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 10.11: 12 October 2022)

Questions

1. How does the level of vaccine 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?
3. How does the level of protection 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 additional dose(s) vs. those who received a complete primary series and additional dose(s) plus a prior infection?

Visual representation of findings

1. The primary series VE against any infections, hospitalisations, and deaths in response to the Omicron variant are presented in Tables 1-3. Figures 1 and 2 provide information on infections and hospitalisations by variant
2. The primary series + additional doses VE against any infections, hospitalisations, and death in response to the Omicron variant are presented in Tables 4-7.
3. The primary series + additional doses vs. primary series only odds ratios (OR) against any infections, hospitalisations, and death in response to the Omicron variant are presented in Tables 8-12.
4. The primary series + additional doses vs. primary series + prior infection OR against any infections, hospitalisations, and death in response to the Omicron variant are presented in Tables 13-15.
5. The equivalent tables for all strain data are presented in **Appendix 2**, including Figure A2-1 which provides information on cases by specific vaccine brand.

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 8**, respectively. A glossary is provided in **Appendix 4**.

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 6**. 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 (**Appendix 5**).

Summaries: We summarized the evidence by presenting meta-analysed pooled estimates with 95% CIs by 4-week blocks (see **Appendix 3** 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.

Flow of included studies

Overall (from the initiation of this review), 15,728 studies were title and abstract screened, 1,149 were full-text appraised, with 69 initially included, 5 studies were excluded (RoB), leaving 64 that were used to complete this summary. The reasons for excluding the 959 studies are reported in **Appendix 8**.

Highlights of changes in this version

- Data tables for two booster doses vs. one booster dose have been added (***one*** new study).

- ***Three*** new studies have been added (marked in blue in **Appendix 1**) that report on the long-term VE of the full vaccine schedule. The information for ***one*** study was updated to reflect the transition from a pre-print to full publication (25F-11 Ferdinands: marked in green in **Appendix 1**) and another study was updated to reflect an update of data from one previously published study to a newer version of the study with a longer follow-up (12L-11 Lin: marked in green in **Appendix 1**).
- ***Two*** new studies have been added (marked in blue in **Appendix 1**) that reports on the long-term VEs of additional doses beyond the full vaccine schedule.
- ***Two*** new studies were added (marked in blue in **Appendix 1**) that reported on the long-term ORs of additional doses beyond the full vaccine schedule compared to the full vaccine schedule.
- ***No*** new studies were added that report on the long-term ORs of additional doses beyond the three/four doses vaccine compared to only three/four doses vaccine with prior infection.

- Data tables for the all-strains analyses have been placed in **Appendix 3**. Only data tables reporting the Omicron variant have been left in the main report. The summaries of the data now start by covering the Omicron variant and then all strain patterns.
- Delta was removed from the tables for version 10.6 onwards, as such, the last report to include delta data was 10.5 (https://www.mcmasterforum.org/docs/default-source/product-documents/living-evidence-syntheses/covid-19-living-evidence-synthesis-10.5---what-is-the-long-term-effectiveness-of-available-covid-19-vaccines-for-adults.pdf?sfvrsn=8cb53a44_8).

High level summary of outcomes for the Omicron variant

Primary vaccine series

- For COVID-19 infections, baseline levels of VE did not meet the WHO level of adequate VE. There was a statistically significant degradation in VE from 16 weeks onwards after receiving the primary vaccine series. There seemed to be no notable difference across vaccines.
- For COVID-19 hospitalisations, baseline levels of VE did not meet the WHO level of adequate VE. There seemed to be relative stability in the VE up to 20 weeks post full schedule. This data predominately reflects mRNA vaccines with too little data to report on other vaccines.
- For COVID-19 mortality, there was to little data to be able to draw any inferences.

One booster dose vs. unvaccinated

- For COVID-19 infections, baseline levels of VE did not meet the WHO level of adequate VE. There was a statistically significant degradation in VE from 12 weeks onwards after receiving the booster dose. This data predominately reflects mRNA vaccines with too little data to report on other vaccines.
- For COVID-19 hospitalisations, baseline levels of VE did not meet the WHO level of adequate VE, though only just (89%). There was a statistically significant degradation in VE from 12 weeks onwards after receiving the booster dose, which would be consistent with our definition of waning. This data predominately reflects mRNA vaccines with too little data to report on other vaccines.
- For COVID-19 mortality, baseline levels of VE did not meet the WHO level of adequate VE, though only just (86%). There was no statistical change in VE up to 16 weeks post booster dose. This data predominately reflects mRNA vaccines with too little data to report on other vaccines.

Two booster doses vs. unvaccinated

- For COVID-19 infections, the very limited available data suggests that baseline levels of VE did not meet the WHO level of adequate VE. There was a non-statistically significant degradation in VE 12 weeks after receiving the booster dose. This data reflects only the mRNA-1273 vaccine.

