Coronavirus Variants Rapid Response Network | Réseau de réponse rapide aux variants du coronavirus

CMCM MBMC Montreal Behavioural Medicine Centre

COVID-END COVID-19 Evidence Network to support Decision-making ... in Canada

COVID-19 Living Evidence Synthesis #10

(Version 10.6: 1st June 2022)

Questions

1. How does the level of vaccine efficacy/ effectiveness (VE) against COVID-19 infection, hospitalisation, and death change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series?
2. How does the level of VE against COVID-19 infection, hospitalisation, and death change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose?

Visual representation of findings

1. The primary series VE against any infections, hospitalisations, and deaths are presented in Tables 1, 3, and 5, respectively; and for for omicron-related outcomes in Tables 2, 4, and 6. Figure 1 provides information on cases by variant and Figure 2 provides information on cases by specific vaccine brand
2. The primary series + additional dose VE against any infections and hospitalisations are presented in Tables 7, 9, and 11, respectively. For omicron-related outcomes in Tables 8, 10, and 12.
3. The primary series + additional dose vs. primary series only OR against any infections and hospitalisations are presented in Tables 13, 15, and 17, respectively. For omicron-related outcomes in Tables 14, 16, and 18.

Methods are presented in Box 1 and in the related appendices.

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 and EMBASE; 2) systematic scanning of COVID-END Forum website, McMaster Health Forum website, and citations of systematic reviews on this topic; and 4) cross-check with updates from the VESPa team. We included studies and updates to living evidence syntheses identified up to five 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. A glossary is provided in **Appendix 3**.

Prioritized outcome measures: Infection, hospitalisation, and death.

Data extraction: We prioritised any infection data over symptomatic or asymptomatic and total population data over sub-groups. We extracted data from each study using a standard template with peer-review to confirm information **Appendix 5**. Only data from four of the Health Canada vaccines (BNT162b2, mRNA-1273, ChAdOx1, and Ad26.COV2.S) and only delta and omicron VOC data were extracted for sub-analyses. VOC data was determined directly when reported by study authors.

Critical appraisal: We assessed risk of bias and certainty of evidence. **Risk of bias:** assessed in duplicate for individual studies using an adapted version of ROBINS-I (see **Appendix 4)**.

Summaries: We summarized the evidence by presenting meta-analysed pooled estimates with 95% CIs by 4-week blocks (see **Appendix 2** for details). For meta-analyses, sub-groups were considered as separate cohorts. Where data was insufficient, we provide an average (and range) of the available VE data or point estimate (and 95%CIs) in there was only a single study.

We update this document every 4th Wednesday and post it on the COVID-END website.

Overall (from the initiation of this review), 14,265 studies were title and abstract screened, 861 were full-text appraised, with 47 initially included, 2 studies were excluded (RoB), leaving 45 that were used to complete this summary. The reasons for excluding the 750 studies are reported in **Appendix 7**.

Highlights of changes in this version

- ***Four*** new studies have been added (marked in blue in **Appendix 1**) that report on the long-term VE of the full vaccine schedule.
- ***Two*** new studies have been added (marked in blue in **Appendix 1**) and ***one*** study was updated (marked in green in **Appendix 1**) that report on the long-term VEs of additional doses beyond the full vaccine schedule.
- No new studies were added that report on the long-term ORs of additional doses beyond the full vaccine schedule compared to the full vaccine schedule.

- Delta has been removed from the tables
- Data capture on comparisons between different primary and booster dosing (no comparison to unvaccinated) has now been included
- We have updated our evidence certainty definitions
- We now provide a definition of waning

High level summary of outcomes

Primary vaccine series

- For COVID-19 cases, there was a statistically and clinically significantly degradation in VE from 16 weeks onwards after receiving the primary. The level of degradation was consistent with our definition of waning.
- For COVID-19 hospitalisations and mortality, though there is a statistically significant decline in VE, the level of decline is not clinically meaningful, indicated that VE is maintained over time, up to 32 and 28 weeks, respectively, after receiving the primary vaccine series.
- Data on the Omicron variant indicates that for cases there is insufficient protection at baseline with a further, statistically significant decrease in VE as of 16 weeks post primary series. For hospitalisations, there was insufficient protection at baseline but there didn't seem to be a decrease over time. For mortality, there was insufficient data available to draw any conclusions

Booster dose vs. unvaccinated

- For COVID-19 cases, the available data reflects the Omicron variant, with no other available variant data. The available data indicates that for cases there is insufficient protection at baseline with no statistical decrease in VE up to 20 weeks post booster dose.
- For COVID-19 hospitalisations, there was statistically and clinically significantly degradation in VE from 12 weeks onwards after receiving the booster dose. The level of degradation was consistent with our definition of waning. The Omicron data is consistent with this pattern.
- For COVID-19 mortality, there was insufficient data to draw any interpretations.

