Change in the level of vaccine protection over time in COVID-19 vaccinated individuals

Running title: Vaccine effectiveness over time in vaccinated individuals

A rapid review

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Land Acknowledgement(s)

The Montreal Behavioural Medicine Centre, Concordia University, UQAM, and the CIUSSS-NIM are located on unceded Indigenous lands. The Kanien'kehá:ka Nation is recognized as the custodians of the lands and waters on which these institutions stand today. Tiohtiá:ke commonly known as Montreal is historically known as a gathering place for many First Nations. Today, it is home to a diverse population of Indigenous and other peoples. We respect the continued connections with the past, present, and future in our ongoing relationships with Indigenous and other peoples within the Montreal community.

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

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

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

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Third-Party Materials

General Disclaimer

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Abbreviations and Definitions

Abbreviations

CI	Confidence Interval
HCW	Healthcare workers
IQR	Interquartile Range
LTC	Long-term care
RCT	Randomized controlled trial
UK	United Kingdom
USA	United States of America
VE	Vaccine effectiveness
VOC	Variants of concern
VOC Alpha	Variant of concern B.1.1.7
VOC Delta	Variant of concern B.1.617.2
WHO	World Health Organization

Key Definitions

Fully vaccinated: A person who is at least 7 days post having received one of the following vaccine schedules:

- the full series of a COVID-19 vaccine authorized by Health Canada (i.e., AstraZeneca/COVISHIELD (AZD1222/ChAdOx1), Janssen (Johnson & Johnson: Ad26.COV2.S), Moderna (mRNA-1273), and Pfizer-BioNTech (BNT162b2)), or a combination of these vaccines
- the full series of the above vaccines plus an additional dose in immunocompromised individuals.(1)

Confirmed infection: A person with confirmation of infection with SARS-CoV-2 documented by:

- The detection of at least 1 specific gene target by a validated laboratory-based nucleic acid amplification test (NAAT) assay (e.g. real-time PCR or nucleic acid sequencing) performed at a community, hospital, or reference laboratory (the National Microbiology Laboratory or a provincial public health laboratory).(2)

Symptomatic illness: A person with confirmation of SARS-CoV-2 infection, presenting symptoms that vary in type, frequency, and severity. The most common symptoms include fever, chills, new or worsening cough, fatigue, headache, and gastrointestinal symptoms.(3)

Asymptomatic infection: A person with confirmation of SARS-CoV-2 infection but with no presentation of symptoms in the course of the disease.

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

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

Variants of concern (VOC): A SARS-CoV-2 variant is considered a VOC in Canada based on a set of criteria including increased transmissibility or detrimental change in COVID-19 epidemiology, increased virulence, decreased effectiveness of vaccines, and so on. As of August 05, 2021, Canada has designated the following SARS-CoV-2 variants as VOCs: Alpha (B.1.1.7), Beta (B.1.351, B.1.351.1., B.1.351.2, B.1.351.3, B.1.351.4), Gamma (P.1, P.1.1, P.1.2), and Delta (B.1.617.2, AY.1, AY.2, AY.3, AY.3.1).(4)

Vaccine effectiveness (VE): In the context of the current report, we have utilised the term vaccine effectiveness to cover all studies. However, we are aware that the studies that have been included range from efficacy through to effectiveness studies. We decided to use this terminology as it is consistent with how most evidence synthesis products describe these studies. To be consistent with this, in the French summary we have utilised the term efficacité, and it is noted that in French there is no distinction between the translations of efficacy and effectiveness.

EXECUTIVE SUMMARY

Background

To date in Canada, four vaccines have been approved to prevent coronavirus disease 2019 (COVID-19). While their short-term (<4 months) effectiveness in preventing COVID-19 infections in the general population has been shown to be strong, it is unclear if this level of effectiveness is maintained over longer periods of time (≥4 months). There is some early phase work which suggests that there may be a reduction in effectiveness post 4 months, referred to as waning effectiveness. This has implications for the continued usage of COVID-19 prevention measures, such as mask wearing, and some jurisdictions are considering the possibility and potential to distribute additional doses of the approved vaccines to negate any potential waning effectiveness.

This rapid review sought to identify, appraise, and summarise emerging research evidence (covering 1st January to 19th November 2021) to support evidence-informed decision making and answer the question: **How does the level of vaccine protection, including effectiveness against asymptomatic and symptomatic infection, and severe outcomes change over time in individuals who have received a complete primary COVID-19 vaccine series?** This report serves as an update to the previous version submitted in October 2021.

Additional sub questions for this update included: Do these outcomes vary by vaccine type/product, especially comparing BNT162b2, mRNA-1273?; and Do these outcomes vary by vaccine schedule (interval between doses or heterologous versus homologous schedules)?

Key points

- Based on data from six (11 cohorts) and five (6 cohorts) studies, respectively, for COVID-19 related hospitalisations and death, vaccine effectiveness for confirmed COVID-19 cases from 7-30 days to 7 months post full schedule seemed to be ***stable over time***. These changes seemed to be consistent in response to the Delta variant and across vaccines (especially BNT162b2 vs. mRNA-1273). Data for hospitalisations was the most consistent, though there was greater heterogeneity in the available data for mortality.
- Based on the data from 9 studies (16 cohorts), there would seem to be a ***decrease*** in vaccine effectiveness for confirmed COVID-19 cases from 7-30 days post full schedule to 7 months post full schedule. Given the heterogeneity in the available data it was not possible to provide specific point estimates for the magnitude of change. Generally, there seemed to be no difference in response between the BNT162b2 and mRNA-1273 vaccines.

Potential implications for health systems decision-making

Though the current review provides some initial evidence for a waning in VE for COVID-19 confirmed cases, it is unclear what might be driving this (e.g., if this is a function of a degradation in the immunogenicity, changes in public health measures, or variations in case numbers and general transmission). This, coupled with the relatively stable VEs for COVID-related hospitalisations and deaths, does not suggest that there would be major benefits in providing additional doses of the currently formulated vaccines 4 to 7 months after completing a full vaccine schedule. However, this needs to be considered in the context of the variability in the available studies and a lack of randomised controlled trial evidence on the utility of providing additional doses. Given the general decrease in VE

for cases, there may be a need to maintain certain COVID-19 prevention policies, e.g., mask wearing and physical distancing, even in fully vaccinated individuals.

RÉSUMÉ

Contexte

À ce jour au Canada, quatre vaccins ont été approuvés pour prévenir la maladie à coronavirus 2019 (COVID-19). Bien que leur efficacité* à court terme (moins de 4 mois) dans la prévention des infections à la COVID-19 dans la population générale se soit avérée élevée, il n'est pas clair si ce niveau d'efficacité se maintient sur de plus longues périodes de temps (4 mois et plus). Certains travaux de phases préliminaires suggèrent qu'il pourrait y avoir une réduction de l'efficacité après 4 mois, ce que l'on appelle le déclin de l'efficacité. Cela a des implications pour l'utilisation continue des mesures de prévention de la COVID-19, telles que le port du masque, et certaines autorités sanitaires envisagent la possibilité et le potentiel de distribuer des doses supplémentaires des vaccins approuvés pour éliminer tout déclin de l'efficacité.

Cette revue rapide vise à identifier, évaluer et résumer les résultats de recherche émergents (1er janvier au 19 novembre 2021) pour soutenir la prise de décision fondée sur des preuves et répondre à la question : **comment le niveau de protection vaccinale, incluant l'efficacité contre les infections asymptomatiques et symptomatiques et contre les résultats sévères, change-t-il au fil du temps parmi les personnes qui ont reçu une série primaire complète de vaccins contre la COVID-19?** Ce rapport est une mise à jour de la version précédente soumise en octobre 2021.

D'autres sous-questions dans cette mise à jour comprenaient : Ces résultats varient-ils selon le type/produit de vaccin, plus particulièrement BNT162b2 et mRNA-1273?; et ces résultats varient-ils selon le calendrier vaccinal (intervalle entre les doses ou calendriers hétérologues contre homologues)?

Points importants

- Sur la base des données de six (11 cohortes) et cinq (6 cohortes) études, respectivement, portant sur les hospitalisations et les décès en lien avec la COVID-19, il semble que l'efficacité du vaccin demeure ***stable*** dans le temps pour les cas confirmés de COVID-19 entre la période de 7 à 14 jours après le calendrier complet et 7 mois après le calendrier complet. Ces changements semblent être similaires face au variant Delta et entre les vaccins utilisés (particulièrement BNT162b2 et mRNA-1273). Les données disponibles sur les hospitalisations sont les plus homogènes, bien que les données disponibles sur la mortalité soient plus hétérogènes.
- Sur la base des données de neuf études (16 cohortes), il semble qu'il y aurait une ***diminution*** de l'efficacité du vaccin pour les cas confirmés de COVID-19 entre la période de 7 à 14 jours après le calendrier complet et 7 mois après le calendrier complet. Étant donné l'hétérogénéité des données disponibles, il n'a pas été possible de fournir des estimations ponctuelles précises quant à l'ampleur du changement. En général, il ne semble pas y avoir de différence de réponse entre les vaccins BNT162b2 et mRNA-1273.

