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 10.16: 29 March 2023)

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.

Future updates of this document will be posted on the COVID-END website.

Flow of included studies

Overall (from the initiation of this review), 17,432 studies were title and abstract screened, 1,450 were full text appraised, with 85 initially included, 5 studies were excluded (RoB; see **Appendix 1b**), leaving 80 that were used to complete this summary. The reasons for excluding the 1,370 studies are reported in **Appendix 7b and 8** (which includes the 55 studies from the current update).

Highlights of changes in this version

- ***Three*** new studies were added (marked in blue in **Appendix 1**) that reported on the long-term VE of the full vaccine schedule compared to unvaccinated individuals.
- ***Two*** new studies were added (marked in blue in **Appendix 1**) that reported on the long-term VE of the full vaccine schedule plus one additional dose compared to unvaccinated individuals.
- ***Three*** new studies were added (marked in blue in **Appendix 1**) that reported on the long-term ORs of additional doses compared to a 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.

  Of note, we had one study that included data on the long-term ORs of a bivalent vaccine; however, it was excluded due to a lack of adjustment of comorbid conditions in a long-term care population (Stirrup et al.).

- As a reminder, 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. By approximately week 32, there seemed to be no noticeable VE benefit from the primary vaccine series. There seemed to be no clinical difference across vaccines, though adenovirus vaccines tended to have a generally lower VE than mRNA vaccines (*Table 1*).
- 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. By approximately week 36, there seemed to be no noticeable VE benefit from the primary vaccine series. There seemed to be no clinical difference across vaccines (*Table 2*).
- For COVID-19 mortality, there was limited data to be able to draw any inferences (*Table 3*).

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 (*Table 4*).
- For COVID-19 hospitalisations, baseline levels of VE did meet the WHO level of adequate VE. 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. Though limited, there is a suggestion that adenovirus vaccines tended to have a generally lower VE than mRNA vaccines (*Table 6*).
- 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 (*Table 7*).

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 (*Table 5*).

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 (*Table 8*).
- For COVID-19 hospitalisations, there was a benefit of the booster compared to a primary series 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). The level of degradation at 12 weeks suggests that there is no noticeable VE benefit of a booster dose relative to the primary vaccine series. This data predominately reflects mRNA vaccines (*Table 9*).
- For COVID-19 mortality, there were no studies that compared a primary series vs. a primary series 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 primary series vs. a primary series plus two booster doses (*Table 10*).

Two booster doses vs. one booster dose

- For COVID-19 infections, there was a benefit of two booster doses compared to a primary series and one booster dose at baseline. This seemed to be stable up to 16 weeks after receiving the second booster dose (compared to the primary series plus one booster dose). This data only reflects mRNA vaccines (*Table 12*).

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.

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 the primary series against the Omicron variant *did 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*, with a potential loss of any benefits 32 weeks after receiving a primary vaccine series, 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). There is some suggestion of *stability in Omicron-based COVID-related hospitalisations* VE's up to 20 weeks post schedule; however, there may be a potential loss of any benefits 36 weeks after receiving a primary vaccine series. There was not enough data to draw any inferences about VEs for Omicron-based COVID-related mortality following a primary series.

Similar to the primary series, baseline levels of VE for the primary series plus additional doses against the Omicron variant did not meet the WHO minimum preferred level of VE for infections and mortality; however, the VE's for *hospitalisations did meet the WHO minimum preferred level*. There was evidence of *long-term waning in VE for both COVID-19 infections and hospitalisations*, which seemed to occur by 12 weeks post additional dose. When compared to those with just a primary series, there is a *clear baseline benefit of an additional dose*. However, as of 12 weeks post one additional dose there was a statistically significant reduction in benefit against infections and hospitalisations. This data is suggestive of the fact that there is *waning in one additional dose* compared to a primary series.

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.

Résumé des résultats pour le variant Omicron

Série primaire de vaccination

- En ce qui concerne les infections liées à la COVID-19, l'efficacité vaccinale au niveau de base était inférieure à ce que l'OMS considère comme étant adéquat. De plus, une dégradation statistiquement significative de l'efficacité vaccinale a été observée à partir de 16 semaines après l'administration de la série primaire. À environ 32 semaines, il ne semblait plus y avoir de bénéfice notable lié à l'efficacité vaccinale de la série primaire. Aussi, il ne semble pas y avoir de différence cliniquement significative entre les types de vaccins, bien que ceux de type adénovirus semblent avoir une efficacité généralement plus faible que ceux de type ARNm (*Tableau 1*).
- Pour ce qui est des hospitalisations en lien avec la COVID-19, l'efficacité vaccinale au niveau de base était inférieure à ce que l'OMS considère comme étant adéquat. Il semblait tout de même y avoir une certaine stabilité quant à l'efficacité vaccinale jusqu'à 20 semaines après l'administration de toutes les doses de la série primaire. À environ 36 semaines, il ne semblait cependant plus y avoir de bénéfice notable lié à l'efficacité vaccinale de la série primaire. Aussi, il ne semblait pas y avoir de différence cliniquement significative entre les différents types de vaccin (*Tableau 2*).
- Quant à la mortalité liée à la COVID-19, il y avait une quantité trop limitée de données disponibles pour pouvoir en tirer des conclusions (*Tableau 3*).

Une dose de rappel vs. non-vaccinés

- En ce qui concerne les infections liées à la COVID-19, l'efficacité vaccinale au niveau de base était inférieure à ce que l'OMS considère comme étant adéquat. À partir de 12 semaines après l'administration de la dose de rappel, une dégradation statistiquement significative de l'efficacité vaccinale a été observée. Les données recueillies se concentrent principalement sur les vaccins de type ARNm, ne permettant ainsi pas de faire de conclusions concernant les autres types de vaccins (*Tableau 4*).
- Pour ce qui est des hospitalisations liées à la COVID-19, l'efficacité vaccinale au niveau de base était inférieure à ce que l'OMS considère comme étant adéquat. Aussi, il y avait une dégradation statistiquement significative de l'efficacité vaccinale à partir de 12 semaines après l'administration de la dose de rappel, ce qui concorde avec notre définition de diminution de l'efficacité. Les données recueillies se focalisent principalement sur les vaccins de type ARNm, mais suggèrent tout de même que les vaccins de type adénovirus ont une efficacité vaccinale moindre (*Tableau 6*).
- Quant à la mortalité liée à la COVID-19, l'efficacité vaccinale au niveau de base était inférieure, bien que très près (86%), à ce que l'OMS considère comme adéquat. Jusqu'à 16 semaines après l'administration de la dose de rappel, il n'y avait aucun changement statistiquement significatif de l'efficacité vaccinale. Les données recueillies représentant majoritairement les vaccins de type ARNm, il est impossible de tirer des conclusions pour les autres types de vaccins (*Tableau 7*).