Booster dose vs. primary series

- There were no studies that provided usable data

Visual representation of data

- For Tables 1-12 and Figures 1 and 2, **percentages** indicate the *level of effectiveness* of the COVID-19 vaccines compared to unvaccinated individuals. A VE of 0% indicates no protection and a VE of 100% indicates that the vaccines maximally prevent COVID-19 events (e.g., cases, death, hospitalisations).
- For Tables 13-18, **the number** indicates the *level of effectiveness* of the COVID-19 vaccines compared to individuals who have received a primary series only. An OR of 1.0 indicates no protection of the booster relative to the primary series and an OR of 0 indicates that the booster maximally prevents COVID-19 events (e.g., cases, death, hospitalisations).
- Meta-analysed point estimates and 95% CIs are provided, along with the number of studies (and cohorts) contributing to the data. It is possible that any particular study may provide more than one cohort, depending on how they reported the data.
- **Colour** indicates **Level of Certainty** based on the evidence*
- In all tables, **days (weeks)** refers to time since the completion of a full vaccine series, i.e., since last vaccine.
- For Tables 1-12, the rows translate to:
  - % Vaccine Efficacy;
  - 95% CIs; and
  - # Studies (# cohorts)
- For Tables 13-18, the rows translate to:
  - Odds ratios;
  - 95% CIs; and
  - # Studies (# cohorts).

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

*It should be noted that previous versions of this report used a slightly different colour scheme to define certainty.

Definition of waning

- There is no formal definition of waning
- The WHO defines preferred levels of initial VE as:
  - VE against symptomatic disease ≥ 70%, with the lower 95% CI ≥ 50%; or
  - VE against severe disease ≥ 90%, with the lower 95% CI ≥ 70%
  - https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines
- In addition, the provides a graded reduction system based on arrows, such that:↓ = 10 to <20 point reduction in VE; ↓↓ = 20 to <30 point reduction in VE; and ↓↓↓ = ≥ 30 point reduction in VE;
  - https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