Implications potentielles pour la prise de décision au sein des systèmes de santé

Bien que la présente revue rapide fournisse des preuves initiales d'une diminution de l'efficacité des vaccins dans les cas confirmés de COVID-19, il n'est pas clair si cela est fonction d'une réduction de l'immunogénicité, de changements au niveau des mesures de santé publique, ou de variations au niveau du nombre de cas et de la transmission générale. Cette observation, associée aux efficacités relativement stables en lien avec les hospitalisations et les décès liés à la COVID-19, ne suggère pas qu'il y aurait un quelconque avantage à fournir des doses supplémentaires des vaccins actuellement formulés 4 à 7 mois après avoir complété le calendrier vaccinal. Cependant, il est important de prendre en considération le nombre limité d'études disponibles et le manque de données issues d'essais

contrôlés randomisés portant sur l'utilité de fournir des doses supplémentaires. Compte tenu du déclin global de l'efficacité vaccinale pour les cas, il peut être nécessaire de maintenir certaines mesures de prévention de la COVID-19, notamment le port du masque et la distanciation physique, même chez les personnes entièrement vaccinées.

Le terme *efficacité* est utilisé pour des raisons de simplicité et ne fait pas de distinction entre les termes anglais « effectiveness » et « efficacy ».

Introduction

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease (COVID-19) has resulted in more than 220,000,000 confirmed cases worldwide as of September 2021.(5) At the time of writing, Health Canada has approved four vaccines to prevent COVID-19: AstraZeneca/COVISHIELD (AZD1222/ChAdOx1), Janssen (Johnson & Johnson: Ad26.COV2.S), Moderna (mRNA-1273), and Pfizer-BioNTech (BNT162b2). While many randomised controlled trials (RCTs) and real-world observational studies have shown their high effectiveness in preventing COVID-19 in the short-term (< 4 months) (6), less is known about their waning effects over time (≥ 4 months), especially with the emergence of new variants of concern (VOC) such as the B.1.1.7 (commonly known as Alpha) and B.1.617.2 (Delta) variants.(7) Our rapid review was requested to support Canadian public health decision makers' response to the COVID-19 pandemic. This rapid review seeks to summarize current evidence on **the level of vaccine protection over time in individuals who have received a complete primary COVID-19 vaccine series**, as an update to our previous report submitted in October 2021.

Below are the main elements of our research question:

- **Population**: Individuals 12 years of age and older. Sub-groups: age specific (older adults 60+, older adults 80+) and healthcare workers.
- **Intervention:** At least four months of elapsed time from receipt of a full primary series with a Health-Canada authorized COVID-19 vaccine (AstraZeneca/COVISHIELD (AZD1222/ChAdOx1), Janssen (Johnson & Johnson: Ad26.COV2.S), Moderna (mRNA-1273), Pfizer-BioNTech (BNT162b2)), We also looked at the following sub-groups: within a homologous series (same product) and heterologous series (mixed products).
- **Control/Comparator**: Protection assessed at baseline (7-14 days after completing vaccine series).
- **Outcomes:** Effectiveness against any infection (symptomatic and asymptomatic) and severe illness (e.g., hospitalization and/or death due to COVID-19). We also explored studies that provided these data as a function of variants of concern (VOC).
- **Study design:** longitudinal studies that had prospective data capture.

Methods

This rapid review has been registered at the National Collaborating Centre for Methods and Tools, registration number 473 (https://www.nccmt.ca/covid-19/covid-19-evidence-reviews/473).

Eligibility Criteria

The following inclusion criteria were applied: 1) inclusion of individuals 12 years of age and older that received a full primary series of any vaccine recognized in Canada (AstraZeneca/COVISHIELD (AZD1222/ChAdOx1), Janssen (Johnson & Johnson: Ad26.COV2.S), Moderna (mRNA-1273), and Pfizer-BioNTech (BNT162b2)); 2) follow-up period of at least 4 months / 16 weeks / 112 days; 3) presentation of one of the following outcomes: effectiveness against any infection (symptomatic and asymptomatic) and severe illness (e.g., hospitalization and/or death due to COVID-19). Studies with prospective longitudinal data were included, such as randomized or non-randomised trials, quasi-randomized studies (e.g., allocated by site, county/city, date of birth design), and observational cohort studies; and 4) published in either English or French.

Exclusion criteria covered studies published in another language or which had a different design other than those included above (e.g. cross-sectional studies, case reports/series, reviews). Studies that included only immunogenicity outcomes (cellular or humoral immune response) were also excluded.

Literature Search

The search was initially performed on September 10th, 2021 and updated on November 19th, 2021 including terms related to vaccination, such as type of vaccine (e.g., “RNA messenger”, “vector*”) and vaccine producer (e.g., “Pfizer”, “Moderna”, “Janssen”). The full search strategy is available in the **Supplementary Material**. The following sources were searched, with a publication limit from 1st January 2021 until 19th November 2021:

- National Institute of Health (NIH) iSearch COVID-19 portfolio, which includes PUBMED, ArXiv, BioRxiv, MedRvix, ChemRvix, SSRN, Preprints.org, Qeios, and Research Square;
- Embase;
- Hand search of the COVID-END Forum website, McMaster Health Forum website, and citations of systematic reviews on this topic.

Study Selection

Screening titles/abstracts and full-text articles was conducted upon completion of a piloting exercise, which included a random sample of 25 studies at each phase. Following the verification of the agreement between the reviewers, studies were screened by single reviewers. In cases of uncertainty, a second reviewer was consulted and disagreements were resolved by discussion. The entire process was performed through the screening management system Rayyan.

Given the smaller volume of articles for this update, title/abstract and full-text articles were screened through peer-review with at least two members of the team reviewing each article.

Data Extraction

Extracted data was recorded into Google Sheets extraction tables designed for this study. Two separate extraction sheets were designed covering the following information: 1) General overview of the study (e.g., year of publication, author, title, publication format, study design, study location, population description, intervention, vaccine dosing strategy, comparator); and 2) Study outcomes (e.g., sample size for the intervention and comparator groups, timing of the outcome assessments; point estimates of clinical outcomes of interest with accompanying 95% CI, and specific information on potential stratifiers).

To ensure reviewers had a common understanding of the extraction worksheet, preliminary meetings were carried out with the entire team to review the strategy and the extraction focus. A validation piloting exercise with two references was performed before moving on to final data extraction by a single reviewer. Discussions were performed in case of uncertainty and resolved with a senior member of the team (JS, PABR, SLB).

Risk of Bias Assessment

The adapted version of the ROBINS-I tool was used (**see Supplementary Material**). This tool assesses seven bias domains and judges each study against an ideal reference randomized controlled trial. The adaptation focused on study characteristics that may introduce bias specific to the vaccine literature (8), and was developed by a living evidence synthesis team focusing on the effectiveness of COVID-19 vaccines against VOCs.(9) The tool classifies Risk of Bias as Low, Moderate, Serious, Critical, or No Information. Single-reviewer procedure was adopted, with one senior member of the

team performing Risk of Bias assessment (SLB), and a second reviewer verifying the assessment table (PABR, KJD, AMV).

Data Synthesis

Due to the limited number and nature of the studies, no formal data synthesis was conducted. This also meant that it wasn't possible to provide specific recommendations, and as such, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results

Study Selection

The study identification and selection process are summarized in **Supplementary Material Figure 1**. In this update, the initial search yielded 629 retrieves and the hand search yielded another 23 retrieves. From these studies, a total of 108 articles were included for full text review. Overall, 7 studies were retained for inclusion in the final review, 2 of which were published, with 5 being preprints. Combined with the previous version, this review has a total of 13 included studies, and the most recent content is in bold, blue font.

Study Characteristics

Table 1 presents the descriptive characteristics of the included studies. Eight studies were cohorts and two were RCTs. Five studies reported data from the USA while one study reported on Canadian data. The majority of studies reported data for the general population, with a number also including specific analyses in sub-groups.

Table 1. Descriptive characteristics of the included studies.

Note: Newly added studies in blue.

