Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Duration of protective immunity following COVID-19 vaccination of individuals with underlying conditions (efficacy and effectiveness)

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

Setting standards for health and social care services — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

Regulating social care services — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

Regulating health services — Regulating medical exposure to ionising radiation.

Monitoring services — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

Health technology assessment — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

Health information — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

National Care Experience Programme — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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List of abbreviations used in this report

aIRR	adjusted incident rate ratio
aOR	adjusted odds ratio
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	Coronavirus disease 2019
CMA	Conditional Marketing Authorisation
C_t	cycle threshold
EMA	European Medicines Agency
HCWs	healthcare workers
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
ICU	intensive care unit
IRR	incidence rate ratio
IQR	interquartile range
LTC	long term care
NE	non estimable
NIH	National Institutes of Health
NPHET	National Public Health Emergency Team

RCT	randomised controlled trial
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
VE	vaccine efficacy / effectiveness
WHO	World Health Organization

Acknowledgements

HIQA would like to thank HSE librarians for their assistance in designing and conducting the database searches for this evidence summary.

Key points

- The duration of protective immunity from COVID-19 following vaccination is an important consideration for Ireland's vaccination strategy, particularly in relation to groups who may have a less than optimal response to vaccination or for whom there is evidence that immunity may wane over time.
- As of November 2021, following conditional marketing authorisation from the European Medicines Agency, four vaccines against COVID-19 are licensed and distributed for use in Ireland. These are ChAdOx1 (AstraZeneca), Ad26.COV2.S (Janssen), and the mRNA vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech). Over 92% of those aged 18 years and older in Ireland are fully vaccinated.
- This review aimed to assess the duration of vaccine efficacy and effectiveness against COVID-19, specifically in individuals with underlying health conditions.
- The distinction between vaccine efficacy and vaccine effectiveness is noted. Efficacy studies provide data on an intervention under highly controlled conditions, such as in randomised controlled trials. In contrast, effectiveness studies provide data on how well a treatment works in the real-world setting.
- Eighteen papers reporting 14 unique studies, with outcomes for individuals with underlying conditions, were included in this evidence summary: three randomised clinical trials (RCTs) and 11 observational studies, of which six were cohort studies and five were case-control studies.
- For the three RCTs included in this evidence summary, the study size ranged from 28,207 to 44,060 participants, with a maximum follow-up period of six months.
    - Two studies enrolled individuals in good health and those with co-morbidities. One study included adults at high risk of infection or severe COVID-19.
    - All three RCTs were peer-reviewed and considered to be at low risk of bias.

- Eleven observational studies reported on vaccine effectiveness; the number of participants within studies ranged from 782 to 4.8 million with a maximum follow-up period of up to nine months in one study. Of these 11 studies:
    - Seven observational studies examined vaccine effectiveness in the general population, two studies exclusively enrolled healthcare and other frontline workers, and two studies were conducted exclusively in populations with underlying conditions. All 11 observational studies presented information on individuals with underlying conditions either as subgroups of a larger population or as the sole focus of the study.
    - The quality varied; five were rated as good quality, five were appraised as being of fair quality and one of poor quality. The primary reasons for concern were bias relating to the measurement of the outcome and lack of adjustment for confounding factors. The majority of the observational studies (7/11) included are currently published as preprints and hence have not been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.
- Overall, there was limited and inconsistent evidence regarding vaccine efficacy and effectiveness in those with underlying conditions. Across both primary (that is, severe disease and mortality) and secondary outcomes (that is, SARS-CoV-2 infection), overall vaccine efficacy or effectiveness in those with underlying conditions were found to be comparable to or lower than estimates for the general population.
- When stratified by age, any statistically significant reduction in protection against severe disease or mortality over time in those with underlying conditions was limited to older adults (either >60 or ≥ 65 years), with protection in younger age groups with underlying conditions found to be largely comparable to that offered to the general population. Additionally, where those with immunocompromising conditions were analysed as a subgroup, vaccine effectiveness against both primary and secondary outcomes was found to be reduced in this group. Thus, it is unclear whether any reduction in vaccine protection in those with underlying conditions is driven by those of older age or with immunocompromising conditions.