One booster dose vs. primary series

- For COVID-19 infections, there was a benefit of the booster compared to full schedule at baseline. There was a statistically significant degradation in the OR from 12 weeks onwards after receiving the booster dose (compared to the primary series only). This data only reflects mRNA vaccines.
- For COVID-19 hospitalisations, there was a benefit of the booster compared to full schedule at baseline. There was too little data to be able to provide any notable inferences about changes in the OR over time, though there seemed to be some degree of stability up to 20 weeks post-booster dose, with a notable drop by 24 weeks. This data only reflects mRNA vaccines.
- For COVID-19 mortality, there were no studies that compared a full schedule vs. a full schedule plus booster doses.

Two booster doses vs. primary series

- For COVID-19 infections, there was only one study that provided data, meaning that it is not possible to provide any inferences for the benefits of a full schedule vs. a full schedule plus two booster doses.

Two booster doses vs. one boost dose

- For COVID-19 infections, there was only one study that provided data, meaning that it is not possible to provide any inferences for the benefits of a full schedule plus one booster dose vs. a full schedule plus two booster doses.

Booster dose vs. booster dose and previous infection

- There were no studies that compared the booster dose to the booster dose plus a previous infection.

Visual representation of data

- For Tables 1-6 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 7-12, **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 (see note after the table about colourations of previous versions).
- 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;
  - 95% PI; and
  - # Studies (# cohorts)
- For Tables 13-18, the rows translate to:
  - Odds ratios;
  - 95% CIs;
  - 95% PI; and
  - # Studies (# cohorts).
- We have indicated statistical significance in the tables using the following symbols:
  - † = statistically different from baseline 1 (0-13 days)
  - * = statistically different from baseline 2 (14-42 days)

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, they 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 levels of initial VE) 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 (Omicron variant) change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series

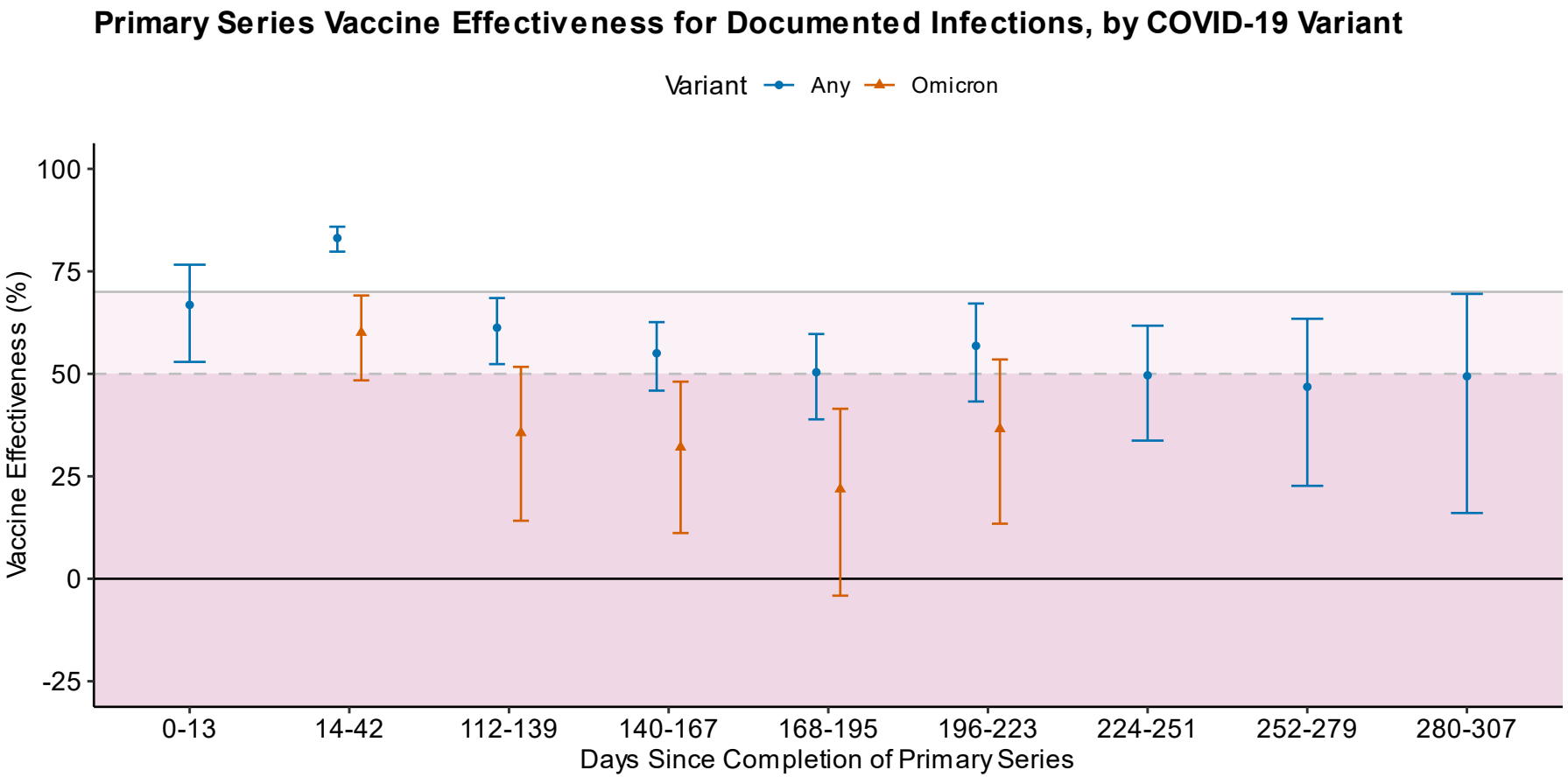
Table 1: VE against COVID-19 infections[#] for completed primary series (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	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	58%	60%	36%*	32%†*	22%†*	37%*	20%†*	28%*	14%†*	19%*	33%	[30, 70]	[0.24, 0.37]	Yes
	[33, 73]	[48, 69]	[14, 52]	[11, 48]	[-4, 41]	[13, 53]	[-20, 49]	[-13, 55]	[-28, 46]	[-30, 54]	[-17, 62]			
	[-13, 84]	[0, 84]	[-39, 75]	[-41, 73]	[-49, 69]	[-38, 75]	[-54, 70]	[-49, 74]	[-57, 68]	[-57, 72]	[-48, 77]			
	2 (3)	10 (19)	5 (9)	6 (13)	4 (9)	4 (6)	2 (2)	2 (2)	2 (2)	1 (1)	1 (1)			
Any mRNA vaccine	31%	66%†	48%*	31%*	24%*	29%*	15%*	24%*	11%*	21%*	34%*	[8, 92]	[0.16, 0.52]	Yes
	[-30, 66]	[50, 77]	[20, 66]	[-4, 55]	[-16, 51]	[-12, 56]	[-31, 50]	[-19, 53]	[-31, 46]	[-26, 53]	[-12, 62]			
	[-62, 82]	[-10, 90]	[-42, 84]	[-56, 79]	[-61, 77]	[-58, 79]	[-66, 75]	[-61, 78]	[-67, 74]	[-64, 77]	[-56, 81]			
	1 (1)	7 (11)	3 (5)	4 (6)	2 (3)	2 (2)	1 (1)	2 (2)	2 (2)	1 (1)	1 (1)			
Any adenovirus		47%	52%	22%	-3%							[100, 0]	[0.26, 0.00]	Yes
		[24, 63]	[-2, 77]	[-13, 47]	[-51, 48]									
		[-13, 75]	[-25, 83]	[-41, 65]	[-63, 61]									
		3 (4)	1 (1)	2 (3)	1 (1)									
BNT162b2		56%	22%*	23%*	11%*	9%*	-8%*	1%*	-18%*	-1%*	16%*	[85, 15]	[0.21, 0.09]	Yes
		[44, 66]	[-12, 46]	[0, 41]	[-22, 38]	[-34, 45]	[-45, 34]	[-39, 40]	[-51, 27]	[-41, 39]	[-30, 50]			
		[23, 75]	[-32, 58]	[-27, 57]	[-40, 52]	[-46, 56]	[-55, 47]	[-51, 52]	[-60, 41]	[-52, 51]	[-43, 60]			
		4 (5)	2 (2)	3 (4)	2 (2)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)			
mRNA-1273		61%	31%	-6%	-6%							[50, 50]	[0.45, 0.45]	Yes
		[-99, 100]	[-100, 100]	[-100, 100]	[-100, 100]									