First author	Location	Study Design	Study Format	Population of interest	Sample size	Vaccine intervention	Comparator
Andrews (10)	UK	Cohort	Pre-print	Persons at least 16 years of age	52,333,72	BNT162b2 or AZD1222 (ChAdOx1) *	Unvaccinated
Bruxvoort (11)	USA	Cohort	Pre-print	KPSC members	352,878 unvaccinated and 352,878 vaccinated	mRNA-1273	Unvaccinated
Chemaitelly *a* (12)	Qatar	Cohort	Pre-print	Residents of Qatar	173,496 PCR + and 1,422,333 PCR -	BNT162b2	Unvaccinated
Tartof (13)	USA	Cohort	Pre-print	KPSC members	3,436,957	BNT162b2	Unvaccinated
Thomas (14)	Global	RCT	Peer-review	Persons at least 16 years of age	44,047	BNT162b2	Unvaccinated (Placebo)
Thompson (15)	USA	Cohort	Peer-review	Adults aged ≥50 years	41,552 hospitalisations + 21,522 ED visits from 187 hospitals	BNT162b2, Ad26.CoV2.S and mRNA-1273	Unvaccinated
Chemaitelly b (16)	Qatar	Case-control	Peer-review	Resident popular in Qatar	494,859	BNT162b2	PCR-negative
El Sahly (17)	USA	RCT	Peer-review	Adults aged ≥18 years with high risk for Covid-19	28,451	mRNA-1273	Unvaccinated (Placebo)
Lin (18)	USA	Cohort	Pre-print	Residents of North Carolina	10,600,823	BNT162b2, Ad26.CoV2.S and mRNA-1273*	Unvaccinated
Poukka (19)	Finland	Cohort	Pre-print	HCWs aged 16-69 years	427,905	BNT162b2, AZD1222 (ChAdOx1) and mRNA-1273	Unvaccinated

Skowronski (20)	Canada	Case-control	Pre-print	Adults aged >18 years in BC and QC	1,235,447 (380,532 BC; 854,915 QC)	BNT162b2, AZD1222 (ChAdOx1) and mRNA-1273*	PCR-negative
De Gier (21)	Netherlands	Case-control	Pre-print	Hospitalizations and ICU admissions - nationwide registry of COVID-19 hospitalizations	15,571	BNT162b2, Ad26.CoV2.S, AZD1222 (ChAdOx1) and mRNA-1273	Partially and unvaccinated
Nordstrom (22)	Sweden	Cohort	Pre-print	Fully vaccinated and matched unvaccinated individuals -Swedish Vaccination Register and SmiNet register	1,684,958	BNT162b2, AZD1222 (ChAdOx1) and mRNA-1273*	Unvaccinated

Legend:BC: British Columbia; HCWs: healthcare workers; PCR: Polymerase chain reaction test; QC: Quebec; RCT: randomized controlled trial; USA: United States of America; UK: United Kingdom; HCW: healthcare workers; KPSC: Kaiser permanente Southern California
*Data are reported separately by the vaccine.

Findings for confirmed COVID-19 cases

A total of six studies provided usable baseline and follow-up information with regards to confirmed COVID-19 case data (a combination of both symptomatic and asymptomatic cases), with a further three studies providing data specifically for confirmed symptomatic COVID-19 case data. Seven studies provided data for only one vaccine with the other two providing data for more than one vaccine. In addition, one Canadian study reported data broken down for British Columbia and Quebec, so these were entered as separate data points and one study provided data specific to the Delta variant only. In total there were 16 individual cohorts of data included for confirmed COVID-19 cases, with 8 cohorts reporting on BNT162b2, 5 on mRNA-1273, 2 on ChAdOx1, and one on Ad26.COV2.S. This allowed us to provide aggregated data for both BNT162b2 and mRNA-1273.

All cases in the general population: As seen in ***Table 2*** and ***Figure 1***, there is a slow degradation of VE for COVID-19 cases in the 4-7 month post full vaccination schedule period when compared to initial VE levels. With all available studies included, there is a progressive drop from an average VE of 79% to 45%. When looking at individual vaccines, this trend was consistent for BNT162b2 but not mRNA-1273, where the change in VE was much less pronounced (going from 87% to 72% at 6 months post full schedule). As can be seen in ***Figure 1***, the large drops in VE for BNT162b2 is driven by two cohorts, one from Qatar (which provided two cohorts) and one from Sweden (which provided one cohort). When these cohorts were removed, the average VE for BNT162b2 was relatively stable (baseline = 78%, 4 months post = 77%, 5 months post = 72%, 6 months post = 71%, 7 months post = 81%) and mirrored that of mRNA-1273. It should be noted that the risk of bias assessment (see ***Table 2***) of these two studies didn't flag anything of note that could account for the differences between these and the rest of the studies. Furthermore, there was a great deal of within and between study variability in the ≥ 4 month measures of VE meaning that there was a great deal of overlap between the point estimates and confidence intervals across studies.

Table 2. Confirmed cases (including any cases or symptomatic cases).

	Baseline	**Follow-up**			
	≤ 31 days	**4-5 months**	**5-6 months**	**6-7 months**	**7+ months**
General population					
All vaccines	**Average 79%** Range 58-96% 16 study arms	**Average 70%** Range 39-92% 11 study arms	**Average 54%** Range -19-91% 14 study arms	**Average 54%** Range 0-86% 10 study arms	**Average 45%** Range -4-81% 4 study arms
BNT162b2	**Average 79%** Range 66-92% 8 study arms	**Average 67%** Range 39-88% 6 study arms	**Average 51%** Range 6-91% 7 study arms	**Average 42%** Range 0-83% 6 study arms	**Average 45%** Range -4-81% 4 study arms

mRNA-1273	**Average 87%** Range 79-96% 5 study arms	**Average 87%** Range 82-92% 3 study arms	**Average 77%** Range 71-84% 4 study arms	**Average 72%** Range 59-86% 3 study arms	-

Percentages indicate level of effectiveness from 0% (no effect) to 100% (full protection). Study arms indicate separate reported analyses, this means that there might be multiple arms in one study. However, no overlapping data is included, e.g., if a study reported combined vaccination data and individual-based vaccine data then only the individual data is reported and not both.

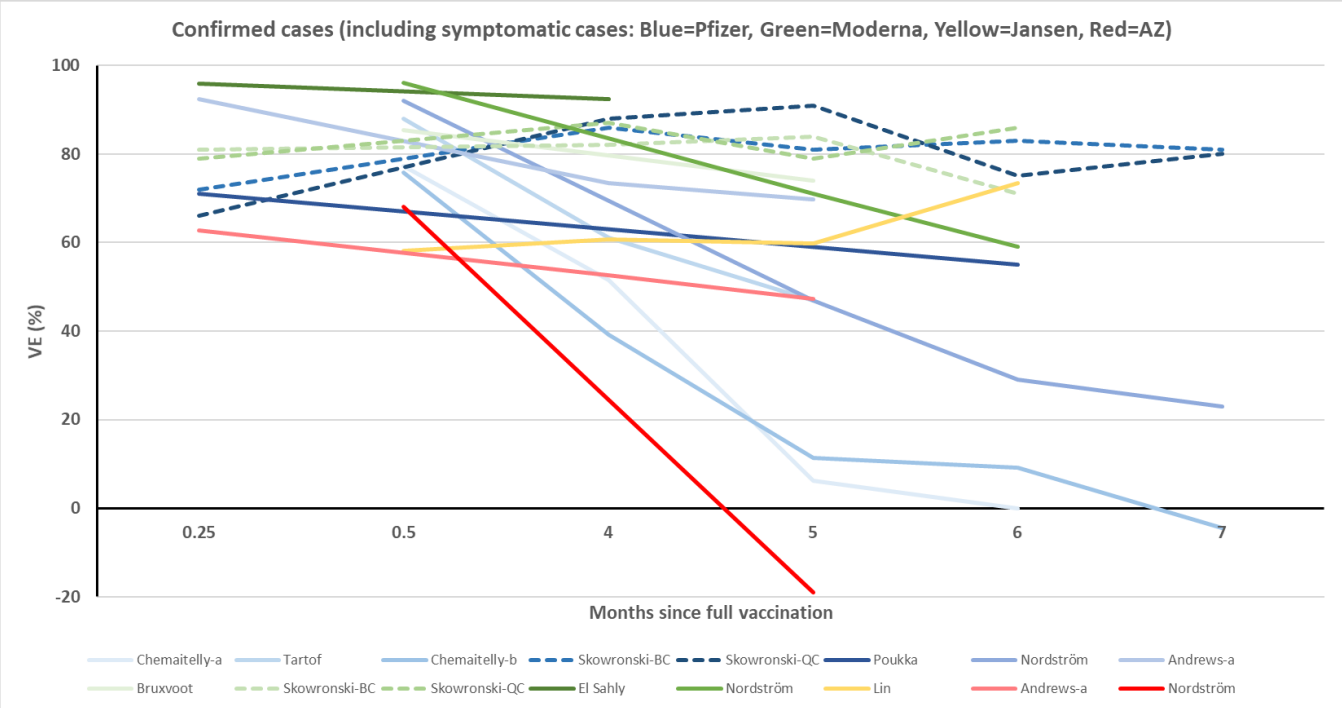

Figure 1 - Confirmed cases (including any cases or symptomatic cases). Studies identified by dashes indicate Canadian specific data.