- Randomised controlled trials have compared vaccine efficacy (VE) in the general population to those with underlying conditions.
    - In the BNT162b2 (Pfizer/BioNTech) trial, similar VE estimates against symptomatic infection were found for participants at risk of severe disease to those not at risk.
    - In the mRNA-1273 (Moderna) trial, VE point estimates for symptomatic infection were lower for those at risk of severe disease than those who were not at risk, particularly those aged 65 and older. However, the confidence intervals overlapped. Lower VE was observed for those with a greater number of risk factors for severe disease.
    - In the Ad26.COV2.S (Janssen) trial, VE point estimates for moderate to severe/critical disease were lower for individuals with comorbid conditions than those without such conditions, particularly those aged 60 and older. However, there was substantial uncertainty associated with these estimates.
- There was some evidence from observational studies that vaccine effectiveness, particularly against infection, waned over time in those with underlying conditions. However, it is unclear whether this waning occurs any faster than in the general population:
    - An observational study based on national Swedish registry data with up to nine months follow-up reported greater reductions in vaccine effectiveness, particularly against infection, in those with underlying conditions, compared with the general population.
    - An observational study conducted by Public Health England observed greater reductions in vaccine effectiveness against hospitalisation in those in a clinical risk group, compared with those not in a clinical risk group, but only in those who were 65 years and older. The ChAdOx1 (AstraZeneca) vaccine was associated with lower protection against hospitalisation compared with BNT162b2 (Pfizer/BioNTech) vaccine across all age groups, particularly for those in clinical risk groups.
    - An observational study conducted by the US Centers for Disease Control and Prevention (CDC) found significant reductions in vaccine effectiveness against hospitalisations over time in those with

immunocompromising conditions compared with trends in those without immunocompromising conditions. However no such significant difference was observed for those with multiple morbidities compared with the overall population.

  - In contrast, an observational study conducted in Qatar reported an initially low but increasing protection over time, against severe, critical, or fatal COVID-19 disease among immunosuppressed kidney transplant recipients.

- The comprehensive rollout of COVID-19 vaccines during the conduct of all the included observational studies led to low numbers in the unvaccinated group, making any comparison between groups less certain over time. Furthermore, the vaccine rollout schedule varied by country, with typically those at highest risk either due to high risk of exposure or risk of severe disease outcomes offered vaccination earlier than those deemed to be at lower risk. These factors together, with changes in the prevalence of disease or variants of concern over time as well as varying public health measures and associated behaviour, make it difficult to ascertain if observed reductions in effectiveness over time relate to waning immunity, reduced effectiveness due to the emergence of a new variant of concern, other unmeasured confounding or a combination of all of these factors.

- A particular limitation in calculating vaccine efficacy and effectiveness in those with underlying conditions is the smaller sample size of these subgroups. As a result, substantial uncertainty in the estimates was observed, with wide and overlapping confidence intervals noted, particularly as the length of follow-up increased or the size of the group decreased. Longer follow-up of larger cohorts is required to provide better information regarding long-term vaccine effectiveness in those with underlying conditions.

- For those with underlying health conditions, the following were the main evidence gaps identified in relation to estimates of effect:

  - vaccine efficacy or effectiveness beyond six months, either for those with underlying conditions as a combined group or by individual condition

  - comparative effectiveness between different vaccines

  - the impact of new variants of concern on vaccine effectiveness.

- Overall, the evidence suggests that vaccination against COVID-19 continues to provide robust protection against severe disease and mortality for at least six months post-vaccination. However, there are data to suggest potential waning of vaccine effectiveness for severe disease, mortality and infection in individuals with underlying conditions, particularly for those aged 65 years and older and in those with immunocompromising conditions. National and international data support a higher risk of severe disease outcomes in older individuals and those with underlying health conditions. Given this and the noted lower initial vaccine efficacy and effectiveness for these populations in many of the included studies, any additional reduction in effect would be of concern. It is important to note that evidence is rapidly emerging in this area and that the conclusions of this review may change as longer-term studies are published.