- For the current report we are using the preferred level system, with ***waning defined as***: A statistical reduction in VE from the second baseline (which must meet the preferred criteria) and one of the following:
  - VE against infection < 70%, with the lower 95% CI < 50%; or
  - VE against hospitalisation or death < 90%, with the lower 95% CI < 70%

Question 1a: VE against COVID-19 infections change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series

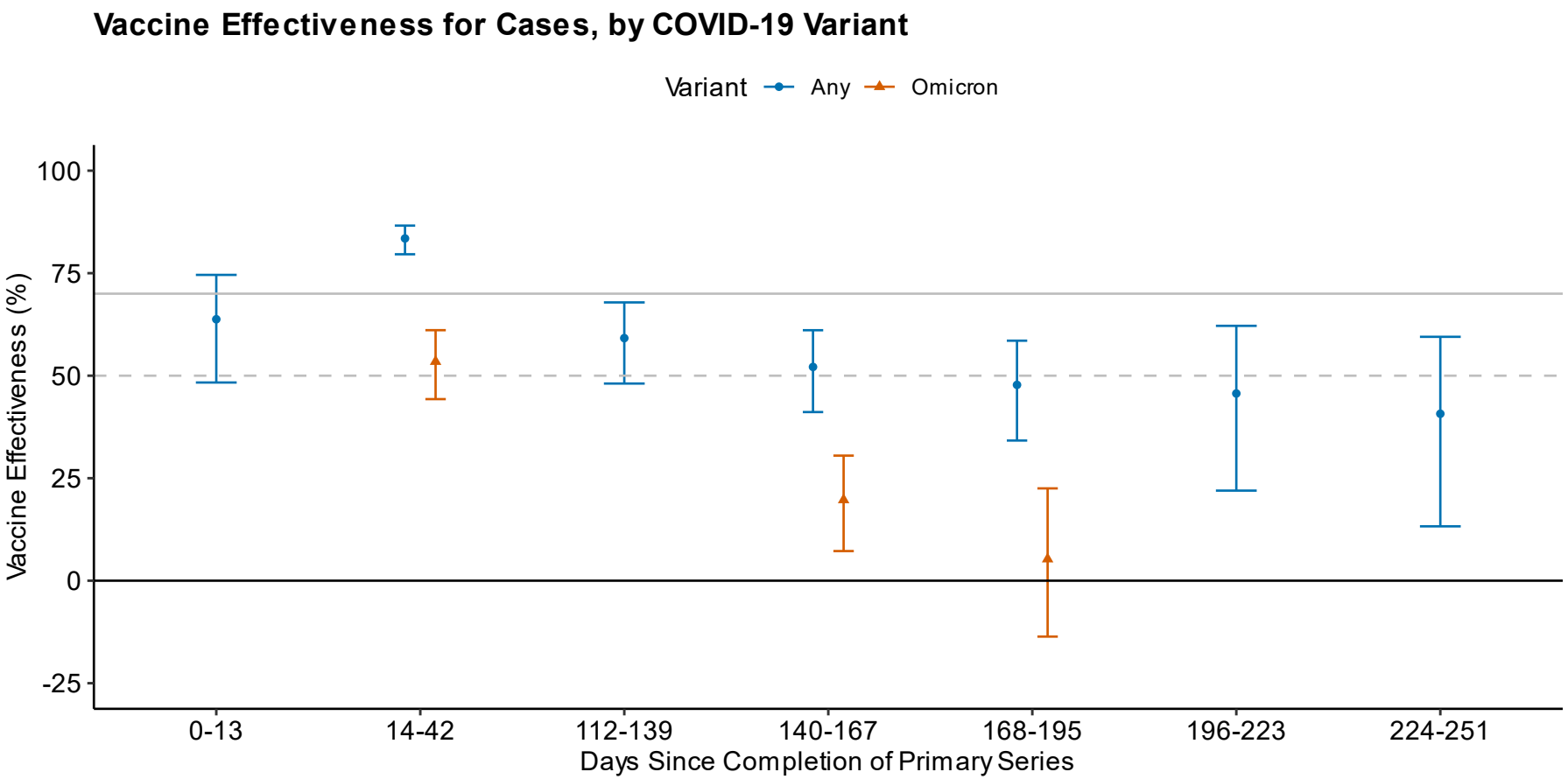
Table 1: VE against COVID-19 cases[#] for completed primary series (**all strains**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-13 (0-2)	**14-42 (2-6)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	**336+ (48+)**	
Any vaccine	64% (48 - 75) 7 (14)	83%† (80 - 87) 26 (69)	59%* (48 - 68) 16 (38)	52%* (41 - 61) 26 (68)	48%†* (34 - 59) 18 (41)	46%* (22 - 62) 6 (10)	41%†* (13 - 59) 7 (9)	43%* (10 - 64) 3 (6)	38%* (-34 - 74) 2 (2)	41%* (-38 - 79) 1 (1)	51%* (-26 - 82) 1 (1)	Yes
Any mRNA vaccine	69% (53 - 79) 6 (8)	87%† (84 - 90) 20 (48)	63%* (51 - 72) 12 (25)	54%†* (41 - 64) 21 (45)	48%†* (32 - 60) 14 (26)	46%†* (23 - 62) 6 (9)	38%†* (10 - 57) 6 (8)	43%†* (11 - 63) 3 (5)	38%* (-25 - 71) 2 (2)	45%* (-23 - 77) 1 (1)	54%* (-8 - 81) 1 (1)	Yes
Any adenovirus	40% (8 - 61) 2 (4)	70%† (61 - 78) 10 (17)	52%* (34 - 64) 6 (10)	46%* (30 - 59) 10 (18)	42%* (23 - 56) 7 (13)	59% (24 - 78) 1 (1)		55% (16 - 76) 1 (1)				Yes
BNT162b2	71% (58 - 80) 5 (7)	86%† (82 - 90) 15 (24)	60%* (46 - 70) 9 (14)	51%†* (37 - 63) 17 (27)	48%†* (31 - 60) 12 (19)	46%†* (23 - 62) 5 (6)	41%†* (16 - 58) 6 (7)	46%†* (17 - 64) 3 (4)	33%†* (-24 - 66) 1 (1)	45%* (-7 - 72) 1 (1)	54%* (9 - 77) 1 (1)	Yes
mRNA-1273		92% (88 - 94) 12 (21)	76%* (62 - 85) 5 (9)	70%* (56 - 80) 11 (18)	67%* (46 - 80) 4 (7)	58%* (28 - 75) 4 (5)	50%* (1 - 74) 2 (3)	50%* (-2 - 76) 2 (3)	65% (-52 - 94) 1 (1)			Yes
ChAdOx1	43% (7 - 65) 2 (3)	72%† (61 - 81) 7 (14)	53%* (30 - 68) 4 (7)	46%* (23 - 62) 7 (15)	38%* (10 - 57) 5 (10)							Yes
Ad26.COV2.S	17% (-51 - 66) 1 (1)	62% (43 - 74) 3 (3)	49% (23 - 66) 2 (3)	50% (27 - 65) 3 (3)	55% (34 - 69) 3 (3)	58% (25 - 77) 1 (1)		55% (17 - 75) 1 (1)				Yes