Delta specific cases in the general population: The pattern of responses for Delta specific cases was similar to all cases (see ***Table 3*** and ***Figure 2***), a slow degradation overtime, with one cohort from Qatar significantly reducing the average VE response. When this one cohort was removed the pattern of VE for BNT162b2 was relatively stable (baseline = 82%, 4 months post = 75%, 5 months post = 80%, 6 months post = 80%, 7 months post = 78%), mirroring that of mRNA-1273.

Table 3. Confirmed cases for Delta (including any cases or symptomatic cases).

	Baseline	Follow-up			
	≤ 31 days	4-5 months	5-6 months	6-7 months	7+ months
General population – Delta variant					
All vaccines	**Average 81%** Range 63-94% 9 study arms	**Average 68%** Range 13-89% 9 study arms	**Average 68%** Range 0-92% 8 study arms	**Average 65%** Range 0-85% 5 study arms	**Average 78%** Range 76-80% 2 study arms
BNT162b2	**Average 82%** Range 70-93% 5 study arms	**Average 63%** Range 13-89% 5 study arms	**Average 60%** Range 0-92% 4 study arms	**Average 53%** Range 0-83% 3 study arms	**Average 78%** Range 76-80% 2 study arms
mRNA-1273	**Average 85%** Range 80-94% 3 study arms	**Average 82%** Range 77-87% 5 study arms	**Average 87%** Range 80-91% 3 study arms	**Average 83%** Average 80-85% 2 study arms	-

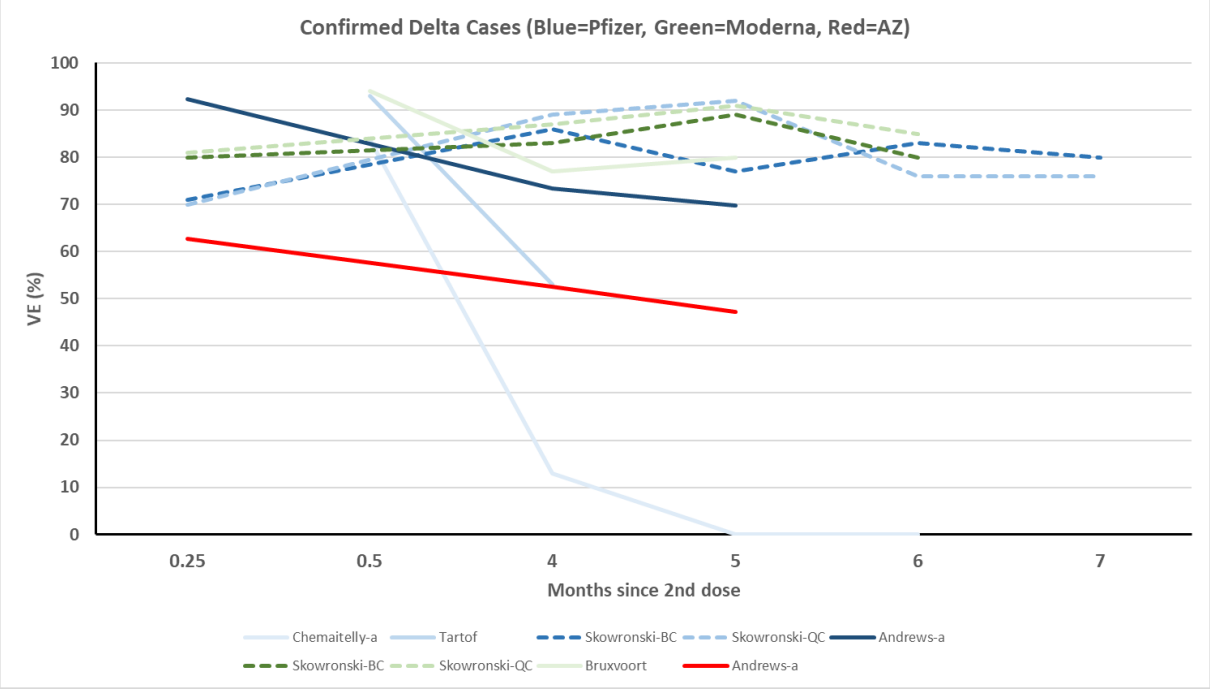

Figure 2 - Confirmed cases for Delta (including any cases or symptomatic cases). Studies identified by dashes indicate Canadian specific data.

Studies that directly compared BNT162b2 and mRNA-1273: Two studies (including 6 cohorts) provide directly comparable data between BNT162b2 and mRNA-1273. As seen in ***Table 4*** and ***Figure 3***, the Canadian data provided by Skowronski et al (20) shows an equally consistent pattern of maintained efficacy over 7 months for both vaccines. The Swedish data from Nordström et al (22) shows a decline in VE, with a more rapid decline for BNT162b2 compared to mRNA-1273.

Table 4. Data from studies that have directly compared BNT162b2 to mRNA-1273.

	Baseline	**Follow-up**			
	≤ 31 days	**4-5 months**	**5-6 months**	**6-7 months**	**7+ months**
Direct comparison between BNT162b2 and mRNA-1273					
BNT162b2 or mRNA-1273	**Average 81%** Range 66-96% 6 study arms	**Average 86%** Range 82-88% 2 study arms	**Average 76%** Range 47-91% 6 study arms	**Average 67%** Range 29-86% 6 study arms	**Average 61%** Range 23-80% 3 study arms
BNT162b2	**Average 77%** Range 66-92% 3 study arms	**Average 87%** Range 86-88% 2 study arms	**Average 73%** Range 47-91% 3 study arms	**Average 62%** Range 29-83% 3 study arms	**Average 61%** Range 23-80% 3 study arms
mRNA-1273	**Average 85%** Range 79-96% 3 study arms	**Average 85%** Range 82-87% 2 study arms	**Average 78%** Range 71-84% 3 study arms	**Average 72%** Range 59-86% 3 study arms	-

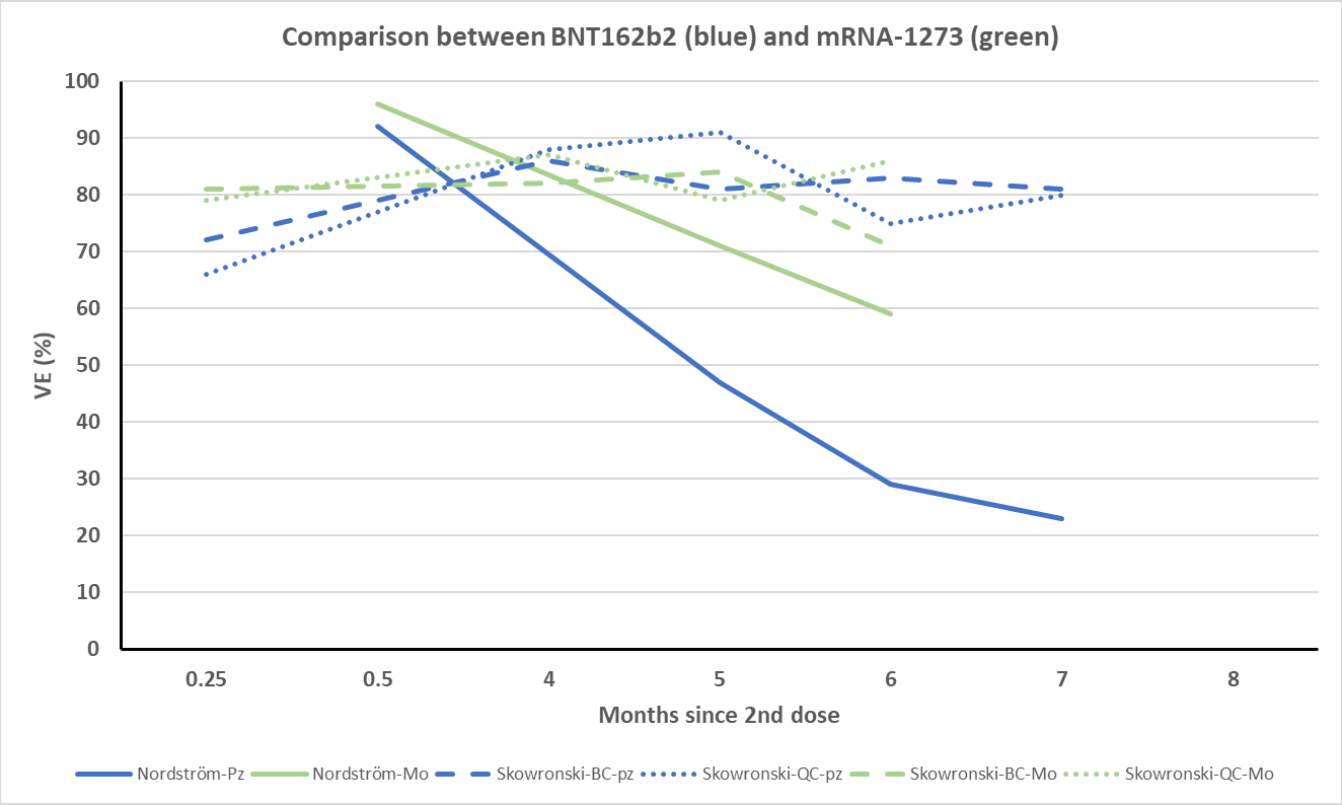

Figure 3 – Comparison between BNT162b2 and mRNA-1273. The dashed nature of the lines indicates data from the same study.