Background

As of 1 November 2021, the European Medicines Agency (EMA) has granted conditional marketing authorisation (CMA) for four vaccines to prevent Coronavirus Disease 2019 (COVID-19), with additional candidate vaccines under rolling review.[1] Upon receiving CMA, authorisation for the use of each COVID-19 vaccine is valid across all EU member states, including Ireland.[2] The COVID-19 vaccine developed by Pfizer in collaboration with BioNTech (BNT162b2) became the first to receive authorisation on the 21 December 2020.[3] Moderna's COVID-19 vaccine (mRNA-1273 or Spikevax) was approved on the 6 January 2021,[4, 5] followed by the ChAdOx1 vaccine, developed by AstraZeneca in collaboration with the University of Oxford, on the 29 January 2021.[6, 7] More recently, the Janssen vaccine (Ad26.COV2.S) was authorised on the 11 March 2021.[8, 9] The EMA subsequently recommended an extension of indication for the BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines to those aged 12 and above on the 28 May 2021 and the 23 July 2021, respectively.[10, 11]

The vaccine rollout in Ireland is detailed in the National COVID-19 Vaccination Programme Strategy.[12] In summary, vaccination began on the 26 December 2020 in a sequenced manner, starting with those at greatest risk of severe illness and death, followed by those at very high or high risk of exposure and transmission receiving priority for the available vaccines. The first group to receive the vaccine included adults aged 65 years or older who were residents of long term care (LTC) facilities, with vaccination also extended to staff working on site. The next priority group included frontline healthcare workers (HCWs) with the sequential rollout based on age and existing medical conditions. As vaccine availability increased, through the approval and acquisition of additional vaccines, the rollout accelerated. As of 28 October 2021, a total of 7.3 million vaccine doses have been administered in Ireland, with an estimated 92.2% of those aged 18 and older considered to be fully vaccinated.[13, 14] The most commonly administered vaccine to date in Ireland is BNT162b2 (Pfizer/BioNTech) with 5.3 million total doses administered, followed by ChAdOx1 (AstraZeneca) with 1.2 million doses, mRNA-1273 (Moderna) with 0.6 million doses, and Ad26.COV2.S (Janssen) with 0.2 million doses.[12]

The approved vaccines fall under two categories, messenger ribonucleic acid (mRNA) and viral vector vaccines. BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) are both mRNA vaccines. These vaccines contain the genetic code that allows the host to produce the same proteins, which are known as 'spike proteins', found on the surface of the SARS-CoV-2 virus that causes COVID-19. After vaccination, the host's immune cells will produce and display these proteins and trigger an immune response.[13, 15] The viral vector vaccines, which include ChAdOx1

(AstraZeneca) and Ad26.COV2.S (Janssen), work by using a weakened form of a different virus as a vector to transport the genetic code for the spike proteins. Once the vaccine is administered, the adenovirus vector enters the immune cells of the host and delivers the genetic code. The host immune cells then produce and display these proteins, triggering an immune response.[13, 15] The immune reaction brought about by both mRNA, and viral vector vaccines lead to the production of antibodies and defensive white blood cells, offering the host protection against the SARS-CoV-2 virus. An individual is considered to be protected once they are fully vaccinated. This occurs once the required time has elapsed since the second or final dose of their respective vaccination schedule is complete. The dosing schedule for each vaccine and additional vaccine identifiers are detailed in Table 1.

Table 1. Vaccination schedule for licensed COVID-19 vaccines in Ireland

Vaccine	Number of doses required	Days from final dose to being considered fully vaccinated	Other vaccine identifiers
BNT162b2 **Pfizer/BioNTech.**[16, 17]	2	7	• Comirnaty® • Tozinameran®
mRNA-1273 **Moderna.**[15]	2	14	• Spikevax® • CX-024414 • TAK-919
ChAdOx1 **AstraZeneca/Oxford.**[18]	2	14	• Vaxzevria® • ChAdOx1-SARS-CoV-2 • Covishield® (Manufactured in India) • AZD1222
Ad26.COV2.S **Janssen.**[19]	1	14	• JNJ-78436735 • VAC31518

When considering the emerging evidence, it is important to note the distinction between vaccine efficacy and vaccine effectiveness. Efficacy studies provide data on the benefits and harms of an intervention under highly controlled conditions, such as in randomised controlled trials (RCTs), whereas effectiveness studies provide data on how well a treatment works in the real world setting (observational studies).

