Effectiveness of the XBB.1.5 COVID-19 vaccines
Living Evidence Synthesis #21
(Version 21.1: 20 February 2024)

Appendix 1a: Summary of Included Studies

Reference (author, year), with URL	Methods	Key findings	Implications	ROBINS-I*
Hansen et al. (2024)[1]	Cohort study using electronic health records and national administrative data. The study included 1,037,479 participants, individuals > 65 years old living in Denmark, capturing approximately 55% of all COVID-19 related hospitalisation during the study period (October 8 to October 26 2023). All individuals included had received at least one booster Hazard Ratio (HR) was estimated in a Cox proportional hazards regression model with calendar time as underlying time scale and adjustment for sex, 5-year age bands, residency region, and number of comorbidities (0, 1, 2, ≥3). Time and setting: Non-specific Omicron variant was the dominant variant (estimated 100%)	**HR against hospitalisation** Among adults aged > 65 years, those who have received the XBB.1.5 COVID-19 vaccine were much less likely to be hospitalised for COVID-19 compared with those who have not received the vaccine HR=0·239, 95% CI 0·152–0·377 after 7+ days since vaccination.	A XBB.1.5 vaccine was associated with a reduced risk of hospitalisation due to COVID-19 among adults > 65 years of age vaccinated with a booster dose. These findings support XBB.1.5 recommendations for persons in this age group	Serious
UK Health Security Agency (2024)[2]	A test-negative case-control study design was used to recruit all individuals aged 65+ years in England from the national database who have had at least 2 days stay in the hospital and a respiratory	**VE against hospitalisation** Compared to those who did not receive the BNT162b2 XBB.1.5	Incremental effectiveness against hospitalisation for XBB.1.5 vaccines peaked at 55.4% after 2-4 weeks since vaccination. These findings	Moderate

	code in the primary diagnostic field during the study period (4th September 2023 to 17th December 2023) All individuals included (n = 16,549) had previously received at least one booster. The relative vaccine effectiveness (VE) of receiving a bivalent BA.1 booster vaccine in addition to at least 2 doses of a prior monovalent vaccine was used in the calculation Time and setting: Non-specific Omicron variant was the dominant variant (estimated 96%)	vaccine, those who received BNT162b2 XBB.1.5. • 9 to 13 days: 42.3% (95% CI, 20.5 to 58.2), • 2 to 4 weeks: 55.4% (95% CI, 45 to 63.8), and • 5 to 9 weeks: 50.9% (95% CI, 37.5 to 61.5)	show that VE against hospitalisation of XBB.1.5 did not meet WHO recommendations of VE against severe disease (≥ 90%, with the lower 95% CI ≥ 70%)	
Tartof et al. (2023)[3]	A test-negative case-control study using the Kaiser Permanente Southern California records. All individuals aged 18+ included (n=24,007) have been diagnosed with an acute respiratory infection (ARI) and tested for COVID-19 while being admitted to the hospital, visited the emergency department, visited the urgent care or had an in-person outpatient encounter during the study period (From October 10, 2023 through December 10, 2023). SARS-CoV-2 PCR tests among cases and controls were restricted to those administered ≤14 days prior to the initial ARI encounter through ≤3 days after the encounter. Patients could contribute ≥1 event to the study if events were >30 days apart.	**OR (95% CI) against hospitalisation:** After a median of 30 days (range: 14 - 73), individuals who received BNT162b2 XBB.1.5- adapted vaccine *compared to individuals who did not receive the XBB.1.5 vaccine* • 18+ years: 0.37 (0.2 to 0.67) • 18 - 64 years: 0.32 (0.04 to 2.48) • 65+ years: 0.37 (0.2 to 0.69) *Compared to individuals who received the BA.4/5-adapted bivalent vaccine but no, XBB.1.5-adapted vaccine.* • 18+ years: 0.4 (0.21 to 0.75) • 18 - 64 years: 0.35 (0.04 to 2.99) • 65+ years: 0.39 (0.2 to 0.76) *Compared to individuals who received ≥3*	XBB1.5-adapted vaccines provided significant additional protection against COVID-19 related hospitalization, ED or UC, and outpatient visits. These findings support XBB.1.5 recommendations for broad age-based use of annually updated COVID-19 vaccines.	Moderate

