuals)	Median (IQR): 63 (48-79)	≥18 years: 54.8 (39.7-66.0)
					Median (IQR): 24 (22-26)	≥18 years: 53.3 (42.4-62.1)
					Median (IQR): 45 (37-50)	≥18 years: 50.2 (20.4-68.8)
					Median (IQR): 68 (62-76)	≥18 years: 57.4 (40.0-69.8)
					Median (IQR): 91 (87-98)	≥18 years: 56.7 (49.9-62.6)
					Median (IQR): 126 (120-140)	≥18 years: 59.9 (25.5-78.4)
					Median (IQR): 58 (41-72)	Immunocompromised or cancer: 56.0 (22.9-74.9)
					Median (IQR): 56 (38-78)	18 to <65 years: 55.8 (16.9-76.5)

					Median (IQR): 64 (49-79)	≥65 years: 55.0 (41.5-65.4)
					Median (IQR): 23 (22-26)	≥65 years: 62.6 (36.6-78.0)
					Median (IQR): 46 (38-50)	≥65 years: 45.9 (14.4-65.8)
					Median (IQR): 68 (62-75)	≥65 years: 57.8 (43.6-68.4)
					Median (IQR): 91 (86-98)	≥65 years: 62.4 (56.8-67.3)
					Median (IQR): 125 (119-135)	≥65 years: 53.2 (21.2-72.2)
					Median (IQR): 59 (44-73) days	65 to 79 years: 63.6 (40.7-77.7)
					Median (IQR): 67 (52-81) days	≥80 years: 49.8 (38.2-59.2)
				Did not receive an XBB.1.5 variant-adapted vaccine and received at least 1 BA.4/5 bivalent dose	Median (IQR): 63 (48-78)	≥18 years: 61.0 (35.1-76.6)
				Only received 2mRNA wild type doses	Median (IQR): 66 (49-80)	≥18 years: 48.8 (44.2-53.0)

				Unvaccinated	Median (IQR): 65 (49-80)	≥18 years: 51.1 (9.8-74.5)
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. (2024) – United States Peer-reviewed	≥18 years who have been at Kaiser Permanente Southern California (KPSC) for at least a year (N=52,036)	Omicron	Received a Pfizer-BioNTech XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine (including unvaccinated individuals)	Median of 57	≥18 years: 57 (45-66)
		JN.1			Median of 57	≥18 years: 54 (33-69)
					14 to <60	≥18 years: 50 (15-71)
					60 to 156	≥18 years: 57 (30-73)
		XBB sublineages			Median of 52	≥18 years: 65 (41-79)
					14 to <60	≥18 years: 74 (49-87)

*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).