Given the unique threat posed by the COVID-19 pandemic, there was limited evidence on the duration of vaccine efficacy when the CMAs were issued,[3, 5, 7, 20, 21] with a median duration of follow-up in trials of approximately two months. All four vaccines were granted their CMA on the basis that the respective applicants were in a position to provide comprehensive clinical data in the future.[22]

With the increasing duration of RCT follow-up and the availability of population-level effectiveness studies, it should be possible to derive a more robust estimate of the duration of vaccine effectiveness. The data will also help identify groups with less than optimal response to vaccination or for whom there is evidence that effectiveness may be waning so that the need for additional mitigation or protective measures, such as additional doses, can be considered.

The Health Information and Quality Authority (HIQA) conducts evidence synthesis to inform national strategic decision-making. These evidence syntheses are conducted at the request of the National Public Health Emergency Team (NPHET) and related groups tasked with the national COVID-19 response.

The following policy question for this evidence summary was outlined by NPHET to inform the work of the National Immunisation Advisory Committee (NIAC):

> "What is the evidence relating to the duration of protective immunity (vaccine efficacy and effectiveness) following COVID-19 vaccination?"

There is no defined threshold of efficacy or effectiveness below which efficacy or effectiveness is classified as lost. Given this and the limited follow-up since the vaccines became available, the following specific research question was developed and forms the basis of this evidence summary:

"To what extent and over what period of time does the efficacy and effectiveness of COVID-19 vaccination change?"

The current review focuses on those with underlying health conditions.

Methods

The aim of this review was to examine the change in efficacy and effectiveness of COVID-19 vaccination over time, specifically in individuals with underlying health conditions. All underlying conditions with relevant vaccine efficacy or effectiveness outcomes were examined in this evidence summary. A detailed summary of the methods used is provided in the protocol, available here.[23] This evidence summary comprises an update of a review that examined the duration of protective immunity following COVID-19 vaccination more broadly (that is, in the general population, in older adults, in healthcare workers, in residents and staff of long term care facilities, as well as in patients with underlying conditions). However, the focus of the current review is specifically on those with underlying health conditions.

An updated systematic search of published peer-reviewed articles and non-peer-reviewed preprints was undertaken. The databases Medline (OVID), Embase (OVID) and Cochrane Library were searched up to 27 October 2021. A preprint search in Europe PMC, MedRxiv and Google Scholar was also conducted on 27 October 2021. For the original review, the literature searches of the electronic databases and preprint servers were conducted on 30 September and 31 August 2021, respectively. No language restrictions were applied. All potentially eligible papers were exported to Covidence (www.covidence.org) for single screening of titles, abstracts, and full texts for relevance based on the criteria outlined in Table 2.

Data extraction and quality appraisal of included studies was completed by a single reviewer and checked by a second reviewer. All studies excluded following full-text review are reported with their reasons for exclusion in Appendix A. Where appropriate, graphical data were extracted using WebPlotDigitiser (Version 4.4) software.[24] The full data extraction tables are located in Appendix C. Quality appraisal of RCTs was completed using the Cochrane risk of bias tool version 1.[25] The relevant National Institutes of Health (NIH) Quality Assessment Tool was used for the quality appraisal of observational studies (Appendix B).[26] Where available, vaccine efficacy or effectiveness data stratified by underlying condition were extracted from individual studies and plotted on a common chart for visual comparison purposes. Plotting of data was performed using RStudio statistical software Version 1.2.5019 using R version 3.6.2.

At the request of the National Immunisation Advisory Committee (NIAC) additional data extraction and quality appraisal was undertaken to examine the change in efficacy and effectiveness of one-dose Janssen (Ad26.COV2.S) vaccination over time (in all populations), based on an updated literature search conducted on 8

November 2021. The updated evidence tables for 17 relevant reports describing 14 unique studies are located in Appendix D.[21, 27-42]