Table 2: VE against COVID-19 cases[#] for completed primary series (**Omicron variant**)

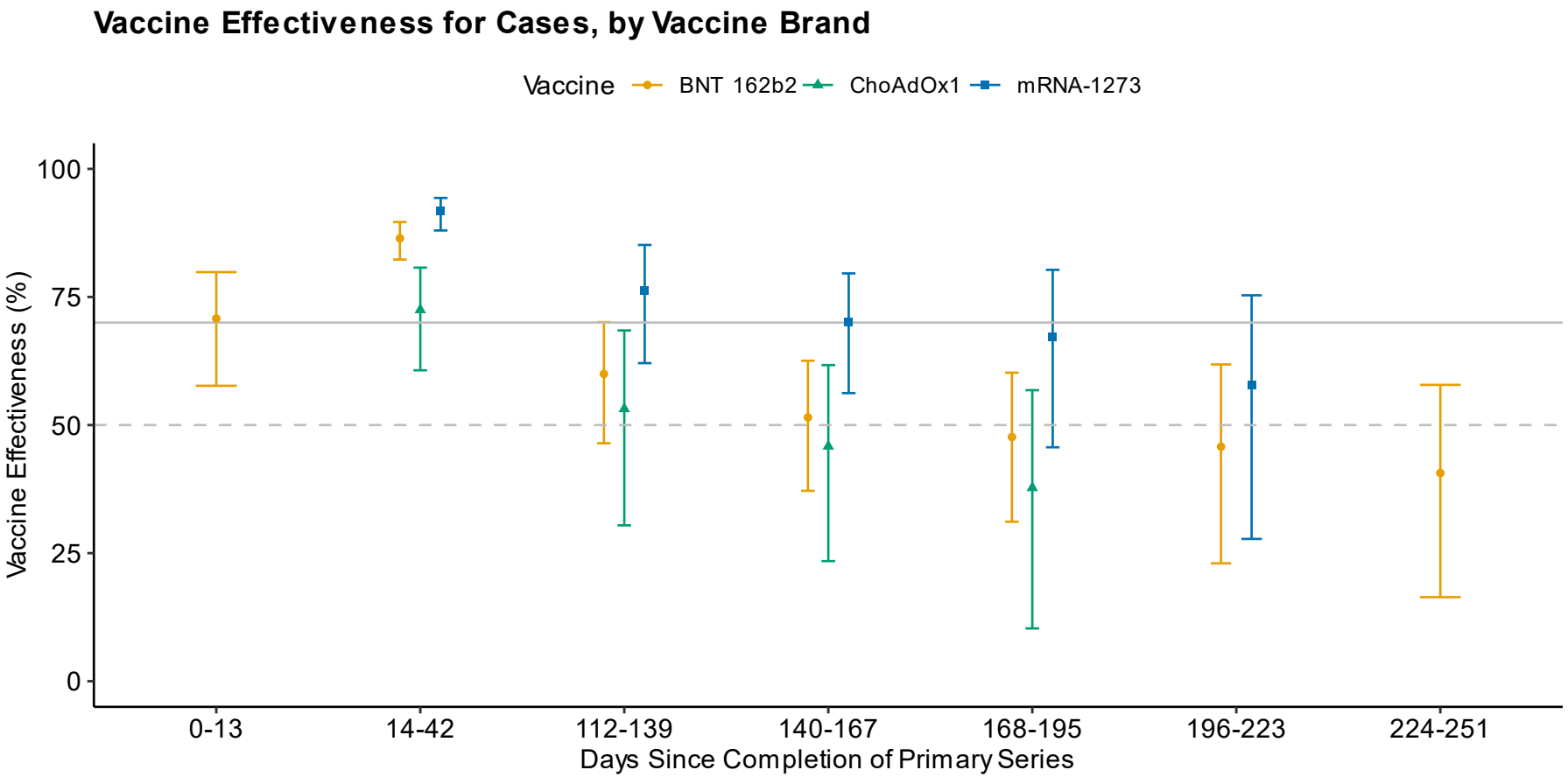
	Baseline days (weeks)		**Follow-up days (weeks)**									**MOD**
	0-13 (0-2)	**14-42 (2-6)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	**336+ (48+)**	
Any vaccine	46% (33 - 57) 3 (7)	53% (44 - 61) 5 (9)	23%†* (-3 - 42) 2 (3)	20%†* (7 - 31) 8 (15)	5%†* (-14 - 23) 4 (6)	4%†* (-21 - 26) 2 (3)	-2%†* (-30 - 26) 2 (2)	-1%†* (-36 - 34) 1 (1)	-20%†* (-48 - 19) 1 (1)	-3%†* (-38 - 33) 1 (1)	14%* (-26 - 45) 1 (1)	Yes
Any mRNA vaccine	45% (25 - 60) 2 (3)	56% (45 - 64) 4 (7)	25%* (-1 - 44) 2 (3)	16%†* (-1 - 31) 6 (9)	4%†* (-19 - 25) 3 (4)	6%†* (-31 - 39) 1 (1)	-11%†* (-43 - 27) 1 (1)	-3%†* (-37 - 34) 1 (1)	-21%†* (-49 - 19) 1 (1)	-4%†* (-39 - 33) 1 (1)	13%* (-27 - 45) 1 (1)	Yes
Any adenovirus	34% (-17 - 64) 1 (2)	50% (-13 - 79) 1 (1)		21% (-22 - 51) 2 (3)	0% (-54 - 55) 1 (1)							Yes
BNT162b2	53% (29 - 69) 1 (2)	57% (41 - 70) 3 (3)	28% (-20 - 59) 1 (1)	21%†* (-4 - 39) 4 (5)	11%†* (-24 - 40) 2 (2)	9%* (-35 - 47) 1 (1)	-8%†* (-46 - 37) 1 (1)	1%†* (-41 - 42) 1 (1)	-18%†* (-52 - 29) 1 (1)	0%†* (-42 - 42) 1 (1)	16%* (-32 - 52) 1 (1)	Yes
mRNA-1273		60% (-37 - 90) 2 (2)		14% (-71 - 78) 2 (2)	13% (-84 - 88) 1 (1)							Yes
ChAdOx1	34% (-17 - 64) 1 (2)	50% (-13 - 79) 1 (1)		21% (-22 - 51) 2 (3)	0% (-54 - 55) 1 (1)							Yes
Ad26.COV2.S												No

Figure 1: VE against COVID-19 cases[#] for any completed primary series by variant (**All** and **Omicron**)



Only time points with at least 4 studies have been included in the figure.
The solid line indicates the WHO definition of preferred minimum level of VE and the dotted line is the minimum lower 95%CIs
[#] This is a combination of any, symptomatic, and asymptomatic infections. If a study reports any infections this is prioritised over symptomatic or asymptomatic (when reported). If the study reports symptomatic and asymptomatic, then symptomatic is prioritised.

Figure 2: VE against COVID-19 cases[#] for specific primary series vaccines (**BNT 162b2**, **ChoAdOx1**, and **mRNA-1273**)



Only time points with at least 4 studies have been included in the figure.
The solid line indicates the WHO definition of preferred minimum level of VE and the dotted line is the minimum lower 95%CIs
[#] This is a combination of any, symptomatic, and asymptomatic infections. If a study reports any infections this is prioritised over symptomatic or asymptomatic (when reported). If the study reports symptomatic and asymptomatic, then symptomatic is prioritised.