Deux doses de rappel vs. non-vaccinés

- En ce qui concerne les infections liées à la COVID-19, les données recueillies sont très limitées, mais suggèrent que l'efficacité vaccinale est inférieure à ce que l'OMS considère comme adéquat. Cependant, il n'y a pas eu de dégradation statistiquement significative de l'efficacité vaccinale 12 semaines après l'administration des doses de rappel. Toutes les données recueillies concernent le vaccin ARNm-1273 (*Tableau 5*).

Une dose de rappel vs. série primaire de vaccination

- En ce qui concerne les infections liées à la COVID-19, la dose de rappel semble offrir un bénéfice en comparaison avec la série primaire. À partir de 12 semaines après l'administration de la dose de rappel, une dégradation statistiquement significative de l'OR a été observée (en comparaison avec la série primaire). Les données recueillies concernent uniquement les vaccins de type ARNm (*Tableau 8*).

- Pour ce qui est des hospitalisations dû à la COVID-19, la dose de rappel offre un bénéfice en comparaison avec la série primaire. À partir de 12 semaines après l'administration de la dose de rappel, une dégradation statistiquement significative de l'OR a été observée (en comparaison avec la série primaire). Le niveau de dégradation après 12 semaines semble suggérer que la dose de rappel n'apporte pas de bénéfice notable en ce qui concerne l'efficacité vaccinale en comparaison à la série primaire. Les données recueillies se focalisent principalement sur les vaccins de type ARNm (*Tableau 9*).
- Quant à la mortalité dû à la COVID-19, aucune étude comparant l'efficacité de l'administration d'une dose de rappel à celle de la série primaire n'a été identifiée.

Deux doses de rappel vs. série primaire de vaccination

- En ce qui concerne les infections liées à la COVID-19, une seule étude pertinente a été identifiée; il n'est donc pas possible de tirer des conclusions quant aux bénéfices qu'apporterait l'administration de deux doses de rappel en comparaison avec la série primaire (*Tableau 10*).

Deux doses de rappel vs. une dose de rappel

- En ce qui concerne les infections liées à la COVID-19, l'administration de deux doses de rappel offre un bénéfice par rapport à l'efficacité vaccinale au niveau de base lorsque comparée à l'administration d'une seule dose de rappel. Seize semaines après l'administration de la deuxième dose de rappel, le bénéfice semble demeurer stable (en comparaison avec l'administration d'une seule dose de rappel). Les données recueillies concernent uniquement les vaccins de type ARNm (*Tableau 12*).

Une dose de rappel vs. une infection précédente et une dose de rappel

- Aucune étude comparant l'administration d'une dose de rappel avec l'administration d'une dose de rappel chez des individus ayant précédemment été infectés par la COVID-19 n'a été identifiée.

Répercussions potentielles sur la prise de décision dans le système de santé

Il est évident selon l'information recueillie lors de cette revue que l'efficacité vaccinale au niveau de base pour la série primaire de vaccins contre les infections liées au variant Omicron est *inférieure à ce que l'OMS considère comme étant adéquat.* De plus, les données indiquent une *diminution de l'efficacité vaccinale à long terme* en ce qui concerne les infections liées à la COVID-19, avec une perte potentielle de tous les bénéfices 32 semaines après l'administration de la série primaire. Le mécanisme engendrant cette perte d'efficacité est cependant incertain (p. ex., dégradation de l'immunogénicité, changement des mesures de santé publique, variation du nombre de cas et de la transmission générale). Certaines données suggèrent que *les cas d'hospitalisations liés au variant Omicron sont stables jusqu'à 20 semaines* après l'administration de la série primaire; or, il pourrait tout de même y avoir une perte potentielle de tous les bénéfices 36 semaines après l'administration de la série primaire. Il n'y avait pas suffisamment de données pour permettre de tirer des conclusions concernant l'efficacité vaccinale contre la mortalité liée au variant Omicron à la suite de l'administration de la série primaire.

De manière similaire à la série primaire, l'efficacité vaccinale de la dose de rappel contre les infections et la mortalité liées au variant Omicron est *inférieure à ce que l'OMS considère comme étant adéquat.* Cependant, l'efficacité vaccinale *contre les hospitalisations correspond à ce que l'OMS considère comme étant adéquat*. Les données recueillies indiquent aussi une *diminution de l'efficacité vaccinale à long terme* en ce qui concerne les infections et les hospitalisations liées à la COVID-19 environ 12 semaines après l'administration de la dose de rappel. En comparaison avec l'administration de la série primaire uniquement, l'administration de la dose de rappel engendre une amélioration notable de l'efficacité vaccinale au niveau de base. Cependant, 12 semaines après l'administration de la dose de rappel il y a tout de même une *diminution de l'efficacité vaccinale à long terme* en ce qui concerne les infections et les hospitalisations. Ces données suggèrent qu'il y a une *diminution de l'efficacité vaccinale liée à l'administration d'une dose de rappel* en comparaison avec la série primaire de vaccins

Puisqu'Omicron est maintenant considéré comme étant le variant dominant au Canada, il pourrait être bénéfique de maintenir certains comportements liés à la prévention de la COVID-19 (p. ex., porter un masque, pratiquer la distanciation physique, se mettre en quarantaine lors d'une infection) et ce, même chez les individus ayant reçu la série primaire avec ou sans doses de rappel, afin de diminuer les risques de transmission du virus et de limiter l'augmentation du nombre de cas. Ces recommandations doivent être considérées en regard du nombre très limité d'études portant sur de multiples méthodes de prévention et de l'absence d'études randomisées contrôlées sur l'utilité de ces méthodes.