Table 2. Population Intervention Outcome Study design (PICOS) criteria

Population	▪ Any persons aged ≥12 years. ▪ Persons from special populations (to include, immunocompromised, people with cancer or severe respiratory disease, older adults (70 years or older), healthcare workers, and residents and staff of long term care facilities. ▪ Depending on data availability, results from relevant subgroups (for example age group, or immunocompromised).
Intervention	**Included:** Vaccines against COVID-19 which are licensed and distributed in Ireland: ▪ ChAdOx1 (AstraZeneca)^ ▪ Ad26.COV2.S (Janssen). ▪ mRNA-1273 (Moderna). ▪ BNT162b2 (Pfizer/BioNTech). Studies which include vaccine regimens with extended intervals between first and second doses or heterologous vaccine regimens were also included. **Exclude:** Studies which only include a single dose regimens (of what are routinely 2-dose vaccine schedules) for those previously infected or which include booster doses.
Comparators	▪ Alternative COVID-19 vaccine licensed in Ireland. ▪ Placebo (or alternative vaccine given as placebo). ▪ No vaccination. ▪ Vaccination at a different time point.
Outcomes*	**Primary Outcomes** ▪ Severe disease as measured by hospitalisations and or ICU admissions for COVID-19.

	▪ COVID-19 mortality and or all-cause mortality. **Secondary Outcomes** ▪ SARS-CoV-2 infection (RT-PCR or antigen-confirmed) by disease severity as defined by study authors (asymptomatic/mild/moderate) and duration (<12 weeks and ≥12 weeks (chronic COVID-19)).[43] Outcomes were extracted for study-defined time points since vaccination.[43] Changes in absolute and relative efficacy or effectiveness were noted. Disaggregated data by variant were extracted if reported. **Excluded**: ▪ Outcomes relating to time points in the period when individuals are waiting for the second dose of a two-dose schedule and in the period immediately after full vaccination, but before immunity is expected to occur.
Types of studies	**Included:** ▪ Randomised controlled trials. ▪ Non-randomised controlled trials. ▪ Quasi-experimental studies. ▪ Prospective and retrospective cohort studies ▪ Case-control studies. ▪ Test-negative case-control studies. ▪ Analytical cross sectional studies. ▪ Studies where the median time from administration of the final regimen dose to outcome ascertainment is ≥ eight weeks~ or studies which report outcomes eight weeks after administration of the final regimen dose. **Excluded:** ▪ Studies that enrolled fewer than 1,000 participants from the general population. ▪ Studies that enrolled fewer than 100 participants of special populations, as defined above. ▪ Animal studies. However, if a subgroup analysis from a study meeting the exclusion criteria above, would have been eligible for inclusion if reported as a study in its own right, data from the relevant subgroups were included and extracted.

*Safety outcomes were considered beyond the scope of this review. Outcomes related to immunogenicity (where there was no long-term efficacy/effectiveness data) and transmission were not included in the review.
^Brands of ChAdOx1 which are not licensed in Ireland (for example Covishield) were included.
~Where median is not reported, the mean time was used to assess eligibility.

Results

An overview of the search findings is presented in the PRISMA diagram (Figure 1).

The original database search of Embase and Medline returned 2,212 citations. An additional 585 citations were identified from MedRxiv/EuropePMC/Google Scholar, ten from EMA and United States' Food and Drug Administration (FDA) reports, and nine from other sources. Following the removal of duplicates, the titles and abstracts of 2,184 citations were screened for relevance. This resulted in 463 reports eligible for full-text review, where a further 406 records were excluded (Appendix A). Following the screening process, 57 papers describing 49 unique studies that met the broad inclusion criteria were identified.

The updated search on 27 October 2021 identified an additional 309 records through electronic database searching and another 300 from other sources. After removing duplicates, 387 records were screened by titles and abstracts, with 76 full text reports subsequently screened for eligibility. A total of 63 records were excluded in this update (Appendix A). Following the screening, an additional 13 studies were identified that met the broad inclusion criteria.