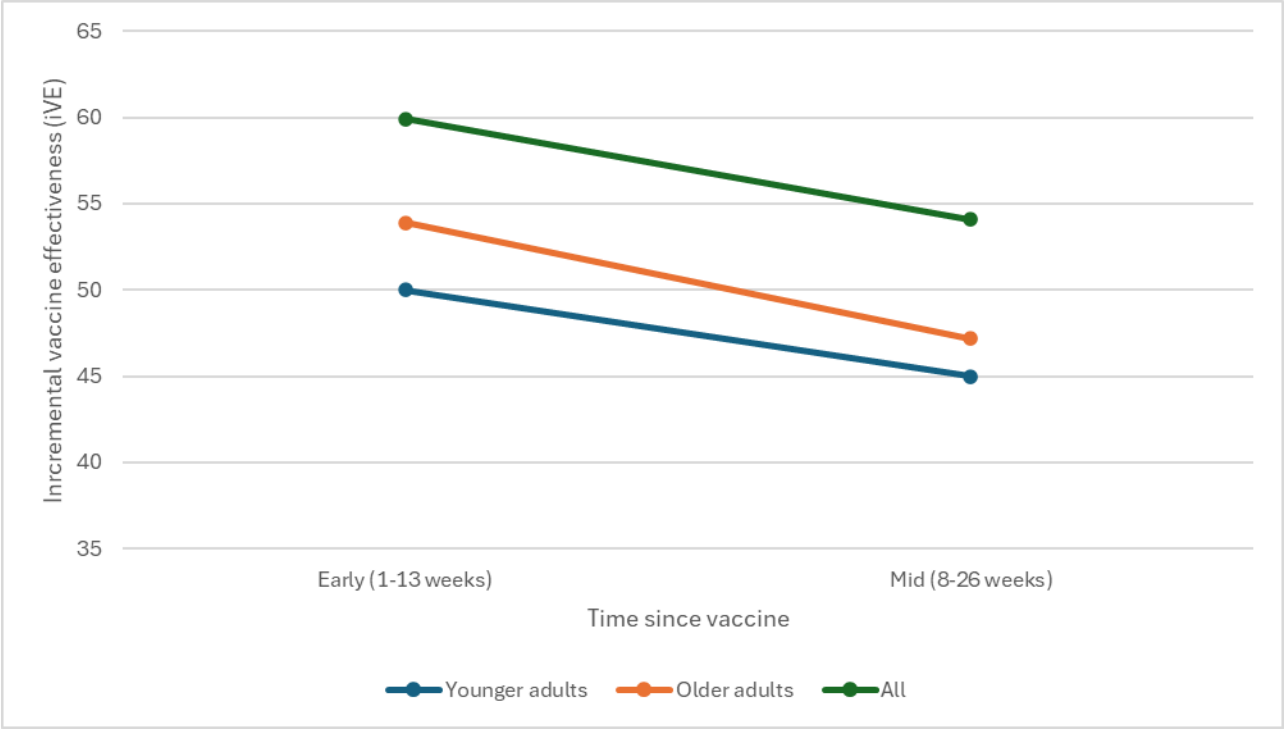

Figure 2: A visual representation of the trend in incremental vaccine effectiveness (iVE) for **COVID-19-related hospitalisations** of the XBB.1.5-adapted COVID-19 vaccine over time (comparator = those who did not receive the XBB.1.5 vaccine, including unvaccinated individuals).

* The following categories consist of the data from 11 included studies: The early time period covers 7-91 days and includes ranges and median times; the mid time period covers 44-179 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 5: 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 = 4).

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 (XBB, EG.5.1, HK.3 and JN)	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)
Lin et al. (2024) – United states (Nebraska) Published	Individuals of all ages whose information is available in the Nebraska Electronic Disease Surveillance System and the Nebraska State Immunization Information System (NESIIS) (N=1,830,088)	XBB.1.5 or JN.1	Received an XBB.1.5 variant-adapted vaccine	Did not receive an XBB.1.5 variant-adapted vaccine (include unvaccinated individuals)	7 to 13	27.2 (9.9-41.3)
					14 to 20	47.1 (18.8-65.5)
					21 to 27	61.5 (26.8-79.7)
					28 to 34	72.0 (34.0-88.1)
					35 to 41	70.5 (36.2-86.3)
					42 to 48	68.8 (37.9-84.4)
					49 to 55	67.1 (39.0-82.3)
					56 to 62	65.3 (39.5-80.1)
					63 to 69	63.4 (38.9-78.1)
					70 to 76	61.4 (37.1-76.4)
					77 to 83	59.3 (33.7-75.1)
					84 to 90	57.1 (28.5-74.3)
					91 to 97	54.8 (21.2-74.0)
					98 to 104	52.3 (11.8-74.2)
					105 to 111	49.7 (0.1-74.7)
					112 to 118	46.9 (-14.2-75.3)
					119 to 125	44.0 (-31.3-76.1)
					126 to 132	41.0 (-51.6-77.0)
					133 to 139	37.7 (-75.7-77.9)
		XBB.1.5			7 to 13	39.0 (11.6-57.9)
					14 to 20	62.8 (21.9-82.3)
					21 to 27	77.3 (31.0-92.6)
					28 to 34	86.2 (39.0-96.9)
					35 to 41	84.6 (40.4-96.0)
					42 to 48	82.7 (41.6-94.9)
					49 to 55	80.7 (42.4-93.5)
					56 to 62	78.4 (42.7-91.8)
					63 to 69	75.8 (42.5-89.8)
					70 to 76	72.9 (41.3-87.5)
					77 to 83	69.7 (38.8-85.0)