Findings for COVID-19 related hospitalisations

A total of six studies provided usable baseline and follow-up information with regards to COVID-19 related hospitalisations. Three studies provided data for only one vaccine with the other three providing data for more than one vaccine. In addition, one Canadian study reported data broken down for British Columbia and Quebec, so these were entered as separate data points. In total there were 11 individual cohorts of data included, with 6 cohorts reporting on BNT162b2, 5 on mRNA-1273, and 1 on ChAdOx1. This allowed us to provide aggregated data for both BNT162b2 and mRNA-1273.

Hospitalisations in the general population: As seen in ***Table 5*** and ***Figure 4***, there was a consistent level of VE for COVID-19 hospitalisations in the 4-7 month post full vaccination schedule period when compared to initial VE levels. This was especially true for both the BNT162b2 (average baseline VE = 93% and 6 months post = 98%) and mRNA-1273 vaccines (average baseline VE = 93% and 6 months post = 96%). The one study that reported on the ChAdOx1 vaccine showed a slight decline up to 5 months post (average baseline VE = 94% and 5 months post = 77%). Unlike the cases data, there was a large degree of consistency in the point estimates and confidence intervals across the studies and time-points.

Table 5. COVID-19 related hospitalisations.

	Baseline	Follow-up			
	≤ 31 days	4-5 months	5-6 months	6-7 months	7+ months
General population					
All vaccines	**Average 93%** Range 87-100% 11 study arms	**Average 91%** Range 83-97% 9 study arms	**Average 93%** Range 77-98% 8 study arms	**Average 97%** Range 96-98% 3 study arms	-
BNT162b2	**Average 93%** Range 87-100% 6 study arms	**Average 92%** Range 83-97% 5 study arms	**Average 93%** Range 88-98% 4 study arms	**Average 98%** Range 98-98% 2 study arms	-
mRNA-1273	**Average 93%** Range 87-97% 4 study arms	**Average 89%** Range 83-93% 3 study arms	**Average 94%** Range 92-96% 3 study arms	**96%** 1 study arm	-

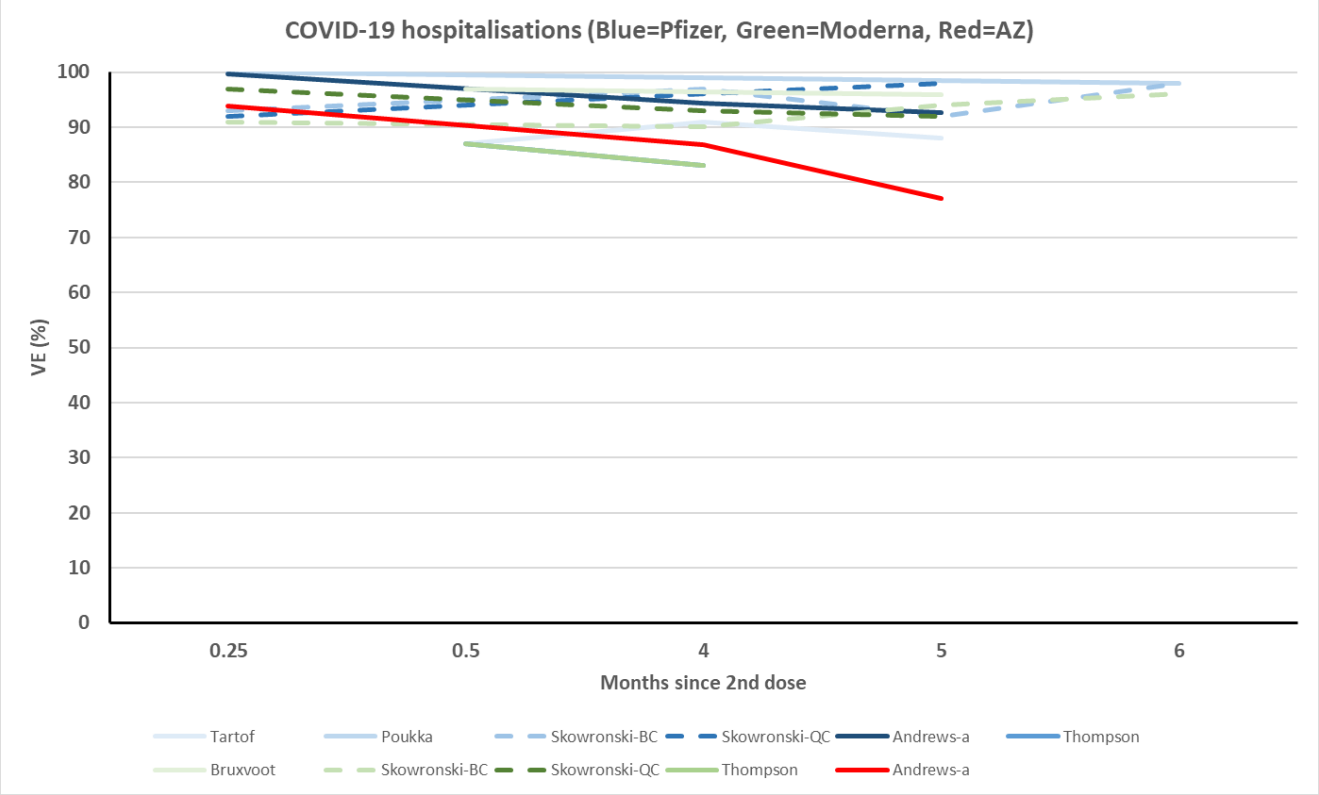

Figure 4 – COVID-19 related hospitalisations. The dashed nature of the lines indicates data from the same study.

Delta specific hospitalisations in the general population: The pattern of responses for Delta specific hospitalisations was similar to all hospitalisations (see ***Table 6*** and ***Figure 5***), a consistent stable trend overtime, with one cohort including the ChAdOx1 vaccine showing a slight decline over time.

Table 6. Delta-related COVID-19 hospitalisations.

	Baseline	Follow-up			
	≤ 31 days	4-5 months	5-6 months	6-7 months	7+ months
General population – Delta variant					
All vaccines	**Average 95%** Range 91-100% 6 study arms	**Average 92%** Range 84-98% 6 study arms	**Average 90%** 77-98% 4 study arms	**98%** 1 study arm	-
BNT162b2	**Average 95%** Range 91-100% 3 study arms	**Average 97%** Range 94-98% 3 study arms	**Average 94%** Range 92-98% 3 study arms	**98%** 1 study arm	-
mRNA-1273	**Average 95%** Range 94-95% 2 study arms	**Average 88%** Range 82-92% 2 study arms	**77%** 1 study arm	-	-