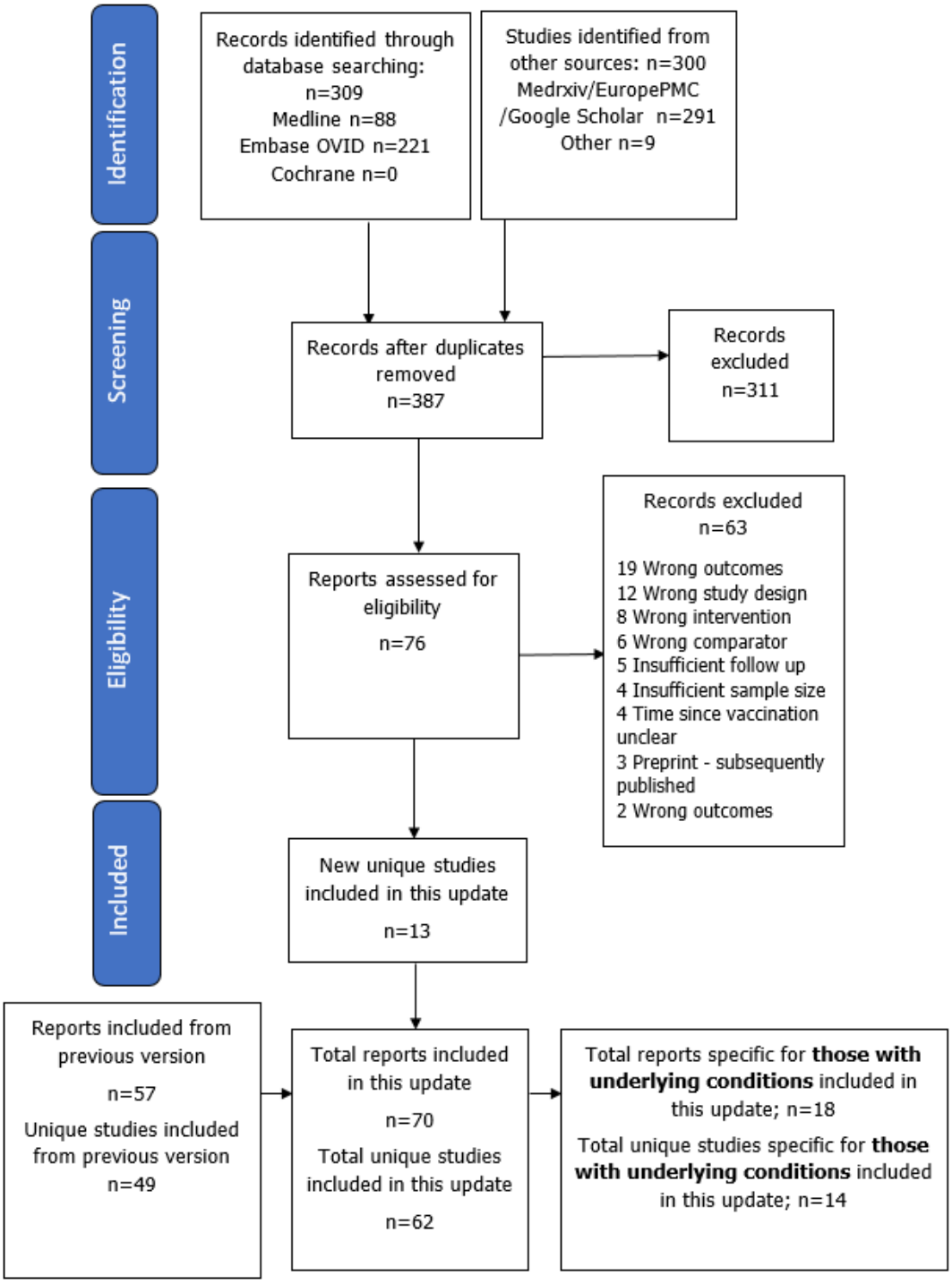
Combining the output of both the original database search and the updated search, a total of 70 papers describing 62 unique studies were identified that met the broad inclusion criteria. Of these, 18 papers describing 14 unique studies provided outcomes specifically in individuals with underlying conditions and were included in the current review.[20, 21, 35, 38, 41, 44-56] Two papers were identified as part of the updated search.[48, 50] Seven of the 18 included papers were only available as preprints.[35, 44, 46, 48-50, 54]

Of the studies identified, three were RCTs,[20, 21, 38, 45, 52, 56, 57] and the remaining 11 were observational study designs.[35, 41, 44, 46, 48-51, 53-55] Characteristics of included studies and study findings are described separately for vaccine efficacy (RCTs) and effectiveness (observational studies). The following conditions or categories of conditions (as defined by the study authors) that had relevant outcomes were reported across the included studies:

- at least one underlying condition[38, 41, 50, 53]
- clinical risk group[44, 45, 49, 52]
- immunocompromised[35, 46, 48]
- hypertension[38, 51, 52, 54]
- diabetes[38, 47, 51, 54]
- overweight or obese [38, 47, 51, 52, 54, 56]