	Adjusted odds ratios (OR) and 95% CI were estimated from multivariable logistic regression models that were adjusted for patient demographic and clinical characteristics. Time and setting: XBB sub lineages were the dominant variants	*doses of wild-type vaccine but no variant-adapted vaccines of any kind.* ● 18+ years: 0.36 (0.2 to 0.65) ● 18 - 64 years: 0.27 (0.03 to 2.14) ● 65+ years: 0.36 (0.19 to 0.68) *Compared to individuals who received ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind.* ● 18+ years: 0.37 (0.2 to 0.67) ● 18 - 64 years: 0.3 (0.04 to 2.32) ● 65+ years: 0.37 (0.2 to 0.7) *Compared to individuals who were unvaccinated.* ● 18+ years: 0.32 (0.16 to 0.64) ● 18 - 64 years: 0.37 (0.04 to 3.22) ● 65+ years: 0.29 (0.14 to 0.61) **OR (95% CI) against COVID related emergency department/urgent care (ED or UC) visits** After a median of 30 days (range: 14 - 73), individuals who received BNT162b2 XBB.1.5- adapted vaccine *compared to individuals who did not receive the XBB.1.5 vaccine* ● 18+ years: 0.42 (0.34 to 0. 53) ● 18 - 64 years: 0.36 (0.24 to 0.54) ● 65+ years: 0.45 (0.34 to 0.59) *Compared to individuals who received the*		

		BA.4/5-adapted bivalent vaccine but no XBB.1.5-adapted vaccine. ● 18+ years: 0.43 (0.34 to 0.55) ● 18 - 64 years: 0.40 (0.26 to 0.62) ● 65+ years: 0.43 (0.31 to 0.58) *Compared to individuals who received ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind.* ● 18+ years: 0.41(0.33 to 0.51) ● 18 - 64 years: 0.34 (0.23 to 0.51) ● 65+ years: 0.45 (0.34 to 0.6) *Compared to individuals who received ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind.* ● 18+ years: 0.42 (0.33 to 0.52) ● 18 - 64 years: 0.35 (0.23 to 0.52) ● 65+ years: 0.46 (0.35 to 0.61) *Compared to individuals who were unvaccinated.* ● 18+ years: 0.4 (0.31 to 0.52) ● 18 - 64 years: 0.37 (0.24 to 0.56) ● 65+ years: 0.33 (0.22 to 0.49) **OR (95% CI) against COVID related outpatient visits** After a median of 30 days (range: 14 - 73), individuals who received BNT162b2 XBB.1.5- adapted		

		vaccine *compared to individuals who did not receive the XBB.1.5 vaccine* ● 18+ years: 0.42 (0.27 - 0.66) ● 18 - 64 years: 0.68 (0.46 - 1.01) ● 65+ years: 0.32 (0.21 - 0.51) *Compared to individuals who received the BA.4/5-adapted bivalent vaccine but no XBB.1.5-adapted vaccine* ● 18+ years: 0.49 (0.35 to 0.68) ● 18 - 64 years: 0.78 (0.5 to 1.21) ● 65+ years: 0.29 (0.18 to 0.47) *Compared to individuals who received ≥3 doses of wild-type vaccine but no variant-adapted vaccines of any kind.* ● 18+ years: 0.44 (0.33 to 0.6) ● 18 - 64 years: 0.6 (0.4 to 0.9) ● 65+ years: 0.35 (0.22 to 0.55) *Compared to individuals who received ≥2 doses of wild-type vaccine but no variant-adapted vaccines of any kind.* ● 18+ years: 0.46 (0.34 to 0.62) ● 18 - 64 years: 0.65 (0.43 to 0.97) ● 65+ years: 0.33 (0.21 to 0.53) *Compared to those who were unvaccinated.* ● 18+ years: 0.57 (0.39 to 0.84) ● 18 - 64 years: 0.83 (0.52 to 1.33) ● 65+ years: 0.4 (0.18 to 0.87)		

ED: emergency department, HR: hazard ratio, OR: odds ratio, UC: urgent care, UK: United Kingdom

References

1. Hansen CH, Moustsen-Helms IR, Rasmussen M, Soborg B, Ullum H, Valentiner-Branth P. Short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. Lancet Infect Dis. 2024;(101130150).