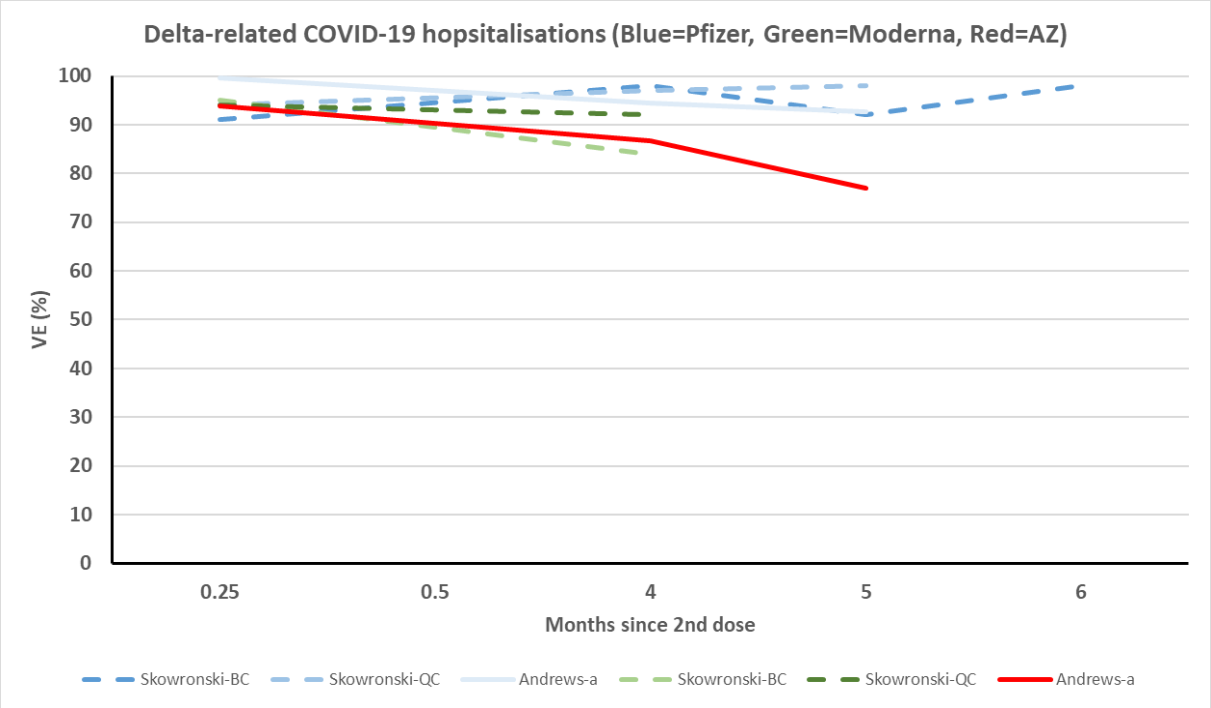

Figure 5 – Delta related COVID-19 hospitalisations. The dashed nature of the lines indicates data from the same study.

Studies that directly compared BNT162b2 and mRNA-1273: Two studies (including 6 cohorts) provide directly comparable data between BNT162b2 and mRNA-1273. As seen in ***Table 6*** and ***Figure 5***, all the data, including the Canadian data provided by Skowronski et al (20), shows an equally consistent pattern of maintained efficacy over 6 months for both vaccines.

Table 6. COVID-19 related hospitalisations for studies that directly compared BNT162b2 to mRNA-1273.

	Baseline	**Follow-up**			
	≤ 31 days	**4-5 months**	**5-6 months**	**6-7 months**	**7+ months**
Direct comparison between BNT162b2 and mRNA-1273					
BNT162b2 or mRNA-1273	**Average 91%** Range 87-97% 6 study arms	**Average 90%** Range 83-97% 6 study arms	**Average 94%** Range 92-98% 4 study arms	**Average 97%** Range 96-98% 2 study arms	-
BNT162b2	**Average 91%** Range 87-93% 3 study arms	**Average 92%** Range 83-97% 3 study arms	**Average 95%** Range 92-98% 2 study arms	**98%** 1 study arm	-
mRNA-1273	**Average 92%** Range 87-97% 3 study arms	**Average 89%** Range 83-93% 3 study arms	**Average 93%** Range 92-94% 2 study arms	**96%** 1 study arm	-

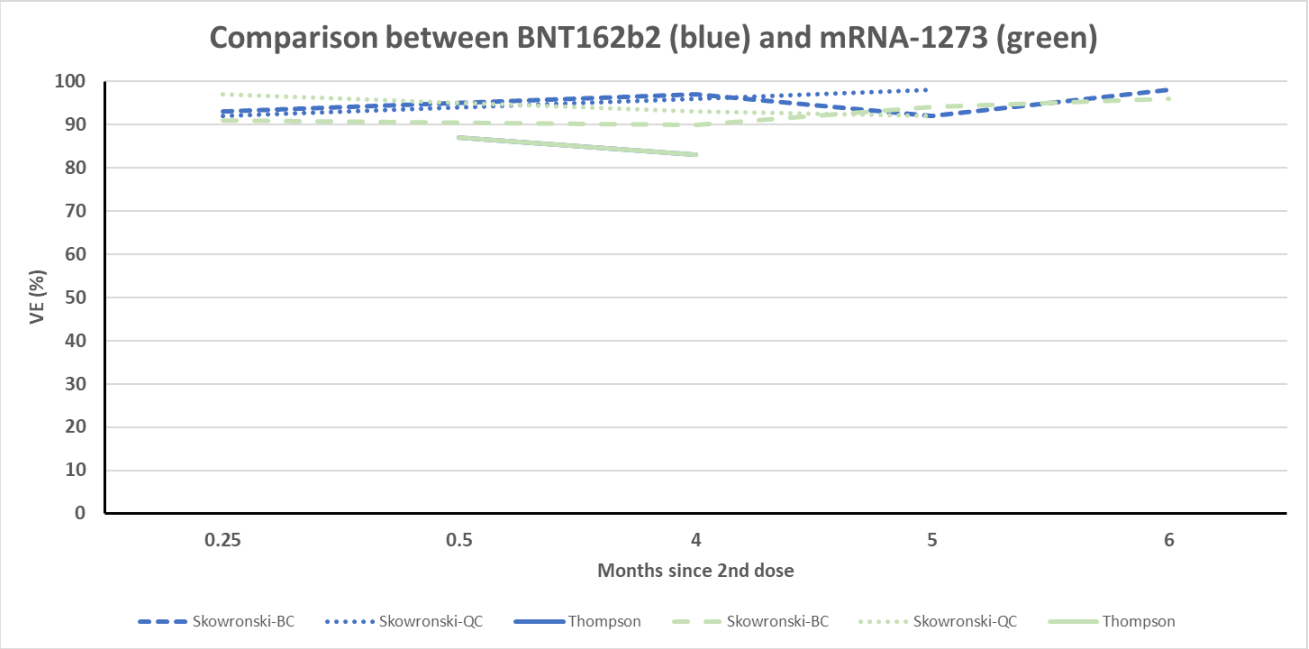

Figure 5 – COVID-19 related hospitalisations for studies that directly compared BNT162b2 to mRNA-1273.

Findings for COVID-19 related deaths or deaths and hospitalisations

A total of two studies provided usable baseline and follow-up information with regards to COVID-19 related deaths (reported alone), another two studies providing data for the combined outcome of deaths and/or hospitalisations, and one study provided both kinds of data. In total there were 6 individual cohorts of data included, with 3 cohorts reporting on BNT162b2, 1 on mRNA-1273, 1 on ChAdOx1, and one which reported on any vaccine. This lack of consistency did not allow us to provide aggregated data for any specific vaccine.

As can be seen in ***Table 7*** and ***Figure 6***, for deaths there seems to be a small decline over 5 months in VE (baseline = 97% to 5 month post = 90%) but it still remained high. When data for deaths and/or hospitalisations were included (see ***Table 7*** and ***Figure 7***), there was a greater decline in VE overtime. This change was largely driven by the studies from Qatar (12,16) and Sweden (22). In general, there was a large amount of variability within and across studies, which likely reflects the low outcome rates that were reported. This means that it was impossible to derive a reliable point estimate.

Table 7. COVID-19 related deaths or combinations of hospitalisation and death.

	Baseline	Follow-up			
	≤ 31 days	4-5 months	5-6 months	6-7 months	7+ months
COVID-19 related deaths only					

All vaccines	**Average 97%** Range 94-100% 4 study arms	**Average 88%** Range 80-94% 3 study arms	**Average 90%** Range 79-100% 3 study arms	-	-
COVID-19 related deaths and deaths or hospitalisation combined					
All vaccines	**Average 95%** Range 89-100% 6 study arms	**Average 88%** Range 86%-94% 4 study arms	**Average 90%** Range 74-100% 6 study arms	**Average 65%** Range 42-82% 3 study arms	**44%** 1 study arm