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

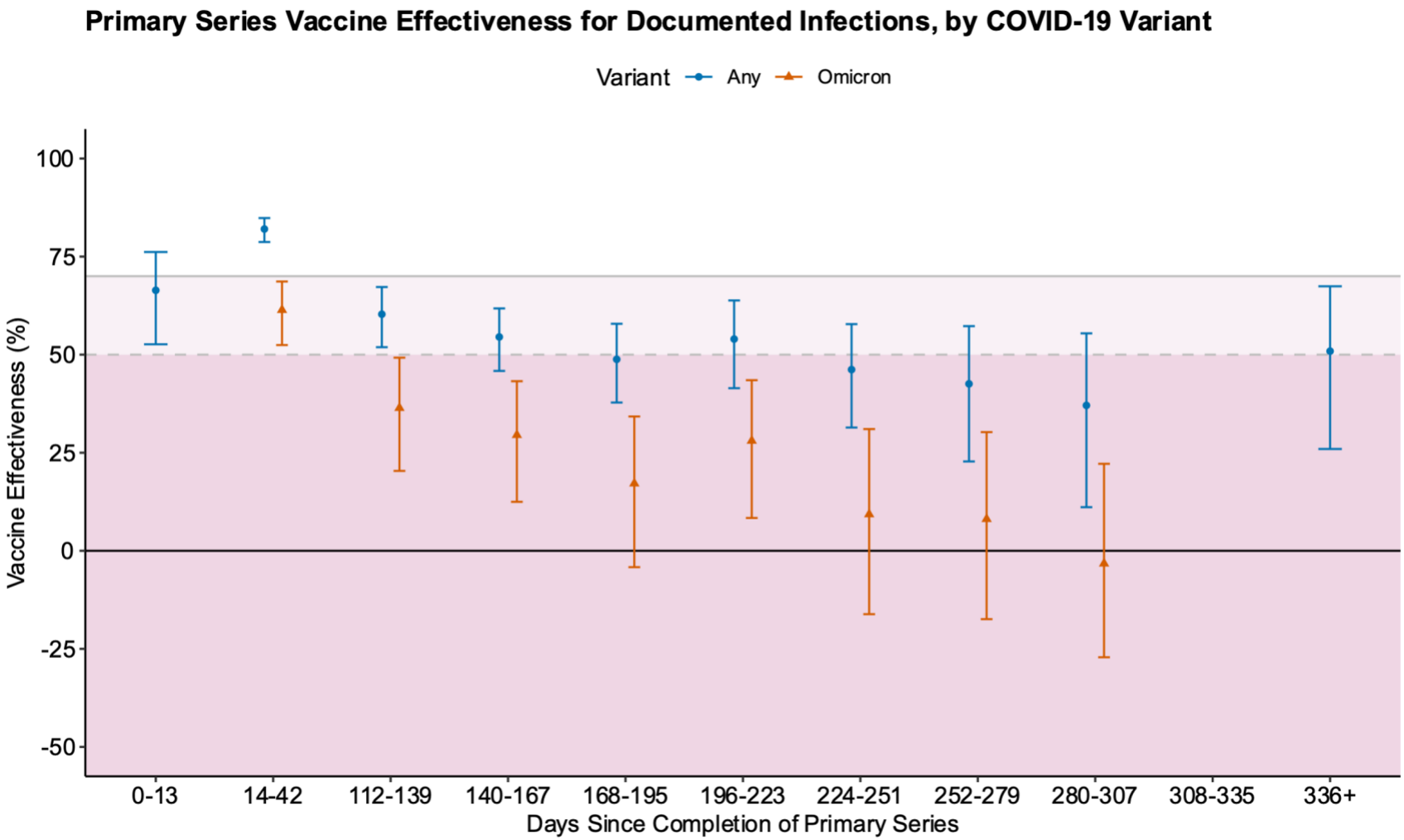
Table 1: VE against COVID-19 infections[#] for completed primary series (**Omicron variant**)

	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	56%	61%	36%*	30%†*	17%†*	28%†*	9%†*	8%†*	-3%†*	21%†*	27%*	[35, 65]	[0.25, 0.34]	Yes
	[31, 72]	[52, 69]	[20, 49]	[12, 43]	[-4, 34]	[8, 43]	[-16, 31]	[-17, 30]	[-27, 22]	[-6, 42]	[-1, 47]			
	[-13, 83]	[8, 84]	[-34, 73]	[-40, 70]	[-50, 65]	[-42, 70]	[-54, 63]	[-55, 62]	[-60, 57]	[-48, 68]	[-44, 70]			
	2 (3)	14 (26)	8 (15)	9 (19)	6 (14)	6 (11)	4 (7)	4 (7)	4 (7)	3 (6)	3 (6)			
Any mRNA vaccine	30%	69%†	46%*	31%*	19%*	23%*	2%*	-3%*	-13%*	8%*	22%*	[12, 88]	[0.19, 0.51]	Yes
	[-31, 67]	[55, 78]	[22, 63]	[0, 52]	[-16, 45]	[-12, 48]	[-32, 35]	[-35, 31]	[-42, 24]	[-30, 40]	[-19, 50]			
	[-62, 82]	[0, 90]	[-42, 83]	[-55, 78]	[-61, 75]	[-60, 76]	[-68, 70]	[-70, 68]	[-73, 64]	[-67, 72]	[-61, 76]			
	1 (1)	9 (14)	5 (8)	5 (8)	3 (5)	3 (4)	2 (3)	3 (4)	3 (4)	2 (3)	2 (3)			
Any adenovirus		45%	31%	19%*	-2%*	5%*	-11%*	-15%*	-18%*	23%	20%	[36, 63]	[0.18, 0.23]	Yes
		[26, 59]	[1, 51]	[-9, 41]	[-31, 28]	[-29, 36]	[-40, 24]	[-42, 21]	[-45, 19]	[-16, 50]	[-24, 51]			
		[-8, 72]	[-29, 66]	[-38, 59]	[-52, 50]	[-49, 54]	[-57, 46]	[-59, 44]	[-61, 42]	[-39, 64]	[-43, 64]			
		4 (6)	2 (3)	3 (5)	2 (3)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)			
BNT162b2		62%	32%*	22%*	5%*	7%*	-14%*	-22%*	-32%*	-9%*	7%*	[67, 32]	[0.21, 0.14]	Yes
		[53, 70]	[11, 48]	[2, 37]	[-19, 27]	[-20, 31]	[-36, 14]	[-42, 5]	[-50, -7]	[-34, 21]	[-25, 35]			
		[34, 78]	[-18, 62]	[-27, 55]	[-41, 47]	[-41, 49]	[-53, 36]	[-57, 29]	[-63, 19]	[-50, 41]	[-42, 50]			
		5 (7)	3 (4)	4 (6)	3 (4)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)			
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		38%	17%	11%*	-13%*	-8%*	-23%*	-26%*	-29%*	11%	8%	[73, 26]	[0.18, 0.11]	Yes
		[22, 51]	[-13, 41]	[-10, 29]	[-33, 13]	[-34, 22]	[-44, 7]	[-47, 3]	[-49, 1]	[-24, 39]	[-31, 41]			
		[-2, 63]	[-31, 53]	[-32, 46]	[-48, 32]	[-47, 37]	[-56, 26]	[-58, 23]	[-59, 21]	[-38, 51]	[-42, 51]			
		3 (5)	1 (2)	3 (5)	2 (3)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)			
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.