		[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]									
		2 (2)	1 (1)	1 (1)	1 (1)									
ChAdOx1		40%		22%	-3%							[100, 0]	[0.22, 0.00]	Yes
		[14, 59]		[-10, 46]	[-48, 45]									
		[-19, 71]		[-37, 62]	[-60, 57]									
		2 (3)		2 (3)	1 (1)									
Ad26.COV2.S		65%	52%											
		[53, 74]	[38, 62]											
		1 (1)	1 (1)											

[#] 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 1: VE against COVID-19 infections[#] for any completed primary series by variant (**All** [**Table A2-1**] and **Omicron** [**Table 1**])



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.

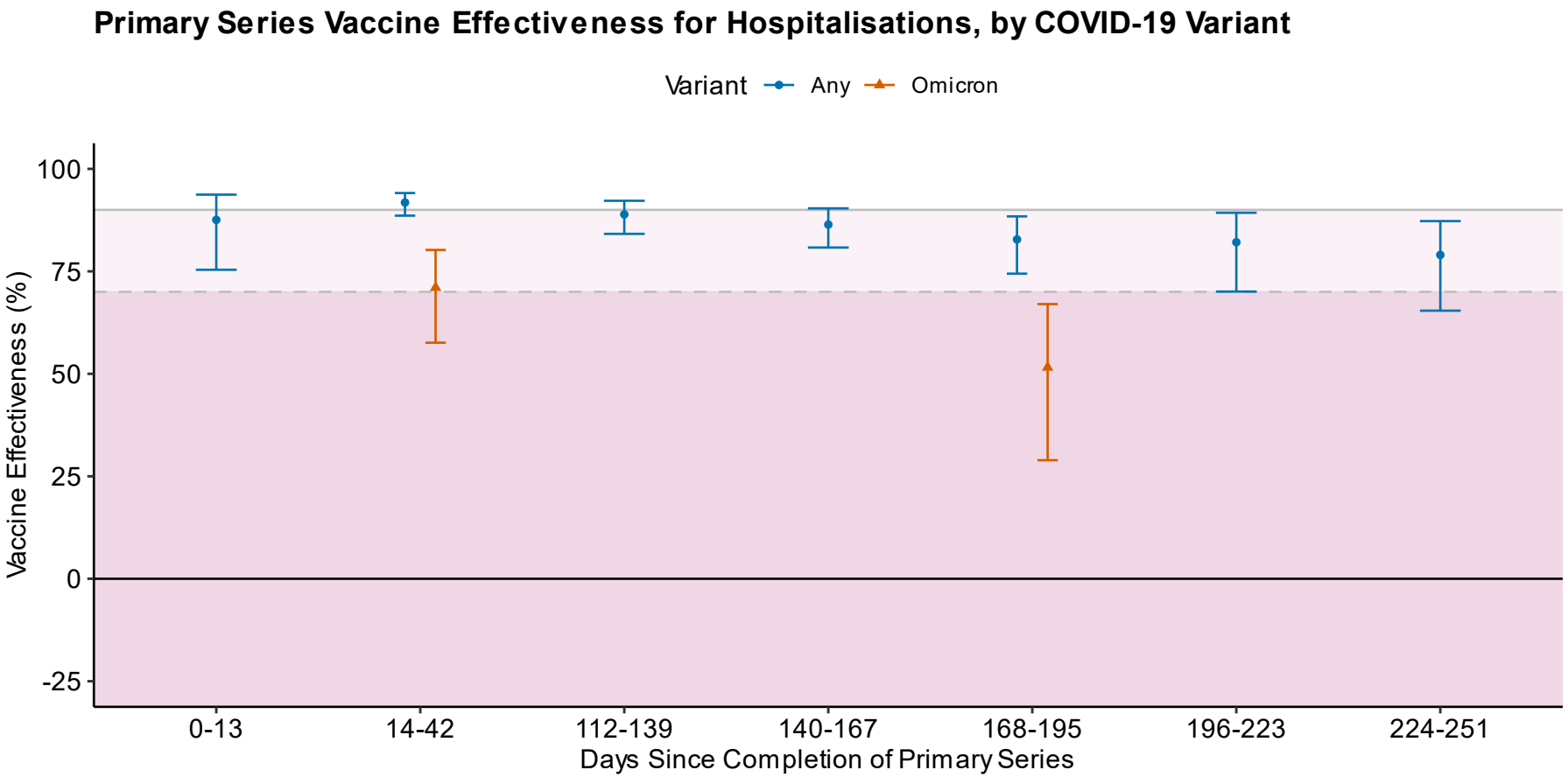
Question 1b: VE against COVID-19 hospitalisations (Omicron variant) change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series

Table 2: VE against COVID-19 hospitalisations for completed primary series (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	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	69%	71%	70%	60%	52%*	48%	38%	51%			55%	[40, 55]	[0.23, 0.27]	Yes
	[2, 90]	[58, 80]	[55, 80]	[35, 75]	[29, 67]	[1, 73]	[-21, 70]	[7, 75]			[15, 77]			
	[-18, 92]	[32, 88]	[29, 87]	[2, 84]	[-12, 79]	[-29, 81]	[-43, 78]	[-24, 82]			[-17, 84]			
	2 (2)	6 (7)	3 (4)	2 (3)	4 (4)	1 (1)	1 (1)	1 (1)			1 (1)			
Any mRNA vaccine	76%	72%	74%	59%	52%	48%*	40%*	51%			55%	[24, 72]	[0.17, 0.31]	Yes
	[-69, 98]	[58, 81]	[60, 83]	[35, 74]	[26, 69]	[6, 71]	[-15, 69]	[12, 73]			[19, 75]			
	[-73, 98]	[32, 88]	[36, 89]	[-2, 83]	[-14, 81]	[-28, 81]	[-41, 79]	[-23, 82]			[-16, 83]			
	1 (1)	6 (6)	3 (3)	2 (2)	3 (3)	1 (1)	1 (1)	1 (1)			1 (1)			
Any adenovirus		60%	46%	45%										
		[33, 76]	[21, 63]	[-89, 97]										
		1 (1)	1 (1)	1 (1)										
BNT162b2	79%	68%	52%	54%	59%	42%	38%	44%			51%	[94, 0]	[0.33, 0.00]	Yes
	[-77, 99]	[44, 82]	[-13, 80]	[-10, 81]	[31, 75]	[-28, 76]	[-36, 76]	[-24, 76]			[-14, 79]			
	[-80, 99]	[12, 89]	[-38, 86]	[-36, 87]	[-11, 85]	[-49, 83]	[-54, 83]	[-47, 83]			[-39, 85]			
	1 (1)	4 (4)	1 (1)	1 (1)	3 (3)	1 (1)	1 (1)	1 (1)			1 (1)			
mRNA-1273		87%		64%		57%		62%			61%			
		[75, 93]		[54, 72]		[49, 64]		[57, 66]			[56, 65]			