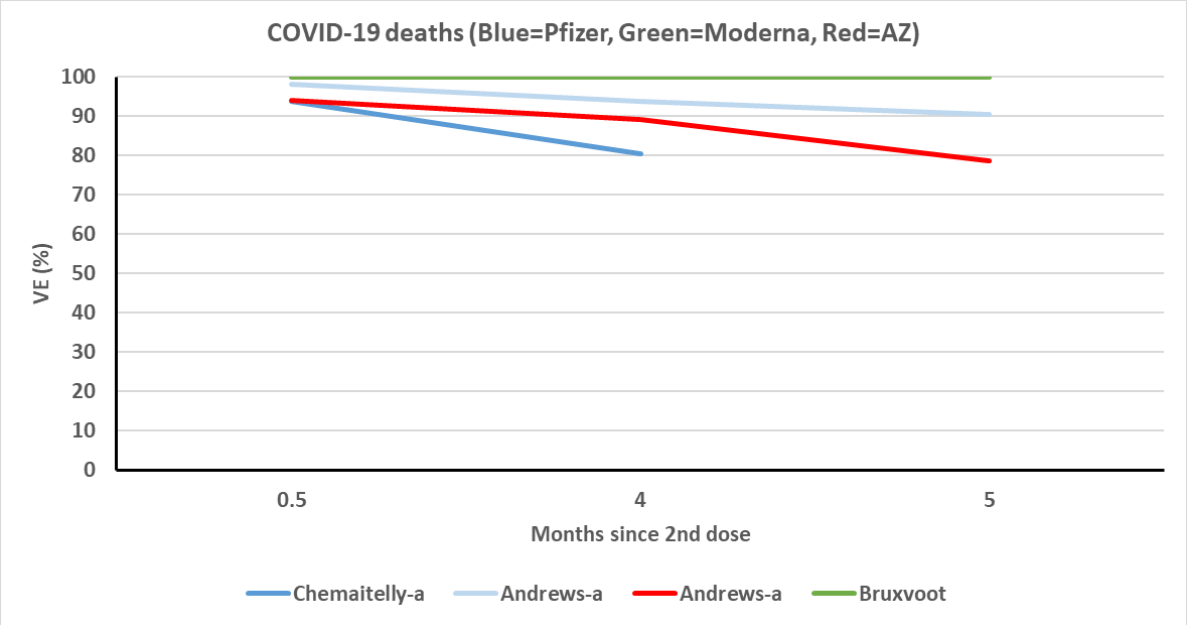

Figure 6 – COVID-19 related deaths.

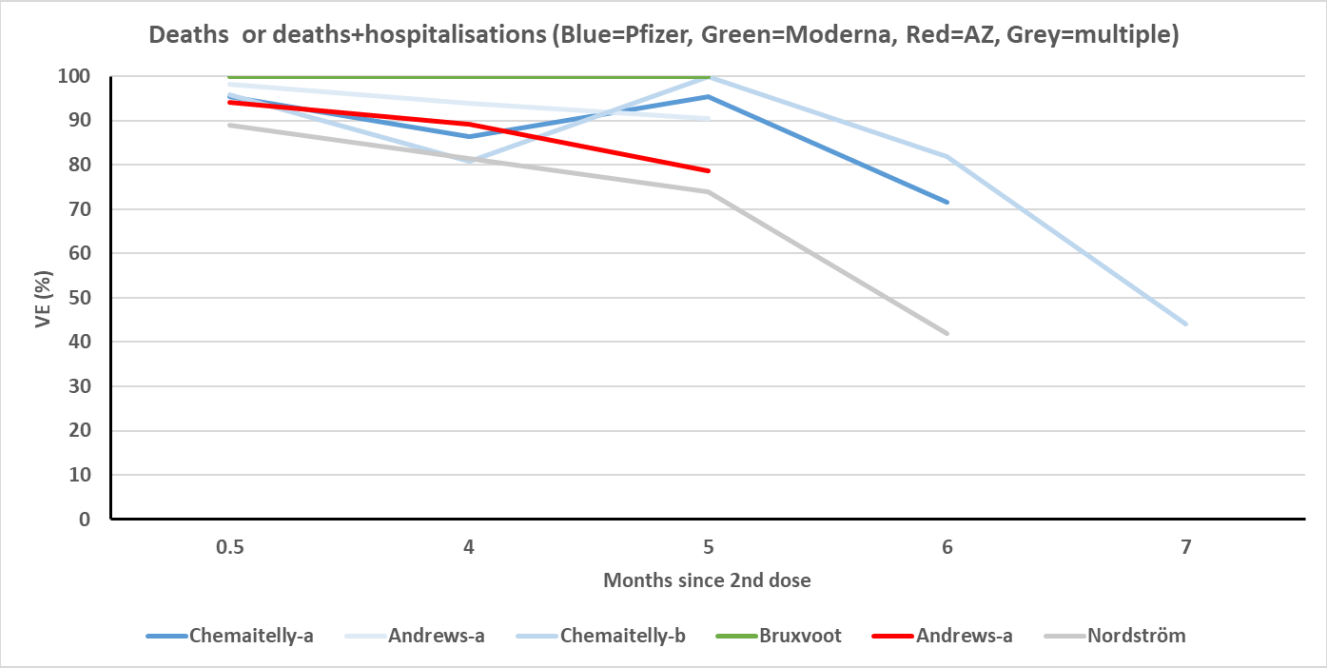

Figure 7 – COVID-19 related hospitalisation combined with deaths.

Study specific results

Tables 4S-12S (Supplementary Material) provide a breakdown of the specific time points and VE (95% CIs) for each study for each outcome. Where possible, this data is provided for any relevant sub-groups.

Risk of bias assessment

The risk of bias data for each individual study is provided in the **Supplementary Material, Table 3S**. Overall, the risk of bias was low for the majority of items and moderate for a few.

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 two other evidence synthesis teams. 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. We would also direct readers to one previous COVID-END report on vaccines and immunogenicity (23) and an ongoing COVID-END living review on vaccines and variants of concern (9). 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).

Conclusions

Overall, it would seem that the effectiveness of the vaccines for confirmed COVID-19 cases diminishes from 7-30 days post full vaccine schedule to 4-7 months post full vaccine schedule, though there was a significant amount of variability in the data. In contrast, there was relative consistency in the VE over time for COVID-19 related hospitalisations, with much less variability in the data, suggesting that there was no waning. The data for COVID-19 related deaths was similar to that of COVID-19 related hospitalisations, i.e., relative consistency in VE overtime with minimal reductions. However, given the small number of outcomes there was more variability around the point estimates and thus caution is needed in drawing a stable VE conclusion. Given that the vaccines were predominantly developed to reduce hospitalisations and death, the fact that VE seems to be stable, in contrast to confirmed cases, suggests that their VE for these outcomes may be consistent over the medium term (4-7 months).

We were also able to evaluate a number of studies which provided Delta-specific outcomes. It would appear that the patterns of VE overtime for the Delta variant mirrored those of the combined general strain data.

There were also a small number of studies which provided a direct comparison between the BNT162b2 and mRNA-1273 vaccines. Collectively, these studies did not suggest that there was a notable difference in patterns of VE overtime between the two vaccines. However, it should be noted that there was significantly less total data for the mRNA-1273 vaccine, both in terms of length of follow-up and absolute number of individuals included in studies. This means that we weren't able to compare the two vaccines at the 6 or 7 months post time points and the confidence intervals for the mRNA-1273 data tended to be larger.

Of note, there was one large study from Canada that provided population level data for British Columbia and Quebec (this data is indicated in most figures by a dashed line). This data indicated that there was no diminishment in VE for COVID-19 cases nor COVID-19 related hospitalisations for either the BNT162b2 or mRNA-1273 vaccines. In contrast, there was data from two countries which provided very different results to the rest of the data (including that of the study from Canada), one from Qatar and one from Sweden. These studies saw dramatic reductions in VE across time, to the point where there was no detectable effectiveness for cases and a halving of effectiveness for a combination of death and hospitalisations. Due to the limited time available to explore the reasoning for this, we are unable to explain these differences.

One aspect that is not included in the current report, but is worth exploring, are the changes in COVID-19 related public health policies and the underlying case counts (nor the proportion of various variants) in the countries during the time of data capture. It is possible that reductions in prevention measures, coupled with increases in cases, may underlie some of the variability seen both within and across studies and jurisdictions.

Community member perspectives - from the original report

We were two patient partners to participate in the study, and we started by meeting Doro (research assistant) and Simon (principal investigator). Doro then took on the role of coordinator between us and the rest of the team and organizing the meetings and their reports. I liked the way the team integrated us, sharing with us all the necessary information. They were able to create a safe environment for us to participate despite the very tight deadlines for the study. Being with my "colleague" Cynthia also made me feel more comfortable. The discussions were very open, the team made it clear what was expected and their progress as they went, and we were able to share our observations easily with them.

~ Émilie Rufray

I'm pleased with the way the team integrated the citizen partners. We first met as a small team consisting of the research assistant, Doro, and the principal investigator, Simon. This setting allowed for a safe pace to get acquainted and clear off the expectations and the possible implications. In addition, it was easier for me to feel the presence of my "colleague" Emilie and to quickly form a sense of belonging to the team with her. Following that meeting, the team worked transparently with us, sharing their working documents, giving us regular updates, and always offering to help us if we had any questions. I really felt that I could share my concerns and understandings, with the confidence that the team would address them with kindness while rigorously addressing what could be addressed.