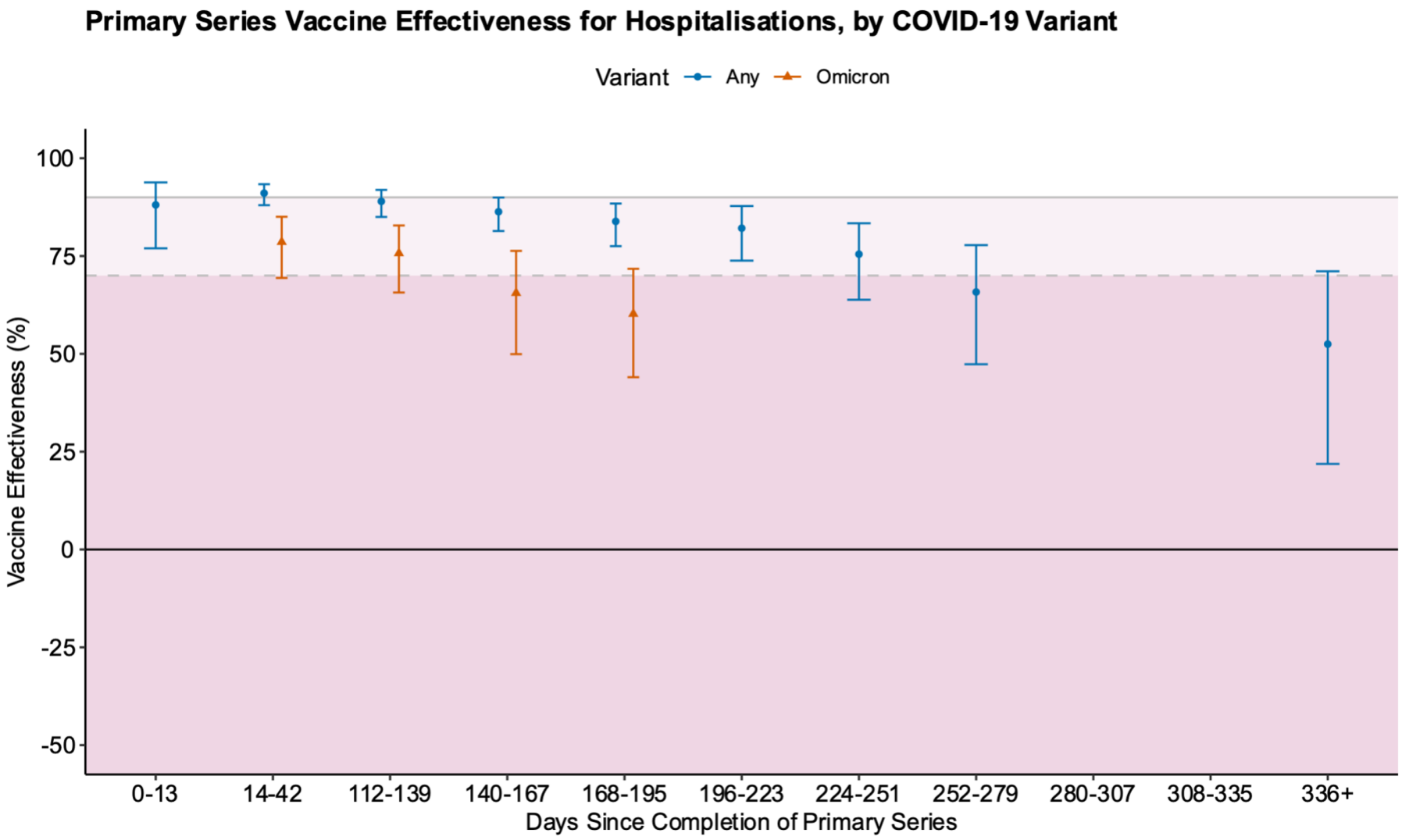
Question 1b: VE against COVID-19 hospitalisations (Omicron variant) change over time (>112 days) in individuals who have received a complete primary COVID-19 vaccine series