2. UK Health Security Agency. COVID-19 vaccine surveillance strategy - Week 4 [Internet]. 2024. Available from: https://assets.publishing.service.gov.uk/media/61f29e68d3bf7f78e2908eea/Vaccine-surveillance-report-week-4.pdf

3. Tartof SY, Slezak JM, Frankland TB, Puzniak L, Hong V, Ackerson BK, et al. BNT162b2 XBB1.5-adapted Vaccine and COVID-19 Hospital Admissions and Ambulatory Visits in US Adults [Internet]. medRxiv; 2023. Available from: https://www.medrxiv.org/content/10.1101/2023.12.24.23300512v1

Appendix 1b: Summary of studies excluded for critical risk of bias

Study ID	First author	Title	Reason for critical bias decision
02V-1	van Werkhoven[1]	Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalisation and admission to intensive care, the Netherlands, 9 October to 5 December 2023	• Meeting serious risk of bias in 3 of 4 domains. o Study design – serious bias in missing data o Assignment of COVID outcome – serious bias in missing data o Accounting for prior infection – not reported o Adjustments – Did not adjust for comorbidities, race/ethnicity, or SES

SES: socio-economic status

References

1. van Werkhoven CH, Valk AW, Smagge B, de Melker HE, Knol MJ, Hahne SJ, et al. Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalisation and admission to intensive care, the Netherlands, 9 October to 5 December 2023. Euro Surveill. 2024;29(1).

Appendix 2: VE against other COVID-19-related outcomes (e.g., outpatient visits) of the XBB.1.5 adapted COVID-19 vaccine compared to those who have not received the XBB.1.5 adapted COVID-19 vaccine

Author (date) - Country Publication status	Population	Dominant variant	Intervention (XBB.1.5 vaccine)	Comparator (reference)	Days since last dose	(Relative) VE% (95% CI)
Case-control						
*Tartof et al. (2023) – United States Preprint	≥18 years who have been at Kaiser Permanente Southern California (KPSC) for at least a year (N=24,007)	Omicron	Received a BNT162b2 XBB1.5-adapted vaccine	Did not receive the XBB.1.5 vaccine	Median (range): 30 (14 to 73)	• ≥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		• ≥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		• ≥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		• ≥18 years: 54 (38 to 66) • 18-64 years: 35 (3 to 57) • ≥65 years: 67 (47 to 79)
				Unvaccinated		• ≥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)

Appendix 3: Search strategy

Medline and Embase

Row #	Syntax
1	vaccination/ or vaccine/
2	"Vaccin*".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
3	1 or 2
4	("XBB.1.5" OR "XBB1.5").mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
5	(effectiveness or efficacy or protection).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]
6	4 AND 5
7	3 AND 6
8	remove duplicates from 7

NIH/iCite (except PubMed)

Syntax	Filters
vaccin* AND (effectiveness OR efficacy OR protection) AND ("XBB.1.5" OR "XBB1.5")	Look up in title and abstract

Appendix 4: Definitions and glossary

Full vaccine series: Receipt of one of the following COVID-19 vaccines authorised by Health Canada:
- Two doses of AstraZeneca/COVISHIELD (AZD1222/ChAdOx1, Vaxzevria), Moderna (mRNA-1273, Spikevax), Novavax, or Pfizer-BioNTech (BNT162b2, Comirnaty);
- One dose of Janssen (Johnson & Johnson: Ad26.COV2.S, Jcovden); or
- A combination of the above

Fully vaccinated: A person who is at least 14 days post having received one of the following vaccine schedules:
- the full series of a COVID-19 vaccine authorized by Health Canada (see above); or
- the full series of the above vaccines plus an additional dose in immunocompromised individuals

Additional dose: A person who has received:
- a full series of a COVID-19 vaccine authorised by Health Canada (see above) plus an additional dose of a COVID-19 vaccine authorised by Health Canada; or
- the full series of the above vaccines plus two additional doses in immunocompromised individuals

Confirmed infection: A person with confirmation of infection with SARS-CoV-2 documented by the detection of at least 1 specific gene target by a validated laboratory-based nucleic acid amplification test (NAAT) assay (e.g. real-time PCR or nucleic acid sequencing) performed at a community, hospital, or reference laboratory (the National Microbiology Laboratory or a provincial public health laboratory) (2).