		1 (1)		1 (1)		1 (1)		1 (1)			1 (1)			
ChAdOx1														
Ad26.COV2.S														

Figure 2: VE against COVID-19 hospitalisations for any completed primary series by variant (**All** [**Table A2-2**] and **Omicron** [**Table 2**])



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

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

Table 3: VE against COVID-19 deaths for completed primary series (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**I^2 [w/b]**	**σ [w/b]**	**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%	62%	18%										
		[-64, 90]	[-76, 97]	[2, 31]										
		1 (2)	1 (2)	1 (2)										
Any mRNA vaccine		3%	91%	19%										
		[-53, 56]	[19, 99]	[-6, 38]										
		1 (1)	1 (1)	1 (1)										
Any adenovirus		84%	-7%	17%										
		[-22, 98]	[-68, 63]	[-4, 34]										
		1 (1)	1 (1)	1 (1)										
BNT162b2														
mRNA-1273														
ChAdOx1														

Ad26.COV2.S														

Question 2a-1: VE against COVID-19 infections (Omicron variant) change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus one or more additional doses – comparison to unvaccinated

Table 4: VE against COVID-19 infections[#] for completed primary series and **ONE** additional dose (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	MOD
	0-6 (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+ (44+)			
Any vaccine		66%	50%*	39%*	-19%*							[33, 67]	[0.35, 0.50]	Yes
		[53, 76]	[30, 64]	[11, 58]	[-49, 24]									
		[-15, 90]	[-43, 86]	[-54, 83]	[-78, 67]									
		12 (25)	10 (20)	7 (14)	2 (6)									
Any mRNA vaccine		66%	50%*	38%*	-19%*							[34, 66]	[0.35, 0.50]	Yes
		[53, 76]	[30, 65]	[10, 58]	[-50, 24]									
		[-17, 91]	[-44, 86]	[-55, 83]	[-78, 67]									
		12 (23)	10 (18)	7 (14)	2 (6)									
Any adenovirus		62%	27%											
		[44, 74]	[-42, 69]											
		1 (2)	1 (2)											
BNT162b2		65%	53%	46%	-36%*							[20, 80]	[0.35, 0.69]	Yes
		[38, 80]	[16, 74]	[-4, 72]	[-76, 40]									
		[-47, 93]	[-60, 91]	[-66, 90]	[-90, 75]									
		7 (13)	6 (12)	4 (5)	1 (1)									
mRNA-1273		71%	31%*	32%*	-6%*							[99, 0]	[0.43, 0.00]	Yes
		[54, 81]	[-25, 64]	[1, 54]	[-38, 30]									
		[19, 89]	[-53, 77]	[-45, 75]	[-65, 61]									

		3 (7)	2 (2)	2 (6)	1 (5)										
ChAdOx1		62%	27%												
		[44, 74]	[-42, 69]												
		1 (2)	1 (2)												
Ad26.COV2.S															

[#] 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.

Table 5: VE against COVID-19 infections[#] for completed primary series and **TWO** additional doses (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	MOD
	0-6 (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+ (44+)			
Any vaccine		59%	12%											
		[42, 72]	[-27, 43]											
		1 (4)	1 (4)											
Any mRNA vaccine		59%	12%											
		[42, 72]	[-27, 43]											
		1 (4)	1 (4)											
Any adenovirus														
BNT162b2														
mRNA-1273		59%	12%											
		[42, 72]	[-27, 43]											
		1 (4)	1 (4)											
ChAdOx1														

Ad26.COV2.S														

[#] 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-1: VE against COVID-19 hospitalisations (Omicron variant) change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus one or more additional doses – comparison to unvaccinated

Table 6: VE against COVID-19 hospitalisations for completed primary series and **ONE** additional dose (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**I^2 [w/b]**	**σ [w/b]**	**MOD**
	0-6 (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+ (44+)**			
Any vaccine	69%	89%†	74%*	71%*	87%							[30, 68]	[0.32, 0.48]	Yes
	[36, 85]	[82, 93]	[60, 83]	[51, 83]	[62, 95]									
	[-20, 92]	[59, 97]	[8, 93]	[-6, 92]	[35, 97]									
	1 (2)	7 (11)	8 (13)	4 (5)	1 (1)									
Any mRNA vaccine	75%	90%	77%*	74%*	86%							[53, 44]	[0.36, 0.33]	Yes
	[38, 90]	[85, 93]	[68, 84]	[59, 84]	[61, 95]									
	[4, 94]	[70, 96]	[35, 92]	[23, 92]	[42, 97]									
	1 (1)	7 (12)	8 (13)	4 (5)	1 (1)									
Any adenovirus	71%		77%											
	[67, 75]		[72, 81]											
	1 (1)		1 (1)											
BNT162b2		86%	77%*	71%*	85%							[41, 56]	[0.28, 0.33]	Yes
		[78, 91]	[65, 85]	[51, 83]	[60, 94]									
		[60, 95]	[37, 92]	[17, 90]	[43, 96]									
		5 (7)	5 (7)	3 (3)	1 (1)									
mRNA-1273		90%	84%	77%										
		[87, 93]	[78, 88]	[63, 86]										