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	72%	79%	76%	66%*	60%*	61%*	38%*	8%*	-34%†*	-31%†*	-17%†*	[57, 40]	[0.42, 0.35]	Yes
	[1, 92]	[69, 85]	[66, 83]	[50, 76]	[44, 72]	[41, 74]	[5, 60]	[-29, 40]	[-61, 9]	[-59, 15]	[-50, 27]			
	[-33, 95]	[32, 93]	[23, 92]	[-9, 89]	[-20, 87]	[-21, 88]	[-50, 81]	[-66, 72]	[-80, 55]	[-79, 57]	[-75, 64]			
	2 (2)	9 (18)	6 (15)	4 (13)	6 (14)	3 (11)	3 (10)	3 (9)	2 (7)	2 (8)	3 (8)			
Any mRNA vaccine	80%	81%	78%	67%*	64%*	63%	39%*	1%*	-43%*	-35%*	-5%*	[56, 42]	[0.47, 0.41]	Yes
	[-63, 98]	[70, 88]	[65, 86]	[44, 80]	[41, 78]	[28, 81]	[-16, 69]	[-49, 50]	[-75, 23]	[-71, 32]	[-53, 48]			
	[-72, 99]	[27, 95]	[16, 94]	[-23, 92]	[-29, 91]	[-35, 91]	[-61, 85]	[-76, 76]	[-87, 61]	[-86, 66]	[-78, 75]			
	1 (1)	9 (11)	6 (8)	4 (6)	5 (7)	3 (5)	3 (5)	3 (4)	1 (2)	2 (3)	2 (3)			
Any adenovirus		75%	72%	63%	57%*	57%	35%*	9%*	-30%*	-29%*	-34%*	[42, 56]	[0.40, 0.47]	Yes
		[51, 88]	[46, 85]	[27, 81]	[16, 78]	[15, 78]	[-25, 68]	[-46, 55]	[-68, 36]	[-68, 38]	[-72, 37]			
		[-2, 94]	[-12, 93]	[-34, 91]	[-43, 89]	[-43, 90]	[-63, 84]	[-74, 78]	[-84, 67]	[-84, 68]	[-85, 67]			
		3 (7)	3 (7)	3 (7)	2 (6)	2 (6)	2 (5)	2 (5)	2 (5)	2 (5)	2 (5)			
BNT162b2	79%	80%	77%	66%	63%*	62%	38%*	-3%*	-45%*	-37%*	-7%*	[53, 45]	[0.50, 0.46]	Yes
	[-65, 99]	[66, 89]	[58, 88]	[37, 82]	[36, 79]	[21, 82]	[-23, 70]	[-54, 51]	[-77, 26]	[-74, 35]	[-58, 50]			
	[-75, 99]	[13, 96]	[-3, 95]	[-35, 93]	[-39, 92]	[-45, 92]	[-66, 87]	[-80, 79]	[-89, 65]	[-88, 69]	[-81, 78]			
	1 (1)	6 (8)	3 (5)	3 (5)	5 (7)	3 (5)	3 (5)	3 (4)	1 (2)	2 (3)	2 (3)			
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		82%	76%	67%	62%*	63%*	46%*	25%*	-16%*	-15%*	-21%*	[49, 50]	[0.42, 0.43]	Yes
		[59, 92]	[48, 89]	[30, 85]	[20, 82]	[20, 82]	[-13, 75]	[-37, 65]	[-64, 49]	[-64, 50]	[-69, 50]			
		[21, 96]	[-3, 94]	[-28, 92]	[-37, 91]	[-37, 91]	[-56, 87]	[-68, 82]	[-81, 73]	[-81, 74]	[-83, 73]			
		2 (4)	2 (4)	2 (4)	2 (4)	2 (4)	2 (4)	2 (4)	2 (4)	2 (4)	2 (4)			
Ad26.COV2.S		-32%	95%	71%	58%	60%	43%	-68%	-61%	-66%	-78%			
		[-91, 81]	[-50, 100]	[58, 79]	[24, 77]	[19, 81]	[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]			
		1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)			

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		82%	81%	73%	60%	51%*	15%*	-41%*	-53%*	-52%*	-51%*	[0, 98]	[0.00, 1.58]	Yes
		[-68, 99]	[-68, 99]	[-77, 98]	[-84, 98]	[-87, 97]	[-93, 95]	[-96, 89]	[-97, 87]	[-97, 88]	[-97, 89]			
		[-96, 100]	[-96, 100]	[-97, 100]	[-98, 100]	[-98, 100]	[-99, 99]	[-100, 99]	[-100, 98]	[-100, 98]	[-100, 98]			
		2 (3)	2 (3)	2 (3)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)			
Any mRNA vaccine		82%	90%	71%	66%	58%	27%	-31%	-45%	-44%	-43%	[22, 76]	[0.79, 1.44]	Yes
		[-88, 100]	[-82, 100]	[-91, 99]	[-96, 100]	[-97, 99]	[-98, 99]	[-99, 98]	[-99, 98]	[-99, 98]	[-99, 98]			
		[-99, 100]	[-99, 100]	[-99, 100]	[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]	[-100, 100]			
		2 (2)	2 (2)	2 (2)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)			
Any adenovirus		84%	-7%	17%										
		[-22, 98]	[-68, 63]	[-4, 34]										
		1 (1)	1 (1)	1 (1)										
BNT162b2		97%	94%	90%	87%	84%	72%	44%	30%	32%	33%			
		[91, 99]	[90, 96]	[85, 93]	[81, 91]	[77, 89]	[59, 81]	[21, 60]	[-7, 55]	[-18, 62]	[-33, 70]			
		1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)			
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	55%	67%	51%*	42%*	-4%†*							[37, 63]	[0.34, 0.45]	Yes
	[32, 70]	[56, 76]	[34, 64]	[21, 58]	[-37, 31]									
	[-33, 86]	[-5, 90]	[-36, 85]	[-46, 82]	[-71, 68]									
	2 (7)	11 (22)	11 (24)	8 (20)	3 (7)									
Any mRNA vaccine	55%	67%	51%*	42%*	-4%†*							[38, 62]	[0.35, 0.45]	Yes
	[32, 70]	[55, 76]	[34, 64]	[20, 58]	[-37, 31]									
	[-34, 86]	[-7, 90]	[-36, 85]	[-47, 82]	[-71, 69]									
	2 (7)	11 (20)	11 (22)	8 (20)	3 (7)									
Any adenovirus		62%	27%											
		[44, 74]	[-42, 69]											
		1 (2)	1 (2)											
BNT162b2	62%	64%	55%	47%	-36%†*							[24, 76]	[0.38, 0.68]	Yes
	[23, 82]	[34, 80]	[19, 75]	[2, 71]	[-77, 44]									
	[-54, 93]	[-49, 93]	[-60, 92]	[-66, 90]	[-90, 76]									
	1 (4)	6 (8)	6 (12)	5 (9)	1 (1)									
mRNA-1273	54%	73%	49%	36%*	-7%†*							[96, 3]	[0.39, 0.07]	Yes
	[18, 75]	[56, 83]	[17, 68]	[13, 53]	[-37, 28]									
	[-20, 83]	[30, 89]	[-24, 80]	[-35, 73]	[-63, 57]									