Question 1b: VE against COVID-19 hospitalisations change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series

Table 3: VE against COVID-19 hospitalisations for completed primary series (**all strains**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-13 (0-2)	14-42 (2-6)	112-139 (16-20)	140-167 (20-24)	168-195 (24-28)	196-223 (28-32)	224-251 (32-36)	252-279 (36-40)	280-307 (40-44)	308-335 (44-48)	336+ (48+)	
Any vaccine	87% (73 - 94) 3 (6)	91% (87 - 94) 18 (46)	89% (83 - 92) 10 (28)	86%* (80 - 90) 16 (43)	82%* (72 - 88) 7 (15)	83% (68 - 91) 4 (6)	76%* (47 - 89) 3 (3)	88% (49 - 97) 1 (1)				Yes
Any mRNA vaccine	88% (65 - 96) 2 (3)	91% (87 - 94) 15 (27)	89% (83 - 94) 7 (14)	86%* (78 - 91) 13 (24)	85% (70 - 92) 4 (5)	84% (68 - 92) 4 (6)	77%* (49 - 90) 3 (3)	88% (48 - 97) 1 (1)				Yes
Any adenovirus		88% (81 - 93) 7 (13)	86% (76 - 92) 4 (8)	84% (75 - 90) 7 (13)	80% (63 - 89) 3 (6)							Yes
BNT162b2	88% (46 - 97) 1 (1)	93% (88 - 96) 10 (14)	90% (81 - 95) 4 (6)	87%* (77 - 92) 9 (13)	85%* (69 - 93) 3 (4)	80%* (58 - 91) 3 (4)	79%* (56 - 90) 3 (3)	88% (31 - 98) 1 (1)				Yes
mRNA-1273	92% (22 - 99) 1 (1)	94% (91 - 97) 4 (7)	96% (92 - 98) 2 (3)	92%* (87 - 95) 4 (7)	91% (74 - 97) 1 (2)	91% (82 - 95) 3 (4)	88% (54 - 97) 1 (1)	93% (40 - 99) 1 (1)				Yes
ChAdOx1		91% (86 - 95) 5 (10)	90% (82 - 94) 3 (6)	87% (80 - 91) 5 (10)	83%* (68 - 91) 2 (5)							Yes
Ad26.COV2.S		80% (32 - 94) 2 (2)	81% (8 - 96) 1 (1)	76% (29 - 92) 2 (2)	82% (-10 - 97) 1 (1)							Yes

Table 4: VE against COVID-19 hospitalisations for completed primary series (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**MOD**
	0-13 (0-2)	**14-42 (2-6)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	**336+ (48+)**	
Any vaccine	67% (3 - 89) 2 (2)	62% (51 - 71) 5 (6)	65% (55 - 73) 3 (4)	58% (47 - 66) 4 (5)	42% (3 - 65) 1 (1)	61% (33 - 77) 1 (1)						Yes
Any mRNA vaccine	79% (-65 - 98) 1 (1)	62% (50 - 71) 5 (5)	69% (61 - 76) 3 (3)	57% (48 - 65) 4 (4)		61% (34 - 77) 1 (1)						Yes
Any adenovirus		60% (33 - 76) 1 (1)	46% (21 - 63) 1 (1)	45% (-89 - 97) 1 (1)								No
BNT162b2	79% (-97 - 100) 1 (1)	62% (-10 - 87) 2 (2)		60% (5 - 83) 2 (2)		61% (-34 - 90) 1 (1)						Yes
mRNA-1273												No
ChAdOx1												No
Ad26.COV2.S												No

Question 1c: VE against COVID-19 deaths change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series

Table 5: VE against COVID-19 deaths for completed primary series (**all strains**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-13 (0-2)	14-42 (2-6)	112-139 (16-20)	140-167 (20-24)	168-195 (24-28)	196-223 (28-32)	224-251 (32-36)	252-279 (36-40)	280-307 (40-44)	308-335 (44-48)	336+ (48+)	
Any vaccine		91% (82 - 95) 7 (17)	89% (75 - 96) 3 (6)	80%* (62 - 90) 5 (11)	84% (67 - 92) 4 (8)							Yes
Any mRNA vaccine		93% (84 - 97) 6 (12)	95% (84 - 99) 2 (3)	83%* (58 - 93) 4 (6)	88% (70 - 95) 3 (7)							Yes
Any adenovirus		85% (70 - 93) 5 (8)	68% (4 - 90) 2 (3)	71% (39 - 86) 4 (5)	82% (56 - 93) 2 (4)							Yes
BNT162b2		96% (92 - 97) 4 (6)	93% (79 - 98) 1 (1)	89%* (80 - 94) 3 (3)	90%* (83 - 94) 2 (4)							Yes
mRNA-1273		98% (89 - 100) 2 (3)		93% (69 - 98) 1 (1)	95% (86 - 98) 1 (2)							Yes
ChAdOx1		94% (88 - 97) 3 (4)	82% (2 - 97) 1 (1)	79%* (63 - 89) 2 (2)	88% (74 - 94) 1 (2)							Yes
Ad26.COV2.S		65% (44 - 78) 3 (3)	76% (8 - 94) 1 (1)	71% (50 - 83) 2 (2)	76% (50 - 89) 2 (2)							Yes