					84 to 90	66.1 (34.4-82.5)
					91 to 97	62.1 (27.2-80.3)
					98 to 104	57.6 (16.4-78.5)
					105 to 111	52.6 (0.9-77.3)
					112 to 118	46.9 (-20.4-76.6)
					119 to 125	40.6 (-49.0-76.3)
					126 to 132	33.6 (-86.7-76.4)
		JN.1			7 to 13	20.4 (-4.6-39.4)
					14 to 20	36.6 (-9.5-63.3)
					21 to 27	49.6 (-14.5-77.8)
					28 to 34	59.8 (-19.8-86.5)
					35 to 41	58.0 (-7.7-83.6)
					42 to 48	56.0 (0.8-80.5)
					49 to 55	54.0 (5.0-77.7)
					56 to 62	51.9 (4.1-75.9)
					63 to 69	49.7 (-2.9-75.4)
					70 to 76	47.3 (-16.8-76.2)
					77 to 83	44.9 (-37.9-78.0)
					84 to 90	42.3 (-67.4-80.1)
Liu et al. (2024) – Australia Preprint	≥65 years individuals recorded in the Census who had not migrated or died by study commencement on the 1 August 2023 (N=4,119,000)	Omicron (1 Aug 2023 to 29 Feb 2024)	Received an mRNA XBB.1.5 variant-adapted vaccine and at least one booster	Received at least one COVID-19 booster at least one year earlier	8 to 90	• ≥65 years: 74.7 (59.9-84.1) • ≥75 years: 76.7 (61.4-85.9)
		JN.1 (1 Dec 2023 to 29 Feb 2024)			8 to 90	• ≥65 years:74.6 (59.4-84.0)
Nunes et al. (2024) - Belgium, Denmark, Italy, Navarre (Spain), Norway, Portugal and Sweden	≥65 years individual residing in one of the regions, included in and eligible to receive the autumnal 2023 vaccine dose at the	BA.2.86 and JN.1	Received the XBB.1.5 vaccine and at least 2 previous COVID-19 vaccine doses	Received at least 2 COVID-19 vaccine doses but have not received the XBB.1.5 vaccine	≥14	• 65-79 years: 57.5 (41.5-69.1) • ≥80 years: 48.4 (38.4-56.8)
					14 to 89	• 65-79 years: 59.2 (41.3-71.7)

Preprint	start of the country-specific vaccination campaign and part of the VEBIS-EHR study (N=20,440,689)					• ≥80 years: 51.2 (41.9-59.0)
					90 to 179	• 65-79 years: 54.0 (-16.8-81.9) • ≥80 years: 9.4 (-85.5-55.8)