	1 (2)	2 (6)	2 (3)	3 (8)	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%	92%†	71%*	50%*	65%*	88%	30%	74%	76%	-10%		[45, 53]	[0.55, 0.59]	Yes
	[14, 89]	[87, 95]	[53, 82]	[11, 72]	[-2, 88]	[-32, 99]	[-93, 97]	[-92, 99]	[-97, 100]	[-100, 100]				
	[-52, 95]	[56, 99]	[-37, 95]	[-64, 91]	[-59, 95]	[-58, 99]	[-95, 98]	[-94, 100]	[-98, 100]	[-100, 100]				
	2 (3)	8 (19)	10 (22)	5 (12)	2 (5)	1 (3)	1 (4)	1 (2)	1 (1)	1 (1)				
Any mRNA vaccine	76%	92%	74%*	53%*	68%*	89%	28%	-2%	60%	5%		[52, 47]	[0.55, 0.52]	Yes
	[14, 93]	[87, 95]	[59, 83]	[19, 72]	[4, 89]	[-59, 99]	[-96, 98]	[-99, 99]	[-99, 100]	[-100, 100]				
	[-43, 97]	[61, 98]	[-21, 95]	[-57, 91]	[-52, 95]	[-71, 100]	[-97, 99]	[-99, 99]	[-99, 100]	[-100, 100]				
	2 (2)	8 (20)	10 (22)	5 (12)	2 (3)	1 (2)	1 (3)	1 (2)	1 (1)	1 (1)				
Any adenovirus	44%	94%	35%*	34%*	43%	58%						[36, 60]	[0.84, 1.09]	Yes
	[-86, 96]	[49, 99]	[-77, 90]	[-86, 94]	[-97, 99]	[-99, 100]								
	[-96, 99]	[-57, 100]	[-95, 98]	[-97, 98]	[-99, 100]	[-100, 100]								
	1 (1)	1 (6)	2 (7)	1 (4)	1 (3)	1 (1)								
BNT162b2		90%	66%*	33%*	60%*	86%	7%	-23%	49%	-18%		[59, 39]	[0.60, 0.49]	Yes
		[83, 95]	[40, 81]	[-22, 65]	[-24, 88]	[-70, 99]	[-97, 98]	[-99, 99]	[-99, 100]	[-100, 100]				
		[49, 98]	[-45, 94]	[-73, 88]	[-65, 94]	[-79, 100]	[-98, 98]	[-99, 99]	[-99, 100]	[-100, 100]				
		6 (15)	6 (15)	4 (10)	2 (3)	1 (2)	1 (3)	1 (2)	1 (1)	1 (1)				
mRNA-1273		90%	84%	77%										
		[87, 93]	[78, 88]	[63, 86]										

		1 (1)	1 (1)	1 (1)										
ChAdOx1	44%	94%	35%*	34%*	43%	58%						[36, 60]	[0.84, 1.09]	Yes
	[-86, 96]	[49, 99]	[-77, 90]	[-86, 94]	[-97, 99]	[-99, 100]								
	[-96, 99]	[-57, 100]	[-95, 98]	[-97, 98]	[-99, 100]	[-100, 100]								
	1 (1)	1 (6)	2 (7)	1 (4)	1 (3)	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	.25	.37	.61†*	.83†*	1.33†*	.77†*						[54, 43]	[0.23, 0.21]	Yes
	[.15, .41]	[.28, .48]	[.45, .83]	[.65, 1.06]	[.98, 1.79]	[.49, 1.23]								
	[.11, .56]	[.18, .73]	[.30, 1.25]	[.42, 1.64]	[.66, 2.68]	[.35, 1.70]								
	1 (2)	6 (10)	4 (5)	6 (11)	2 (7)	2 (2)								
Any mRNA vaccine		.36	.67*	.75*	1.20*	.75*						[66, 31]	[0.26, 0.18]	Yes
		[.27, .47]	[.45, .99]	[.57, .99]	[.83, 1.74]	[.46, 1.23]								
		[.17, .73]	[.31, 1.44]	[.37, 1.52]	[.56, 2.55]	[.33, 1.72]								
		6 (10)	3 (3)	5 (9)	1 (5)	2 (2)								
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														

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 9: 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	.56	.16	1.00*	1.71*	1.67*	1.15*	1.19	2.00	.27	1.43		[44, 55]	[0.67, 0.75]	Yes
	[.06, 5.31]	[.05, .48]	[.32, 3.07]	[.59, 5.00]	[.23, 11.86]	[.21, 6.33]	[.01, 156.55]	[.00, 1081.05]	[.00, 240.77]	[.00, 7049.98]				
	[.03, 11.82]	[.02, 1.62]	[.10, 10.38]	[.17, 17.40]	[.10, 28.62]	[.08, 16.61]	[.01, 237.20]	[.00, 1500.07]	[.00, 326.36]	[.00, 9009.85]				
	1 (1)	2 (9)	2 (9)	3 (9)	1 (4)	2 (4)	1 (3)	1 (2)	1 (1)	1 (1)				
Any mRNA vaccine	.55	.17	1.00*	1.70*	1.93*	1.13*	1.54	1.86	.65	1.43		[46, 53]	[0.71, 0.75]	Yes
	[.06, 5.52]	[.05, .52]	[.32, 3.16]	[.57, 5.07]	[.22, 17.05]	[.19, 6.73]	[.01, 240.50]	[.00, 986.51]	[.00, 1466.89]	[.00, 7243.33]				
	[.02, 12.51]	[.02, 1.83]	[.09, 11.04]	[.16, 18.27]	[.09, 39.96]	[.07, 17.84]	[.01, 366.64]	[.00, 1391.91]	[.00, 1944.83]	[.00, 9358.67]				
	1 (1)	2 (9)	2 (9)	3 (9)	1 (2)	2 (3)	1 (3)	1 (2)	1 (1)	1 (1)				
Any adenovirus		.34	2.65	2.48	1.60	1.78								
		[.20, .59]	[.88, 8.00]	[.50, 12.43]	[.02, 122.50]	[.00, 3157.95]								
		1 (6)	1 (6)	1 (4)	1 (3)	1 (1)								
BNT162b2		.20	1.21*	2.23*	2.31*	.27	1.85	2.24	.78	1.72		[41, 58]	[0.71, 0.84]	Yes
		[.05, .80]	[.30, 4.81]	[.55, 9.03]	[.23, 23.69]	[.00, 36.80]	[.01, 311.38]	[.00, 1267.58]	[.00, 1877.48]	[.00, 9257.68]				