Hospitalisation due to COVID-19: Inpatient admission to a hospital and/or ICU unit, associated with laboratory-confirmed SARS-CoV-2 infection.

ICU admission due to COVID-19: Inpatient admission to the ICU unit, associated with laboratory-confirmed SARS-CoV-2 infection.

Death due to COVID-19: Death resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, with no presence of clear alternative causes unrelated to COVID-19 (e.g., trauma, poisoning, drug overdose).

Post-COVID-19 conditions: Occurs in individuals with a history of probable or confirmed SARSCoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

MIS-C: Multisystem inflammatory syndrome in children is a post-viral inflammatory syndrome that temporally follows coronavirus disease 2019 (COVID-19). Symptoms may include fever, abdominal pain, vomiting, diarrhea, skin rash and other signs of inflammation. MIS-C occurs in children and adolescent 0-19 years of age with fever for three or more days AND two of the following:
1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet),
2. Hypotension or shock,
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/N-terminal pro-brain natriuretic peptide (NT-proBNP),

4. Evidence of coagulopathy (by prothrombin time, partial thromboplastin time, elevated D-dimer),
5. Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain) AND Elevated markers of inflammation such as C-reactive protein, erythrocyte sedimentation rate or procalcitonin AND no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes AND Evidence of COVID-19

Variants of concern (VOC): A SARS-CoV-2 variant is considered a VOC in Canada based on a set of criteria including increased transmissibility or detrimental change in COVID-19 epidemiology, increased virulence, decreased effectiveness of vaccines, and so on. As of January 17, 2022, there is currently no VOCs.

Vaccine effectiveness (VE): A measure of how well a vaccine protects people from getting the outcome of interest in real-world practice (For example: VE of 92% against infection means that 92% of people will be protected from becoming infected with COVID and 8% of people will still be at risk of becoming infected with COVID). In the context of the current report, we have utilised the term vaccine effectiveness to cover all studies. However, we are aware that the studies that have been included range from efficacy through to effectiveness studies. We decided to use this terminology as it is consistent with how most evidence synthesis products describe these studies. To be consistent with this, in the French summary we have utilised the term efficacité, and it is noted that in French there is no distinction between the translations of efficacy and effectiveness.

Relative vaccine effectiveness: The term used to refer to the effectiveness of a vaccine when it is measured by comparing people who have received one vaccine type or regimen to those who received a different vaccine type or regimen.

AZ: AstraZeneca

CIs: Confidence Intervals

ED: emergency department

HCW: Healthcare workers

ICU: Intensive care unit

LTC: Long-term care

LTCF: Long-term care facility

MOD: Moderna

Obs: observational study

Omicron: variant of interest (XBB.1.5, EG.5, BA.2.86, JN.1)

OR: odds ratio

PF: Pfizer

RCT: Randomized controlled trial

RoB: Risk of Bias

UC: Urgent care

UK: United Kingdom

USA: United States of America

VOI: variant of interest

WHO: World Health Organization

Appendix 5: Critical appraisal process

We appraised the quality of the individual studies using an adapted version of ROBINS-I. This tool classifies the Risk of Bias of a study as **Low, Moderate, Serious, Critical, or No Information**. *Low Risk of Bias indicates High Quality, and Critical Risk of Bias indicates Very Low (insufficient) Quality*. ROBINS-I appraises 7 bias domains and judges each study against an ideal reference randomised controlled trial. To improve the utility of ROBINS-I for assessing studies reporting vaccine effectiveness, we have focused on study characteristics that introduce bias as reported in the vaccine literature (see WHO. Evaluation of COVID-19 vaccine effectiveness. Interim Guidance. 17 March 2021). An overall judgement of "critical" is given when the study is judged to be at critical risk of bias in at least one domain or if three or more domains are judged to be "serious".