- HIV[38, 47]
- chronic lung disease[41, 47]
- serious cardiac disease[38, 47]
- liver disease[47]
- kidney transplant recipient[46]
- asthma.[51]

Figure 1: PRISMA diagram of study selection



Vaccine efficacy

Characteristics of included studies

Five papers describing the results of three RCTs were identified (summarised in Table 3).[38, 45, 47, 52, 56] Studies with a follow-up of at least eight weeks post final

vaccination and with outcomes for those with underlying conditions were identified for Ad26.COV2.S (Janssen), mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech). No relevant RCT was identified for ChAdOx1 (AstraZeneca). Additional data (primarily for subgroup analysis) are provided in reports published by the EMA,[5] and the FDA.[21] All three included RCTs have been peer-reviewed.[38, 45, 47, 52, 56] The pivotal trials for each of the licensed vaccines were extensively reviewed by regulatory agencies to inform conditional market authorisation. Consistent with the aim of this review, this section focuses on information relating to the length of follow-up and presents updated data from the pivotal RCTs, specifically in those with underlying conditions. The maximum follow-up reported was six months.

Two studies enrolled individuals in good health and those with co-morbidities,[38, 52, 56] and one study included adults at high risk of infection or severe COVID-19.[45]

RCTs required at least eight weeks of follow-up before authorisation could be approved. Hence, two of the three RCTs initially published interim results with median cut-offs close to this date.[38, 45, 52] Updated analyses with up to six months of follow-up have been published for the pivotal BNT162b2 (Pfizer/BioNTech)[56] and mRNA-1273 (Moderna) trials.[47] All of the trials were set across multiple countries, further details are available in Appendix C.

All three RCTs were conducted before substantial data on variants of concern emerged, although some efficacy data are available for the Beta variant. The studies are presented by vaccine type.

Table 3. Summary of RCTs reporting data for primary outcomes (vaccine efficacy against COVID-19 related severe disease and mortality), secondary outcomes (vaccine efficacy against any symptomatic SARS-CoV-2 infection) and change in efficacy over time

Author, Country	Exposure[#]	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
Sadoff ,[38] peer-reviewed International	Ad26.COV2.S (Janssen)	**N:** 39,321 Intervention: 19,630 Placebo:19,691	Median: 8.3 (range 0.1 - 17)	**≥28 days post vaccination** For total population VE: 100% (74.3 to 100) Underlying Conditions Outcomes [£] *Serious heart conditions*: VE = 79.4% (-83.7 to 99.6) *HIV:* VE = 47.5% (-266 to 95.3) *Hypertension:* VE = 35.7% (-45.6 to 72.8) *Obesity:*	**≥28 days post vaccination** VE: 75% (-25.2 to 97.4)	NR	**≥28 days post vaccination** VE 66.5% (55.5 to 75.1)	The onset of efficacy was evident as of 14 days after administration for moderate to severe–critical disease and as of 7 days after administration for severe–critical disease. Efficacy continued to increase through approximately 8 weeks after administration, especially for severe–critical Covid-19. No evidence of waning efficacy was noted among the approximately 3000 participants who were followed for 11 weeks or among 1000 participants who were followed for 15 weeks .	Low

Author, Country	Exposure[#]	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
				VE = 65.9% (47.8 to 78.3) *Diabetes Mellitus, type 2* VE: 23.0% (-90.1 to 69.8) *Moderate to* Severe-Critical COVID-19 With comorbidities[@] (and stratified by age) VE = 58.6% (40.6 to 71.6) 18-59, VE 64.0% (44.3, 77.3) ≥60 years VE 42.3% (-13.1, 71.6) Without comorbidities[@] (and stratified by age) VE = 68.8% (59.0 to 76.6)					

Author, Country	Exposure[#]	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
				18-59 VE= 68.0% (56.8, 76.6) ≥60 years, VE 72.4% (45.0, 87.3)					
Polack, [52]* peer-reviewed International	BNT162b2 (Pfizer/ BioNTech)	**N**:43,448 Intervention: 21,720 Placebo: 21,728	Mean: 7.6 Maximum: 14	VE: 75% (-52.0 to 99.5)	NR	NR	<u>Overall population</u> VE 95.0% (90.3 to 97.6) Underlying conditions population At risk[$] VE = 95.3 (87.7 to 98.8) Not at risk[$] 94.7 (85.9 to 98.6) Obese[€] VE = 95.4 (86.0 to 99.1) Non-Obese [€] VE = 94.8 (87.4 to 98.3)	No evidence of waning VE against symptomatic infection after dose 1 in Kaplan Meier plot for the overall population.	low