		[.01, 2.83]	[.09, 17.08]	[.16, 31.83]	[.09, 59.25]	[.00, 60.42]	[.01, 501.20]	[.00, 1873.44]	[.00, 2588.54]	[.00, 12398.93]				
		2 (9)	2 (9)	2 (8)	1 (2)	1 (2)	1 (3)	1 (2)	1 (1)	1 (1)				
mRNA-1273														
ChAdOx1		.34	2.65	2.48	1.60	1.78								
		[.20, .59]	[.88, 8.00]	[.50, 12.43]	[.02, 122.50]	[.00, 3157.95]								
		1 (6)	1 (6)	1 (4)	1 (3)	1 (1)								
Ad26.COV2.S														

Table 10: 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											
	[.39, .61]		[.53, 1.26]											
	1 (1)		1 (1)											
Any mRNA vaccine	.49		.82											
	[.39, .61]		[.53, 1.26]											
	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 11: OR against COVID-19 deaths for completed primary series and **ONE** additional dose vs. primary series only (**Omicron variant**)

No data to report

Question 2a-3: 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 more than one additional doses – comparison to those who have received the primary series and at least one additional dose

Table 12: 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		.39	.41		.99*							[50, 9]	[0.22, 0.09]	Yes
		[.28, .56]	[.22, .80]		[.51, 1.92]									
		[.20, .76]	[.17, .98]		[.42, 2.36]									
		2 (5)	1 (4)		1 (1)									
Any mRNA vaccine		.39	.41		.99*							[50, 9]	[0.22, 0.09]	Yes
		[.28, .56]	[.22, .80]		[.51, 1.92]									
		[.20, .76]	[.17, .98]		[.42, 2.36]									
		2 (5)	1 (4)		1 (1)									
Any adenovirus														
BNT162b2		.48			1.02									
		[.42, .55]			[.76, 1.37]									

		1 (1)			1 (1)									
mRNA-1273		.35	.40											
		[.25, .50]	[.25, .63]											
		1 (4)	1 (4)											
ChAdOx1														
Ad26.COV2.S														

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 – compared to unvaccinated
A total of sixteen studies (29 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 (**Figure 1**). As of 32 weeks post full schedule the VE point estimate level and CIs indicates that there may no longer be any benefit of the primary series relative to being unvaccinated. The majority of this data reflected mRNA vaccines. From the limited adenovirus vaccine studies, it would seem that the overall level of VE was lower compared to mRNA vaccines, but that the rate of decline in VE was consistent.

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 some degree of benefit persisting to 48+ 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 – compared to unvaccinated
A total of 11 studies (20 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 (**Figure 2**). However, there was a statistical decline in VE as of 20 weeks post full schedule. As of 36 weeks post full schedule the VE point estimate level and CIs indicates that there may no longer be any benefit of the primary series relative to being unvaccinated. The majority of this data reflected mRNA vaccines, though there seemed to be limited differences in the patterns between these and adenovirus vaccines.

For the all-strain data (**Appendix 2**), the baseline levels were above the WHO minimum level and there was a consistent statistically significant decease in VE up to 48 weeks post full schedule, though VE levels remained relatively high up to 32 weeks post full schedule (though below the WHO minimum level). There seemed to be no difference between vaccine type.

1c. Findings for COVID-19 related deaths primary series only – compared to unvaccinated
A total of two studies (3 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 (**Appendix 2**), 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.

2a-1. Findings for confirmed COVID-19 infections primary series plus one or more additional doses – compared to unvaccinated
A total of 13 studies (29 cohorts) reported Omicron variant data (one additional dose), 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***. As of 20 weeks post one additional dose the VE point estimate level and CIs indicates that there may no longer be any benefit of the primary series plus one additional dose relative to being unvaccinated. The majority of this data reflected mRNA vaccines.

Only one study (4 cohorts) reported Omicron variant data (two additional doses), 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 10 studies (22 cohorts) reported Omicron variant data (one additional dose), for which the baseline levels of VE did meet the WHO minimum preferred level of VE. There was a statistical decrease in VE as of 12 weeks. Virtually all this data reflected mRNA.

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 (one additional dose), 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 seven studies (12 cohorts) reported Omicron variant data (one additional dose). These studies found a benefit at baseline of *one additional dose* compared to full schedule (OR = 0.37). 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 overtime and a potential loss of any benefit, relative to a primary series, as of 20 weeks post booster dose. All this data reflected mRNA vaccines.

2b-2. Findings for COVID-19 related hospitalisations primary series plus one or more additional doses – compared to full vaccine series

A total of three studies (10 cohorts) reported Omicron variant data for *one additional dose* compared to a primary series only. These studies found a benefit at baseline of the booster compared to full schedule (OR = 0.16). There was a statistically significant increase in the OR (i.e., less benefit) as of 12 weeks post booster dose, with level of degradation indicating a potential loss of any benefit, relative to a primary series. Virtually all this data reflected mRNA vaccines and predominately the BNT162b2 vaccine.

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 12 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.

2a-3. Findings for confirmed COVID-19 infections primary series plus more than one additional dose – compared to full vaccine series and one additional dose

A total of two studies (5 cohorts) reported Omicron variant data. These studies found a benefit at baseline of *two additional doses* compared to *one additional dose* (OR = 0.39). This benefit seemed to be maintained at 16 weeks post second booster dose, with a significant increase in OR (i.e., less benefit) by 20 weeks post second booster dose. All this data reflected the mRNA-1273vaccine.

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 (les10.16_vaccine_waning_adults_3_RoB_2023-03-29.xlsx). Overall, the risk of bias was serious for the majority of studies (74%), primarily due to the lack of adjustment of prognostic factors. Five studies (Young-Xu et al. [24Y-3], Menni et al. [36M-5], Lee et al. [53L-7], Paranthaman et al. [54P-7], Stirrup et al. [84S-16]) were deemed as having a critical RoB and were excluded from the analyses. In addition, the data captured for long-term care residents for Stirrup et al. [59S-15] was excluded, but the data for long-term care staff was included. 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. (both papers) did not account for medical conditions in long-term care cohorts.

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).