		1 (1)	1 (1)	1 (1)										
ChAdOx1	71%		77%											
	[67, 75]		[72, 81]											
	1 (1)		1 (1)											
Ad26.COV2.S														

Question 2c-1: VE against COVID-19 deaths (Omicron variant) change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus one or more additional doses – comparison to unvaccinated

Table 7: VE against COVID-19 deaths for completed primary series and **ONE** additional dose (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**I^2 [w/b]**	**σ [w/b]**	**MOD**
	0-6 (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	76%	86%	86%	83%	75%							[33, 60]	[0.22, 0.29]	Yes
	[43, 90]	[72, 93]	[73, 92]	[63, 92]	[-45, 97]									
	[14, 93]	[56, 96]	[55, 95]	[42, 95]	[-56, 97]									
	1 (2)	2 (2)	3 (4)	1 (1)	1 (1)									
Any mRNA vaccine	72%	87%	87%	84%	76%							[0, 88]	[0.00, 0.24]	Yes
	[16, 91]	[77, 93]	[78, 92]	[73, 91]	[-58, 98]									
	[-7, 93]	[67, 95]	[68, 95]	[59, 94]	[-63, 98]									
	1 (1)	2 (2)	3 (3)	1 (1)	1 (1)									
Any adenovirus	74%		77%											
	[60, 83]		[67, 84]											
	1 (1)		1 (1)											
BNT162b2		87%	87%	83%	78%							[0, 96]	[0.00, 0.41]	Yes
		[48, 97]	[47, 97]	[33, 96]	[-83, 99]									
		[-19, 99]	[-21, 99]	[-38, 98]	[-89, 99]									
		2 (2)	2 (2)	1 (1)	1 (1)									
mRNA-1273														

ChAdOx1	74%		77%											
	[60, 83]		[67, 84]											
	1 (1)		1 (1)											
Ad26.COV2.S														

Question 2a-2: OR against COVID-19 infections (Omicron variant) change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus one or more additional doses – comparison to those who have only received the primary series

Table 8: OR against COVID-19 infections[#] for completed primary series and **ONE** additional dose vs. those who have only received the primary series (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	MOD
	0-6 (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+ (44+)			
Any vaccine		.29	.64*	.72*	1.14*							[64, 32]	[0.28, 0.20]	Yes
		[.19, .44]	[.37, 1.14]	[.50, 1.06]	[.73, 1.76]									
		[.13, .68]	[.25, 1.63]	[.32, 1.65]	[.48, 2.68]									
		3 (7)	2 (2)	3 (7)	1 (5)									
Any mRNA vaccine		.29	.64*	.72*	1.14*							[64, 32]	[0.28, 0.20]	Yes
		[.19, .44]	[.37, 1.14]	[.50, 1.06]	[.73, 1.76]									
		[.13, .68]	[.25, 1.63]	[.32, 1.65]	[.48, 2.68]									
		3 (7)	2 (2)	3 (7)	1 (5)									
Any adenovirus														
BNT162b2		.37	.74*	.78*								[10, 86]	[0.07, 0.21]	Yes
		[.17, .82]	[.33, 1.63]	[.36, 1.69]										

		[.11, 1.28]	[.21, 2.56]	[.23, 2.66]										
		2 (2)	1 (1)	2 (2)										
mRNA-1273		.21	.47	.66	1.02									
		[.15, .29]	[.27, .81]	[.48, .90]	[.83, 1.25]									
		1 (5)	1 (1)	1 (5)	1 (5)									
ChAdOx1														
Ad26.COV2.S														

Table 9: OR against COVID-19 infections[#] for completed primary series and **TWO** additional doses vs. those who received the primary series and **ONE** additional dose (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	MOD
	0-6 (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+ (44+)			
Any vaccine		.35	.40											
		[.25, .50]	[.25, .63]											
		1 (4)	1 (4)											
Any mRNA vaccine		.35	.40											
		[.25, .50]	[.25, .63]											
		1 (4)	1 (4)											
Any adenovirus														
BNT162b2														
mRNA-1273		.35	.40											
		[.25, .50]	[.25, .63]											
		1 (4)	1 (4)											
ChAdOx1														

Ad26.COV2.S														

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

Table 10: OR against COVID-19 hospitalisations for completed primary series and **ONE** additional dose vs. primary series only (**Omicron variant**)

	Baseline days (weeks)		Follow-up days (weeks)									I^2 [w/b]	σ [w/b]	MOD
	0-6 (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+ (44+)			
Any vaccine	.34	.38	.48	.58		.82						[48, 48]	[0.21, 0.21]	Yes
	[.00, 3029.54]	[.01, 21.99]	[.01, 17.06]	[.04, 8.87]		[.02, 32.94]								
	[.00, 6417.12]	[.00, 96.85]	[.00, 86.41]	[.01, 60.82]		[.00, 160.18]								
	1 (1)	1 (1)	1 (1)	2 (2)		1 (1)								
Any mRNA vaccine	.34	.38	.48	.58		.82						[48, 48]	[0.21, 0.21]	Yes
	[.00, 3029.54]	[.01, 21.99]	[.01, 17.06]	[.04, 8.87]		[.02, 32.94]								
	[.00, 6417.12]	[.00, 96.85]	[.00, 86.41]	[.01, 60.82]		[.00, 160.18]								
	1 (1)	1 (1)	1 (1)	2 (2)		1 (1)								
Any adenovirus														
BNT162b2		.35	.44	.47										
		[.26, .47]	[.41, .47]	[.44, .51]										
		1 (1)	1 (1)	1 (1)										

mRNA-1273														
ChAdOx1														
Ad26.COV2.S														

Table 11: OR against COVID-19 hospitalisations for completed primary series and **TWO** additional doses vs. primary series only (**Omicron variant**)