~ Cynthia Lisée

Constraints on Generality According to Population (23) - from the original report

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 question was more limited in scope. For example, ten of the 12 studies included in this review relied on samples from predominantly wealthy nations: the United States, the United Kingdom, Qatar, and Israel—four countries that have further demarcated themselves globally by being at the forefront of early vaccine deployment efforts. There was some representation of participants from Latin America and South Africa, but these represented less than 1% of the total sample 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), it is currently unclear whether our conclusions would generalize to a wider global context. For example, if our observation of decreasing VE against new infections can be attributable to the increasing prevalence of new variants (e.g., the Delta variant), then changes in VE could manifest differently in countries where such variants are more (where we might expect a higher decline in VE) vs. less prevalent (where we might expect a lower decline in VE).

*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. With this in mind, during the early planning stages for this review, our team consulted with Canadian public health decision makers to identify key subpopulations of interest for whom: (a) there were reasons to suspect differences in vaccine effectiveness compared to the general population; and/or (b) there may be differential susceptibility to COVID-19 infections that warrant special attention. Initially, while screening articles for relevance, our team explored whether VE data could be isolated for the following subgroups of interest: 1) individuals aged 60 years and above; 2) individuals aged 80 years and above; 3) healthcare professionals; 4) immunocompromised individuals; 5) individuals with comorbid conditions; 6) pregnant women; 7) individuals residing in congregate living conditions; and 8) individuals residing in long-term care. Screening of articles suggested that data may only feasibly be extractable for the first three of these categories. Consequently, we focused our research question (and data extraction efforts) on these three groups. However, upon closer investigation during the data extraction stage, we were only able to consistently extract results for the first grouping; that is, for individuals aged 60 and above.

Overall, this experience suggests that studies should make efforts to provide more detailed findings broken down by populations that may be of specific interest to policy makers (e.g., this could be provided in online supplements). The eight categories noted above are example categories of interest, but are not exhaustive (e.g., breakdowns by other characteristics such as sex and race would also be desirable). However, we note that because we were conducting a rapid review, we did not make efforts

to contact investigators to request additional data. Future synthesists may consequently wish to pursue this option.

Team positionality statement - from the original report

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. In the text below, we summarize our reflection along four themes.

1. **How does our team's background influence our engagement with science?** Our team is composed of individuals with academic training in diverse fields that intersect with health research (e.g., from epidemiology, to physiology, microbiology, and psychology). Our training is predominantly informed by Western scientific paradigms, and this leads us to generally favour quantitative approaches to understanding scientific phenomena (e.g., prioritizing evidence from strong randomised control trials and meta-analyses). However, many members of our team also hold or intersect with non-traditional and underrepresented identities in research. For example, several team members come from middle-income countries, and many of us have lived experiences with themes such as immigration, poverty, 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 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 (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, with worries about how such acts can lead to detrimental effects for certain individuals, especially members of already underserved communities. However, we note that our team lacked direct representation from several key perspectives; for instance, that of policy-makers (who propose and enact policies tied to COVID-19 vaccines) and of frontline healthcare workers (directly involved in distributing COVID-19 vaccines), among others.
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. 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 a plain language summary and an infographic designed for public 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 create 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) and to delay certain procedures (e.g., the creation of a positionality statement) until after a preliminary version of the report had been produced. 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 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 the **Supplementary Material**.

Potential implications for health systems decision-making

Though the current review provides some initial evidence for a waning in VE for COVID-19 confirmed cases, it is unclear what might be driving this (e.g., a degradation in immunogenicity, changes in public health measures, or variations in case numbers and general transmission) nor the absolute decrease in this VE. This, coupled with the relatively stable VEs for COVID-related hospitalisations and deaths, does not suggest that there would be any benefit in providing additional doses of the currently formulated vaccines 4 to 7 months after completing a full vaccine schedule.

However, this needs to be considered in the context of the large variability in the available studies and a lack of randomised controlled trial evidence on the utility of providing additional doses. Furthermore, to reduce the transmission of the virus and limit increases in cases, there may be a need to maintain some COVID-19 prevention behaviours, e.g., mask wearing and physical distancing, in individuals who are fully vaccinated. 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.

References

1. Ontario Ministry of Health. COVID-19 Fully Immunized and Previously Positive Individuals: Case, Contact and Outbreak Management Interim Guidance [Internet]. 2021 [cited 2021 Sep 21]. Available from: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/contact_mngmt/COVID-19_fully_vaccinated_interim_guidance.pdf

2. Public Health Agency of Canada. National case definition: Coronavirus disease (COVID-19) [Internet]. 2021 [cited 2021 Sep 21]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/national-case-definition.html

3. Public Health Agency of Canada. COVID-19 signs, symptoms and severity of disease: A clinician guide [Internet]. 2020 [cited 2021 Sep 21]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/signs-symptoms-severity.html

4. Public Health Agency of Canada. SARS-CoV-2 variants: National definitions, classifications and public health actions [Internet]. 2021 [cited 2021 Sep 21]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/testing-diagnosing-case-reporting/sars-cov-2-variants-national-definitions-classifications-public-health-actions.html

5. Covidtracker - Covid-19 Coronavirus Tracker [Internet]. [cited 2021 Sep 20]. Available from: https://www.covidtracker.com/

6. Pormohammad A, Zarei M, Ghorbani S, Mohammadi M, Razizadeh MH, Turner DL, et al. Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Vaccines. 2021 May;9(5):467.

7. Gupta RK. Will SARS-CoV-2 variants of concern affect the promise of vaccines? Nat Rev Immunol. 2021 Jun;21(6):340–1.

8. World Health Organization. Evaluation of COVID-19 vaccine effectiveness [Internet]. 2021 Mar. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1

9. Iorio, A, Little, J, Linkings, L, Abdelkader, W, Bennet, D, Lavis, JN. COVID-19 living evidence synthesis #6 (version 6.19): What is the efficacy and effectiveness of available COVID-19 vaccines in general and specifically for variants of concern?

10. Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Vaccine effectiveness and duration of protection. 2021;25.

11. Bruxvoort K, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Real-World Effectiveness of the mRNA-1273 Vaccine Against COVID-19: Interim Results from a Prospective Observational Cohort

Study. SSRN Electron J [Internet]. 2021 [cited 2021 Sep 21]; Available from: https://www.ssrn.com/abstract=3916094

12. Chemaitelly H, AlMukdad S, Joy JP, Ayoub HH, Yassine HM, Benslimane FM, et al. SARS-CoV-2 vaccine effectiveness in immunosuppressed kidney transplant recipients [Internet]. Epidemiology; 2021 Aug [cited 2021 Sep 21]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.08.07.21261578

13. Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Six-month effectiveness of BNT162b2 mRNA COVID-19 vaccine in a large US integrated health system: a retrospective cohort study. 2021;24.

14. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021 Sep 15;NEJMoa2110345.

15. Thompson MG, Stenehjem E, Grannis S, Ball SW, Naleway AL, Ong TC, et al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. N Engl J Med. 2021 Sep 8;NEJMoa2110362.

16. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. N Engl J Med. 2021 Oct 6;NEJMoa2114114.

17. El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021 Nov 4;385(19):1774–85.

18. Lin D-Y, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. Effectiveness of Covid-19 Vaccines in the United States Over 9 Months: Surveillance Data from the State of North Carolina [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Oct [cited 2021 Nov 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.10.25.21265304

19. Poukka E, Baum U, Palmu AA, Lehtonen TO, Salo H, Nohynek H, et al. Cohort study of Covid-19 vaccine effectiveness among healthcare workers in Finland, December 2020 - October 2021 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Nov [cited 2021 Nov 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.11.03.21265791

20. Skowronski DM, Setayeshgar S, Febriani Y, Ouakki M, Zou M, Talbot D, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Oct [cited 2021 Nov 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.10.26.21265397

21. de Gier B, Kooijman M, Kemmeren J, de Keizer N, Dongelmans D, van Iersel SCJL, et al. COVID-19 vaccine effectiveness against hospitalizations and ICU admissions in the Netherlands, April-

August 2021 [Internet]. Infectious Diseases (except HIV/AIDS); 2021 Sep [cited 2021 Nov 26]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.09.15.21263613

22. Nordström P, Ballin M, Nordström A. Effectiveness of Covid-19 Vaccination Against Risk of Symptomatic Infection, Hospitalization, and Death Up to 9 Months: A Swedish Total-Population Cohort Study. SSRN Electron J [Internet]. 2021 [cited 2021 Nov 26]; Available from: https://www.ssrn.com/abstract=3949410

23. Rapid Review: What is the effectiveness, immunogenicity and safety of COVID-19 vaccines in persons who have had a prior, confirmed COVID-19 infection? [Internet]. 2021 Jun p. 47. Available from: https://www.nccmt.ca/covid-19/covid-19-rapid-evidence-service/36