Appendix 6: Data-extraction template

Study details	
Source	First author of study and year of publication
Location	Country data was collected in
COI	If conflicts of interest were reported
Funding	public or industry
Study design	RCT/cohort/data-linkage/test-negative/case-control/other
Publication format	Peer-reviewed / pre-print / report
Population(s)	general public/HCW
Total (N)	Total study sample
Age	Description of age of the population
Female	number or %
Race/ethnicity	Description of the race/ethnicity of the population
Population (primary serie)	Details on primary serie received previously
Population (boosters)	Details on boosters received previously
Population (COVID-19 history)	Details on the COVID-19 history of the population
Definition of infections	How were COVID-19 infections defined
Definition of COVID hospitalisations	How were COVID-19 hospitalisations defined
Definition of COVID outpatient visits	How were COVID-19 outpatient visits defined
Definition of COVID emergency department visits	How were COVID-19 emergency department visits defined
Definition of COVID ICU admission	How were COVID-19 ICU admissions defined
Definition of post-COVID conditions	How were post-COVID-19 conditions defined
Definition of MIS-C	How was MIS-C defined
Definition of COVID deaths	How were COVID-19 deaths defined
Vaccines	Details of what vaccines were included in the study
Comparator	What comparison group was used to generate VE
Study calendar time	When was the study conducted
Outcomes	
Variant sub-group	Was a specific variant being studied (any, delta, or omicron)
Was VOC or VOI sequenced	Yes or no, only applicable if looking at a variant
Outcome	Cases, hospitalisations, ICU, deaths, post-COVID-conditions, or MIS-C

Specific vaccine	If individual vaccine data is reported
Vaccine class	mRNA, adenovirus, protein subunit, or mixed (reporting mRNA, adenovirus, and/or mixed doses)
Effect measure used	VE, RR, or other
Level of CIs	95% or 99%
Time window	Time since second dose administered
VE outcome	Reported point estimate
Lower CI	Reported lower CI
Upper CI	Reported upper CI
Adjustments	What variables were used to adjust for in analyses
Comments	

Appendix 7a: Flow chart of studies included in the current update:

*One of these was excluded for having a critical risk of bias

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 7b. Summary of excluded studies during full text screening

Author (year of publication)	Title	Reason for exclusion
Hansen et al. (2024)	Short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study	Previously identified
Kirsebom et al. (2023)	Long-term duration of protection of ancestral-strain monovalent vaccines and effectiveness of the bivalent BA.1 boosters against COVID-19 hospitalisation during a period of BA.5, BQ.1, CH.1.1. and XBB.1.5 circulation in England	Wrong intervention
Lewnard et al (2023)	Increased vaccine sensitivity of an emerging SARS-CoV-2 variant	Wrong intervention
Lin et al (2023)	Effects of COVID-19 vaccination and previous SARS-CoV-2 infection on omicron infection and severe outcomes in children under 12 years of age in the USA:an observational cohort study	Wrong intervention
Link-Gelles et al (2023)	Early Estimates of Bivalent mRNA Booster Dose Vaccine Effectiveness in Preventing Symptomatic SARS-CoV-2 Infection Attributable to Omicron BA.5- and XBB/XBB.1.5-Related Sublineages Among Immunocompetent Adults - Increasing Community Access to Testing Program, United States, December 2022-January 2023	Wrong intervention

Appendix 7b. Summary of excluded studies during hand search

Author (year of publication)	Title	Reason for exclusion
Lee et al. (2023)	Clinical and Economic impact of updated Fall 2023 COVID-19 vaccines in the Immunocompromised Population in Canada	Wrong study design (modelling study)
Stankov et al. (2024)	Humoral and cellular immune responses following BNT162b2 XBB.1.5 vaccination	Previously identified
Van Werkhoven et al. (2023)	Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalization and ICU admission, the Netherlands, 9 October - 5 December 2023	Previously identified