	Baseline days (weeks)		**Follow-up days (weeks)**									**I^2 [w/b]**	**σ [w/b]**	**MOD**
	0-6 (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+ (44+)**			
Any vaccine	.49		.82	.49										
	[.39, .61]		[.53, 1.26]	[.39, .61]										
	1 (1)		1 (1)	1 (1)										
Any mRNA vaccine	.49		.82	.49										
	[.39, .61]		[.53, 1.26]	[.39, .61]										
	1 (1)		1 (1)	1 (1)										
Any adenovirus														
BNT162b2														
mRNA-1273														
ChAdOx1														

Ad26.COV2.S														

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

Table 12: OR against COVID-19 deaths for completed primary series and **ONE** additional dose vs. primary series only (**Omicron variant**)

No data to report

Question 3a: OR against COVID-19 infections, hospitalisations, and deaths (Omicron variant), change over time (>84 days) in individuals who have received a complete primary COVID-19 vaccine series plus one or more additional doses – comparison to those who have received a complete primary COVID-19 vaccine series plus one or more additional doses and have been previously infected

Table 13: OR against COVID-19 infections[#] for completed primary series and **ONE** additional dose vs. primary series, booster dose, and previous infection (**Omicron variant**)

No data to report

Table 14: OR against COVID-19 hospitalisations for completed primary series and **ONE** additional dose vs. primary series, booster dose, and previous infection (**Omicron variant**)

No data to report

Table 15: OR against COVID-19 deaths for completed primary series and **ONE** additional dose vs. primary series, booster dose, and previous infection (**Omicron variant**)

No data to report

Narrative overview of findings

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

A total of twelve studies (22 cohorts) reported Omicron variant data, for which the 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. The majority of this data reflected mRNA vaccines. There did not seem to be a difference between mRNA and adenovirus vaccines, but given the limited number of adenovirus studies caution is needed in this interpretation.

The all-strain data (**Appendix 2**) found similar patterns except the baseline levels of VE were above the WHO minimum preferred level. The analyses indicated that VE for infections started to wane as of 16 weeks post full vaccine schedule. With regards to individual vaccines, there seemed to be a slight benefit of the mRNA-1273 vaccine over the other vaccines (Figure A2-1).

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

A total of eight studies (nine cohorts) reported Omicron variant data, for which the baseline levels of VE did not meet the WHO minimum preferred level of VE. There was no statistical decline in the VE up to 20 weeks post full schedule. However, there was a statistical decline in VE as of 24 weeks post full schedule. The majority of this data reflected mRNA vaccines.

For the all-strain data, the baseline levels were above the WHO minimum level. As of 16 weeks post full schedule there was a statistically significant decease in VE which lasted up to 40 weeks post full schedule. This drop pushed the VE to below the WHO minimum level, but only slightly (89% at 16 weeks to 80% by 40 weeks).

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

A total of one study (2 cohorts) reported Omicron variant data, for which the baseline levels of VE did not meet the WHO minimum preferred level of VE. There is too little data to draw any conclusions about potential further reductions and differences across vaccines.

For the all-strain data, the baseline levels were above the WHO minimum level and there was a statistically significant decease in VE 20 weeks post receipt of a vaccine series, which was clinically meaningful, i.e., waning, but the VE still remained relatively high (85%).

2a-1. Findings for confirmed COVID-19 infections primary series plus one or more additional doses – compared to unvaccinated

A total of twelve studies (25 cohorts) reported Omicron variant data, for which the baseline levels of VE did not meet the WHO minimum preferred level of VE. There was a statistical decrease in VE from 12 weeks post *one additional dose*. The majority of this data reflected mRNA vaccines. There is a small suggestion that BNT162b2 may be better than mRNA-1273, but this needs to be interpreted with caution due to the small number of studies.

A total of one study (4 cohorts) reported Omicron variant data, for which the baseline levels of VE did not meet the WHO minimum preferred level of VE. There was a non-statistical decrease in VE from 12 weeks post *two additional doses*. All of this reflected the mRNA-1273 vaccine.

2b-1. Findings for COVID-19 related hospitalisations primary series plus one or more additional doses – compared to unvaccinated
A total of eight studies (13 cohorts) reported Omicron variant data, for which the baseline levels of VE did not meet the WHO minimum preferred level of VE, just (i.e., 89%). There was a statistical decrease in VE as of 12 weeks. Virtually all this data reflected mRNA vaccines and predominately the BNT162b2 vaccine.