Table 6: VE against COVID-19 deaths for completed primary series (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**MOD**
	0-13 (0-2)	**14-42 (2-6)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	**336+ (48+)**	
Any vaccine		49% (-64 - 90) 1 (2)	62% (-76 - 97) 1 (2)	18% (2 - 31) 1 (2)								No
Any mRNA vaccine		3% (-53 - 56) 1 (1)	91% (19 - 99) 1 (1)	19% (-6 - 38) 1 (1)								No
Any adenovirus		84% (-22 - 98) 1 (1)	-7% (-68 - 63) 1 (1)	17% (-4 - 34) 1 (1)								No
BNT162b2												No
mRNA-1273												No
ChAdOx1												No
Ad26.COV2.S												No

Question 2a: VE against COVID-19 cases change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose – comparison to unvaccinated

Table 7: VE against COVID-19 cases[#] for completed primary series and an additional dose (**all strains**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-7 (0-1)	7-28 (1-4)	84-111 (12-16)	112-139 (16-20)	140-167 (20-24)	168-195 (24-28)	196-223 (28-32)	224-251 (32-36)	252-279 (36-40)	280-307 (40-44)	308-335 (44-48)	
Any vaccine	64% (33 - 81) 2 (4)	63% (38 - 78) 6 (13)	55% (25 - 73) 6 (12)	54% (21 - 74) 4 (9)	-30%†* (-71 - 42) 1 (1)							Yes
Any mRNA vaccine	64% (32 - 81) 2 (4)	62% (36 - 78) 6 (11)	55% (24 - 73) 6 (12)	55% (22 - 75) 4 (7)	-30%†* (-72 - 44) 1 (1)							Yes
Any adenovirus		62% (44 - 74) 1 (2)		27% (-42 - 69) 1 (2)								No
BNT162b2	44% (-37 - 80) 1 (2)	65% (20 - 85) 5 (10)	57% (0 - 82) 4 (9)	56% (-8 - 82) 3 (4)	-41%†* (-82 - 48) 1 (1)							Yes
mRNA-1273		54% (24 - 72) 2 (2)	32% (-14 - 60) 2 (2)	38% (-20 - 69) 1 (1)								Yes
ChAdOx1		62% (44 - 74) 1 (2)		27% (-42 - 69) 1 (2)								No
Ad26.COV2.S												No

Table 8: VE against COVID-19 cases[#] for completed primary series and an additional dose (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-7 (0-1)	**7-28 (1-4)**	**84-111 (12-16)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	
Any vaccine	64% (33 - 81) 2 (4)	63% (38 - 78) 6 (13)	55% (25 - 73) 6 (12)	54% (21 - 74) 4 (9)	-30%†* (-71 - 42) 1 (1)							Yes
Any mRNA vaccine	64% (32 - 81) 2 (4)	62% (36 - 78) 6 (11)	55% (24 - 73) 6 (12)	55% (22 - 75) 4 (7)	-30%†* (-72 - 44) 1 (1)							Yes
Any adenovirus		62% (44 - 74) 1 (2)		27% (-42 - 69) 1 (2)								No
BNT162b2	44% (-37 - 80) 1 (2)	65% (20 - 85) 5 (10)	57% (0 - 82) 4 (9)	56% (-8 - 82) 3 (4)	-41%†* (-82 - 48) 1 (1)							Yes
mRNA-1273		54% (24 - 72) 2 (2)	32% (-14 - 60) 2 (2)	38% (-20 - 69) 1 (1)								Yes
ChAdOx1		62% (44 - 74) 1 (2)		27% (-42 - 69) 1 (2)								No
Ad26.COV2.S												No

[#] This is a combination of any, symptomatic, and asymptomatic infections. If a study reports any infections this is prioritised over symptomatic or asymptomatic (when reported). If the study reports symptomatic and asymptomatic, then symptomatic is prioritised.

Question 2b: VE against COVID-19 hospitalisations change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose – comparison to unvaccinated

Table 9: VE against COVID-19 hospitalisations for completed primary series and an additional dose (**all strains**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-7 (0-1)	7-28 (1-4)	84-111 (12-16)	112-139 (16-20)	140-167 (20-24)	168-195 (24-28)	196-223 (28-32)	224-251 (32-36)	252-279 (36-40)	280-307 (40-44)	308-335 (44-48)	
Any vaccine	83% (75 - 88) 4 (9)	92%† (87 - 94) 3 (5)	75%* (66 - 82) 6 (13)	68%†* (52 - 79) 4 (6)	83% (52 - 94) 1 (1)							Yes
Any mRNA vaccine	85% (79 - 89) 4 (8)	92%† (89 - 94) 3 (5)	78%* (73 - 83) 6 (12)	70%†* (58 - 79) 4 (6)	81% (53 - 93) 1 (1)							Yes
Any adenovirus	82% (54 - 93) 1 (2)		76% (72 - 80) 1 (2)									No
BNT162b2	83% (73 - 90) 2 (4)	89% (77 - 94) 1 (1)	77% (67 - 85) 3 (5)	66%* (38 - 82) 2 (2)	81% (51 - 93) 1 (1)							Yes
mRNA-1273		90% (87 - 93) 1 (1)	84% (78 - 88) 1 (1)	77% (63 - 86) 1 (1)								No
ChAdOx1	82% (54 - 93) 1 (2)		76% (72 - 80) 1 (2)									No
Ad26.COV2.S												No