Constraints on Generality According to Populations Included
In this review, we wished to draw inferences about the effects of COVID-19 vaccination on humans aged 12 years and older. However, the selection of studies we uncovered to answer our research questions was more limited in scope. For example, the majority of studies (>80%) included in this review relied on samples from North American or European nations, with over 40% of studies coming from the United States and the United Kingdom. Of note, there were 7 studies (ca. 9%) which were derived from Canada. There was some representation of participants from South America and Africa, but these represented approximately 8% of studies in the current review. Given differences in sociopolitical contexts across nations, along with differences in pandemic-related policies (e.g., mask-wearing policies, intervals between doses) and situations (e.g., prevalence of different VOCs) overtime, it is currently unclear whether our conclusions would generalise to a wider global context. It is also important to note that a number of studies were reporting outcomes in the same population. For example, there were 9 publications using English population data. Though the combination of vaccines, time intervals, and outcomes varied across

these publications, the fact that they are drawn from the same inherent sample means that there is a lack of independence, something that we didn't account for in our statistical analyses.

Constraints for specific populations of interest

In considering the generality of our inferences, it is also important to note that we predominantly focused on extracting the average effectiveness of the vaccines for each study. Although patterns were often consistent across studies, there could still be substantial heterogeneity within each study. For example, the impacts of vaccines may vary due to factors such as: 1) age; 2) occupation; 3) health status; and 4) residential status. Though certain studies provided specific data for some of these factors, they were not consistently reported across studies. Furthermore, due to time constraints we were not able to extract these additional data elements. Future iterations of this question could consider looking at these factors in greater detail, as the level of individual risk or personal circumstance will likely impact the VEs overtime.

Team positionality statement

We recognize that the positionality of our team (e.g., how our team members' backgrounds relate to society and to the current study topic) can influence our work and the conclusions we draw. In order to explore the impact of our positionality, we engaged in an open-ended activity that encouraged each member of our team to reflect on ways in which their personal backgrounds and experiences (both within and outside our team) may have shaped the current review. The activity was engaged in during the first and final rounds of the living review. In the text below, we summarize our reflections along four themes.

1. How does our team's background influence our engagement with science? Our team is composed of university-educated individuals with training in diverse fields that intersect with health research (e.g., from epidemiology and pharmaceutical sciences, to physiology, microbiology, and psychology), obtained in a variety of countries. Our training leads us to generally favour quantitative approaches to understanding scientific phenomena (e.g., prioritizing evidence from randomised control trials and meta-analyses) over qualitative approaches. Many members of our team further operate in clinical/applied settings, leading the team as a whole to focus on the practical implications of research findings over their theoretical effects. Additionally, many members of our team also hold or intersect with non-traditional and underrepresented identities in research. For example, several team members come from low-to-middle-income countries, and many of us have lived experiences with themes such as immigration, poverty, conflict, uncommon health conditions, and being minorities. These experiences, along with training and work (e.g., advocacy) on themes tied to equity, diversity and inclusion, have led us to be sensitive to discrepancies in representation and in the impacts that research can have for members of different groups.

2. How do our experiences impact our perspectives on COVID-19 vaccination? Overall, before and while conducting this review, our team members generally held positive attitudes and beliefs towards the COVID-19 vaccines—a position informed by our past works and readings of the research—and many of us have been involved in works to directly and indirectly promote vaccination and other public health efforts (e.g., the MBMC has been involved in creating research as well as public materials to understand and reduce vaccine hesitancy during the pandemic). That said, given our backgrounds, many of us also hold cautious views towards an uncritical implementation of health policies (e.g., mandated vaccination), with worries about how such acts can lead to detrimental effects for certain individuals, especially members of already underserved communities. Several members of our team have experienced hesitancy towards vaccination as well, with concerns for the possibility of side effects. Overall, in working on this project, we have been mindful that evidence around vaccination is a complex phenomenon, far from a binary between effective vs. ineffective. However, we note that our team lacked direct representation from several key perspectives; for instance, that of policy-makers, frontline healthcare workers, and immunologists.

3. What are factors that influence how we communicate our findings? As noted above, our team holds predominantly favourable views towards COVID-19 vaccines. This, together with the team's education, will have shaped the writing of this report. For example, we may interpret VE data from an optimistic lens, but we also lean towards using cautious language to convey limitations in our certainty when making inferences. Given our backgrounds, our writing further tends to focus on implications for groups and populations, rather than for individuals. Throughout our communications, our hope was not to dictate what individuals and policymakers should choose, but rather give them better tools and data to make informed decisions for themselves. Additionally, as our team holds values tied to making science accessible, we were aware that our report's academic tone could make it complex to read and sought alternate ways to make findings more accessible. Thus, we worked collaboratively (leveraging our team's diverse experiences and expertise creating knowledge translation materials) to develop plain language summaries and infographics designed for public audiences–though our reflections suggest that more work remains to be done to adequately convey the complexities of the topic to lay audiences. These were produced in English, and then translated to French. It should be noted that because the review was requested by the Public Health Agency of Canada, our team developed this project, and wrote our report, with a Canadian perspective in mind. However, given that this review may be of interest to a wider global audience, we have made sure to acknowledge ways in which our findings may or may not generalise.

4. How did our team operate in the context of this rapid review? When organising our team for this review, we sought to promote a collaborative environment to improve the rigour of the research while also allowing growth and learning within the team (which included several trainees, early career researchers, and community investigators). The varied levels of expertise allowed for richer perspectives, but also entailed challenges such as ensuring everyone felt they could meaningfully contribute to discussions. The work was also conducted within a narrow time period, which required us to streamline processes and allowed for fewer opportunities for discussion and involvement than we would have hoped for; as a result, it was not possible to include all team members in each stage of the review. Time constraints also led us to simplify the scope of our review (e.g., extracting fewer elements than initially planned; not examining results for different populations), limit our reflections at each stage (e.g., the frequency for which we reflected on our positionality), and constrained the scope of our knowledge translation efforts. Despite these challenges, our reflection at the end of the review revealed that all team members felt the team had succeeded in creating an environment that allowed them to express their opinions openly, feel included, and contribute to collective decisions throughout the review.

All team members completed an individual reflection on intersectionality, positionality, and their implications for our project. A full anonymized, randomized list of reflections is available in **Appendix 9.**

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, Paquet L, Ribeiro PAB, Yip D, Stojanovic J. COVID-19 living evidence synthesis #10 (version 10.16): 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 additional doses? The Montreal Behavioural Medicine Centre, META group, 29 March 2023.