2c-1. Findings for COVID-19 related deaths primary series plus one or more additional doses – compared to unvaccinated
A total of three studies (4 cohorts) reported Omicron variant data, for which the baseline levels of VE did not meet the WHO minimum preferred level of VE, just (i.e., 86%). There was no statistical change in VE up to 16 weeks post booster dose. Virtually all this data reflected mRNA vaccines and predominately the BNT162b2 vaccine.

2a-2. Findings for confirmed COVID-19 infections primary series plus one or more additional doses – compared to full vaccine series
A total of three studies (7 cohorts) reported Omicron variant data. These studies found a benefit at baseline of *one additional dose* compared to full schedule (OR = 0.29). There was a statistically significant increase in the OR (i.e., less benefit) as of 12 weeks post booster dose, with further degradations in OR up to 24 weeks post booster dose. All this data reflected mRNA vaccines.

A total of one study (4 cohorts) reported Omicron variant data. This study found a benefit at baseline of *two additional doses* compared to *one additional dose* (OR = 0.35). This benefit seemed to be maintained at 16 weeks post second booster dose. All this data reflected the mRNA-1273vaccine.

2b-2. Findings for COVID-19 related hospitalisations primary series plus one or more additional doses – compared to full vaccine series
A total of two studies (2 cohorts) reported Omicron variant data for *one additional dose* compared to a full series. These studies found a benefit at baseline of the booster compared to full schedule (ORs = 0.38 and 0.34). There were non-statistical increases in the OR's as of 12 weeks post additional dose, which rose significantly by 24 weeks post additional dose (OR = 0.82). All studies used mRNA vaccines.

A total of one study (1 cohort) reported Omicron variant data for *two additional doses* compared to a full series. This study found a benefit at baseline of the boosters compared to full schedule (OR = 0.49) with a dramatic decrease in protection at 16 weeks post the last booster dose (OR = 0.82). This study used mRNA vaccines.

2c-2. Findings for COVID-19 related deaths primary series plus one or more additional doses – compared to full vaccine series
There was no available data to report on this.

3a. Findings for confirmed COVID-19 infections primary series plus one or more additional doses – compared to primary series, booster, and previous infection
There was no available data to report on this.

3b. Findings for COVID-19 related hospitalisations primary series plus one or more additional doses – compared to primary series, booster, and previous infection
There was no available data to report on this.

3c. Findings for COVID-19 related deaths primary series plus one or more additional doses – compared to primary series, booster, and previous infection
There was no available data to report on this.

Risk of bias (RoB) assessment
The risk of bias data for each individual study is provided in the Supplementary File (les10.10_vaccine_waning_adults_3_RoB_2022-09-14.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 risk of bias. Five studies (Young-Xu et al., Menni et al., Lee et al., Paranthaman et al., Stirrup et al) were deemed as having a critical RoB and were excluded from the analyses. Young-Xu et al., Menni et al., and Lee et al., did not account for calendar time; Menni et al also used self-reported vaccination and infection data; and both Paranthaman et al. and Stirrup et al. did not account for medical conditions in a long-term care cohort.

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
It is clear from the evidence reported in the current review that the baseline levels of VE for both the primary series and the primary series plus additional doses against the Omicron variant *do not meet the WHO minimum preferred level* of VE for infections. Furthermore, there was evidence of further *long-term waning in VE for COVID-19 infections*, though 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 strong evidence of large degradations in VEs for Omicron-based COVID-related hospitalisations and mortality*, though there were statistical reductions overtime for hospitalisations but not mortality, especially for those with a primary series plus one additional dose.

When compared to those with just a primary series, there is a clear baseline benefit of additional doses. However, as of 12 weeks post one additional dose there seems to be a statistically significant reduction in benefit against infections and a non-statistically significant reduction against hospitalisations. This data is suggestive of the fact that there is *waning in one additional dose* compared to a primary series. One study suggested that when comparing two additional doses to one additional dose, there was a baseline benefit and this was maintained 16 weeks post second additional dose.

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, physical distancing, and quarantining when infected, in individuals who are fully vaccinated with or without additional doses. 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.

Funding
To help Canadian decision-makers as they respond to unprecedented challenges related to the COVID-19 pandemic, the COVID-19 Evidence Network to support Decision-making (COVID-END) in Canada is preparing rapid evidence responses like this one. The development and continued updating of this living evidence synthesis has been funded by the Canadian Institutes of Health Research (CIHR) and the Public Health Agency of Canada (PHAC).

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). Drs. Wu and Joyal-Desmarias and Ms. Sanuade are supported by the CIHR-SPOR Mentoring Chair program (SMC-151518). Ms. Vieira is supported by a FRQS PhD scholarship.

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.

Citation
Bacon SL, Wu N, Joyal-Desmarais K, Vieira AM, Sanuade C, Jagwani M, Ribeiro PAB, Yip D, Stojanovic J. COVID-19 living evidence synthesis #10 (version 10.11): What is the long-term effectiveness of available COVID-19 vaccines for adults, including for variants of concern and over time frames beyond 112 days in those with a primary series and beyond 84 days in those with a primary series and an additional dose? The Montreal Behavioural Medicine Centre, META group, 12 October 2022