Table 10: VE against COVID-19 hospitalisations for completed primary series and an additional dose (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**MOD**
	0-7 (0-1)	**7-28 (1-4)**	**84-111 (12-16)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	
Any vaccine	81% (72 - 87) 4 (7)	91%† (86 - 94) 3 (5)	75%* (66 - 81) 6 (11)	68%* (53 - 78) 4 (6)	82% (50 - 93) 1 (1)							Yes
Any mRNA vaccine	85% (79 - 89) 4 (7)	91%† (88 - 93) 3 (5)	78%* (72 - 82) 6 (11)	69%†* (57 - 78) 4 (6)	81% (54 - 92) 1 (1)							Yes
Any adenovirus	71% (67 - 75) 1 (1)		77% (72 - 81) 1 (1)									No
BNT162b2	83% (73 - 90) 2 (4)	89% (77 - 94) 1 (1)	77% (67 - 85) 3 (5)	66%* (38 - 82) 2 (2)	81% (51 - 93) 1 (1)							Yes
mRNA-1273		90% (87 - 93) 1 (1)	84% (78 - 88) 1 (1)	77% (63 - 86) 1 (1)								No
ChAdOx1	71% (67 - 75) 1 (1)		77% (72 - 81) 1 (1)									No
Ad26.COV2.S												No

Question 2c: VE against COVID-19 deaths change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose – comparison to unvaccinated

Table 11: VE against COVID-19 deaths for completed primary series and an additional dose (**all strains**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**MOD**
	0-7 (0-1)	**7-28 (1-4)**	**84-111 (12-16)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	
Any vaccine	82% (73 - 88) 2 (5)		84% (75 - 90) 2 (5)		71% (-40 - 95) 1 (1)							Yes
Any mRNA vaccine	81% (71 - 87) 2 (3)		87% (81 - 91) 2 (3)		71% (-51 - 96) 1 (1)							Yes
Any adenovirus	83% (61 - 93) 1 (2)		82% (50 - 94) 1 (2)									No
BNT162b2	82% (70 - 89) 1 (1)		68% (-65 - 96) 1 (1)		71% (-13 - 93) 1 (1)							No
mRNA-1273												No
ChAdOx1	83% (61 - 93) 1 (2)		82% (50 - 94) 1 (2)									No
Ad26.COV2.S												No

Table 12: VE against COVID-19 deaths for completed primary series and an additional dose (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									MOD
	0-7 (0-1)	**7-28 (1-4)**	**84-111 (12-16)**	**112-139 (16-20)**	**140-167 (20-24)**	**168-195 (24-28)**	**196-223 (28-32)**	**224-251 (32-36)**	**252-279 (36-40)**	**280-307 (40-44)**	**308-335 (44-48)**	
Any vaccine	77% (58 - 87) 2 (3)		83% (69 - 90) 2 (3)		71% (-56 - 96) 1 (1)							Yes
Any mRNA vaccine	78% (46 - 91) 2 (2)		87% (72 - 94) 2 (2)		71% (-84 - 99) 1 (1)							Yes
Any adenovirus	74% (60 - 83) 1 (1)		77% (67 - 84) 1 (1)									No
BNT162b2	82% (70 - 89) 1 (1)		68% (-65 - 96) 1 (1)		71% (-13 - 93) 1 (1)							No
mRNA-1273												No
ChAdOx1	74% (60 - 83) 1 (1)		77% (67 - 84) 1 (1)									No
Ad26.COV2.S												No

Question 2a: OR against COVID-19 cases change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose – comparison to those who have only received the primary series

Table 13: OR against COVID-19 cases[#] for completed primary series and an additional dose vs. those who have only received the primary series (**all strains**)

No data to report

Table 14: OR against COVID-19 cases[#] for completed primary series and an additional dose vs. those who have only received the primary series (**Omicron variant**)

No data to report

Question 2b: OR against COVID-19 hospitalisations change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose – comparison to those who have only received the primary series

Table 15: OR against COVID-19 hospitalisations for completed primary series and an additional dose vs. primary series only (**all strains**)

No data to report

Table 16: OR against COVID-19 hospitalisations for completed primary series and an additional dose vs. primary series only (**Omicron variant**)

No data to report

Question 2c: OR against COVID-19 deaths change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus an additional dose – comparison to those who have only received the primary series

Table 17: OR against COVID-19 deaths for completed primary series and an additional dose vs. primary series only (**all strains**)

No data to report

Table 18: OR against COVID-19 deaths for completed primary series and an additional dose vs. primary series only (**Omicron variant**)

No data to report

Narrative overview of findings

1a. Findings for confirmed COVID-19 cases primary series only

A total of 33 studies provided usable baseline and follow-up information with regards to COVID-19 related cases. The analyses indicated that VE for cases started to wane 16 weeks up to 40 weeks post full vaccine schedule. With the exception of mRNA-1273, the waning was seen across all vaccines (with variable follow-up times). For mRNA-1273, though there was a statistically significant decline in VE as of 16 weeks post full schedule it didn't reach the level of waning until 24 weeks post full schedule.