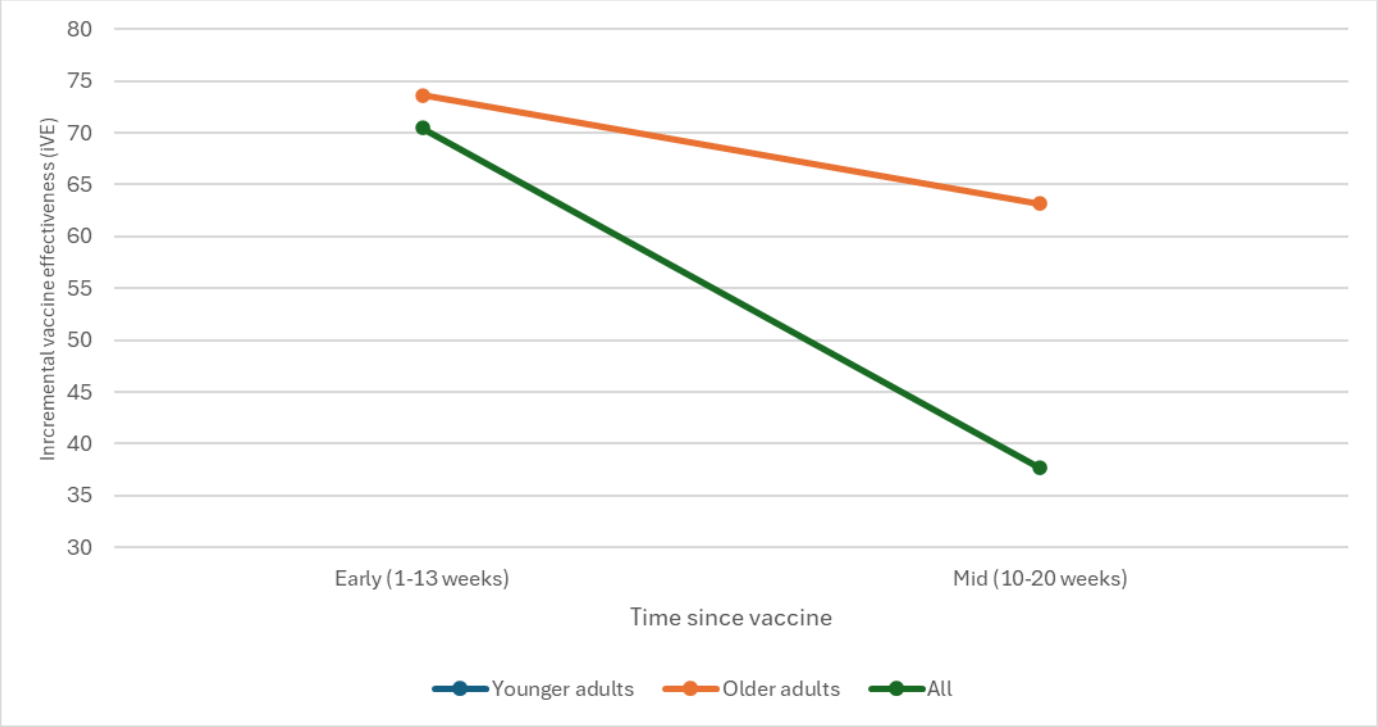

Figure 3: A visual representation of the trend in incremental vaccine effectiveness (iVE) for **COVID-19-related deaths** of the XBB.1.5 adapted COVID-19 vaccine over time (comparator = those who did not receive the XBB.1.5 vaccine, including unvaccinated individuals).
* The following categories consist of the data from 4 included studies: The early time period covers 8-91 days and includes ranges and median times; the mid time period covers 71-139 days and includes ranges and median times; the older adults include those who are ≥65, there were no studies of younger adults (18-64). A simple averaging of data was applied across studies.

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 (les21.4_vaccine_effectiveness_3_RoB_2025-01-07.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.

Funding and acknowledgment

This living evidence synthesis was commissioned and funded by the Office of the Chief Science Officer, Public Health Agency of Canada. The opinions, results, and conclusions are those of the team that prepared the evidence synthesis, and independent of the Government of Canada and the Public Health Agency of Canada. No endorsement by the Government of Canada or the Public Health Agency of Canada is intended or should be inferred.

The members of the Montreal Behavioural Medicine Centre are supported by a variety of career and scholarship awards. Dr. Bacon is supported by the CIHR-SPOR initiative through the Mentoring Chair program (SMC-151518) and by the Fonds de recherche du Québec: Santé (FRQS) through the Chaire de recherche double en Intelligence Artificielle / Santé Numérique ET sciences de la vie program (309811). Dr. Wu, Ms. Sanuade and Mr. O'Neill are supported by the CIHR-SPOR Mentoring Chair program (SMC-151518). Dr. Wu and Ms. Vieira are currently supported by a FRQS post-doctoral and PhD scholarships.

The opinions, results, and conclusions are those of the team that prepared the living evidence synthesis, and independent of the Government of Canada, CIHR, PHAC, or FRQS. No endorsement by the Government of Canada, CIHR, PHAC, or FRQS is intended or should be inferred.

We would like to thank the Vaccine Effectiveness Surveillance Program (VESPa) within the Centre for Immunization Surveillance (CIS) at the Public Health Agency of Canada, for their contributions to the living evidence synthesis, including providing background information, refining the questions and providing feedback on earlier drafts of the living evidence synthesis.

Citation

Bacon SL, Wu N, Paquet L, Vieira AM, Sanuade C, O'Neill J, Burdick,J, Aghili, P. Living evidence synthesis #21 (version 21.4): What is the effectiveness of the XBB.1.5 COVID-19 vaccines? The Montreal Behavioural Medicine Centre, META group, 21 October 2024.