With regards to the eight studies Omicron variant data, baseline levels of VE did not meet the WHO minimum preferred level of VE. As of 16 weeks post full schedule there was a further statistical decline in the VE. One study provided a direct comparison between the Omicron BA.1 and BA.2 variants (Kirsebom et al.). Aggregating data across ChAdOx1-S, BNT162b2, and mRNA-1273 vaccines they didn't find a large difference between the variants for VE at 25+ weeks (17.4% vs. 24.3%, respectively).

1b. Findings for COVID-19 related hospitalisations primary series only

A total of 21 studies provided usable baseline and follow-up information with regards to COVID-19 related hospitalisations. The analyses indicated that there was a statistically significant decease in VE, across time in the ability of the vaccines to prevent COVID-19-related hospitalisations, which was not clinically meaningful. The results were consistent across vaccines. With regards to the seven Omicron variant studies, baseline levels of VE did not meet the WHO minimum preferred level of VE. That being said, there wasn't a statistical decrease in VE across 20 weeks post vaccine series.

1c. Findings for COVID-19 related deaths primary series only

A total of seven studies provided usable baseline and follow-up information with regards to COVID-19 related deaths. There was a non-clinically significant, but statistically significant decrease in the ability of the vaccines to prevent COVID-19-related deaths VE for COVID-19 related across the 24 weeks post receipt of a vaccine series. There seemed to be a qualitatively better retention of VE for the mRNA vaccines compared to the adenovirus vaccines, but there was too little data to provide any specific comparisons. With regards to the one Omicron variant study, baseline levels of VE did not meet the WHO minimum preferred level of VE.

2a. Findings for confirmed COVID-19 cases primary series plus additional dose – compared to unvaccinated

A total of eight studies provided usable baseline and follow-up information with regards to confirmed COVID-19 case data. These studies all reported on the Omicron variant. The baseline levels of VE did not meet the WHO minimum preferred level of VE. That being said, there wasn't a statistical decrease in VE across 20 weeks post vaccine series. One study provided a direct comparison between the Omicron BA.1 and BA.2 variants (Kirsebom et al.). Aggregating data across BNT162b2 and mRNA-1273 booster doses, they didn't find a large difference between the variants for VE at 15+ weeks (45.5% vs. 48.4%, respectively).

2b. Findings for COVID-19 related hospitalisations primary series plus additional dose – compared to unvaccinated

A total of seven studies provided usable baseline and follow-up information with regards to COVID-19-related hospitalisations. These studies all reported on the Omicron variant. The analyses indicated that VE for hospitalisations, waning started from 16 weeks post booster vaccine.

2c. Findings for COVID-19 related deaths primary series plus additional dose – compared to unvaccinated

A total of two studies provided usable baseline and follow-up information with regards to COVID-19-related deaths. There were too few studies to provide any meaningful interpretation of the data.

Risk of bias (RoB) assessment

The risk of bias data for each individual study is provided in the Supplementary File (les10.6_vaccine_waning_adults_RoB_3_2022-06-01.xlsx). Overall, the risk of bias was serious for the majority of studies due to the lack of adjustment of prognostic factors. Beyond that most items were related low. Two studies (Young-Xu et al. and Menni et al.) were deemed as having a critical RoB due to not accounting for calendar time (both) and self-reporting vaccines and infections (Menni) and were excluded from the analyses.

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 were also limited in the scope of potential sub-groups that could be included and we were not able to extract any immunogenicity data. However, we were able to identify data for several key sub-groups within the extracted studies. The lack of time also meant that 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).

Potential implications for health systems decision-making

Though the current review provides evidence for *long term waning in VE for COVID-19 confirmed cases*, it is unclear what might be driving this (e.g., a degradation in immunogenicity, changes in public health measures, or variations in case numbers and general transmission). Contrasting this, there is *no evidence of waning in VEs for COVID-related hospitalisations and deaths*. These patterns seem to be consistent for the Omicron variant. However, the baseline levels of VE did not meet the WHO minimum preferred level of VE, suggesting that the *VE response to the Omicron variant is lower in general*.

With regards to long-term waning of an additional vaccine dose, the majority of the available data is derived from Omicron studies, which indicate that the baseline levels of VE do not meet the WHO minimum preferred level of VE. In spite of that, we still see signs of statistical reductions in VE for cases with relative stability for COVID-19 hospitalisations.

Given that Omicron has become the dominant variant in Canada, to reduce the transmission of the virus and limit increases in cases, there may be a need to maintain some COVID-19 prevention behaviours, e.g., mask wearing and physical distancing, in individuals who are fully vaccinated with or without an additional dose. Once again, this needs to be considered in the context of the limited number of studies available looking at multiple transmission prevention strategies and a lack of randomised controlled trial evidence on the utility of combinations of prevention measures.

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.

SPOR Evidence Alliance operates from the St. Michael's Hospital, Unity Health Toronto which is located on the traditional land of the Huron-Wendat, the Seneca, and the Mississaugas of the Credit. Today, this meeting place is still the home to many Indigenous people from across Turtle Island.

COVID-END is housed within McMaster University which is located on the traditional territories of the Mississauga and Haudenosaunee nations, and within the lands protected by the "Dish With One Spoon" wampum, an agreement to peaceably share and care for the resources around the Great Lakes.

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

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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.

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