Author, Country	Exposure[#]	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
							Hypertension VE = 94.6 (68.7 to 99.9) <u>By Risk Group and Age</u> *16 – 64 years and not at risk* 94.2 (84.4 to 98.5) *16 – 64 and at risk* 95.9 (87.6 to 99.2) *≥65 and not at risk* 100 (29.0 to 100) *≥65 and at risk* 91.7 (44.2 to 99.8) Obese and age group 16–64 and not obese 95.2 (87.3 to 98.7)		

Author, Country	Exposure#	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
							16–64 and obese 94.9 (84.4 to 99.0) ≥65 and not obese 91.8 (44.5 to 99.8) ≥65 and obese 100 (27.1 to 100)		
Thomas,[56]* peer-reviewed, follow-up of Polack [52] International	BNT162b2 (Pfizer/BioNTech)	**N**:44,060 Intervention: 22,030 Placebo: 22,030	Mean: 16.7 51% of the participants in each group had 4 to < 6 months of follow-up; 8% (6%) of the participants in the treatment (placebo) group had ≥6 months of follow-up	VE: 95.7% (73.9 to 99.9)	NR	NR	Overall population 91.3% (89.0 to 93.2) Underlying condition population At risk$ VE = 91.6 (88.2 to 94.3) Not at risk$ VE = 91.0 (87.6 to 93.6) 16–64 and at risk$ VE = 91.5 (87.5 to 94.4) ≥65 and at risk$	VE against symptomatic infection Overall population ≥7 days to <2 months: VE 96.2% (93.3 to 98.1) ≥ 2 months to < 4 months: VE 90.1% (86.6 to 92.2) ≥ 4 months: VE 83.7% (74.7 to 89.9)	

Author, Country	Exposure[#]	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
							VE = 91.8 (81.4 to 97.1) By age and obesity Obese[€] 91.6 (87.6 to 94.6) Not Obese[€] VE = 91.1 (88.1 to 93.5) 16-64 and obese VE = 91.3 (86.7 to 94.5) ≥65 and obese[€] VE = 93.2 (78.9 to 98.7)		
Baden,[(45)] peer-reviewed US	mRNA-1273 (Moderna)	**N:** 28,207 Intervention: 14,134 Control:14,073	Median: 9 (Range 0 – 13.9)	Overall population VE: 100% (NE to 1.0)	NR		Overall population VE 94.1% (89.3 to 96.8%) Underlying conditions population At risk #	No evidence of waning efficacy in Kaplan Meier for the 2,381 patients followed for 12 weeks post dose 2, in the overall population.	low

Author, Country	Exposure[#]	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
							VE = 90.9 (74.7 to 96.7) Not at risk# VE 95.1% (85.2 to 96.8) 18 and <65 and at risk# VE = 94.4% (76.9 to 98.7) ≥65 and at risk# VE = 75.2% (NE, 94.7) No risk factors # VE = 95.1 (89.6 to 97.7) 1 risk factor # VE = 91.7 (73 to 97.4) ≥ 2 risk factors #,% VE = 87.2 (-2.7 to 98.4)		
El Sahly,[47] **US**	mRNA-1273 (Moderna)	**N:**	Median – 26.1 (IQR 37.5 to 32.1).	VE: 98.2% (92.8 to 99.6)	VE: 100%	VE: 82.0% (79.5 to 84.2)	Overall population	Symptomatic infection over time (PP)	low

Author, Country	Exposure#	Sample Size	Time since final vaccination (weeks)	Primary outcomes: overall follow up VE (95% CI)		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
Follow up of Baden (45)~		Efficacy population - 28,451 FAS – 30,346 Significant Cardiac Disease – 5.0% Severe obesity (BMI >40) - 7.0% Diabetes – 9.6% Liver disease – 0.7% HIV – 0.6%			(NE to 100)		VE: 93.2 (90.9 to 94.8) Chronic lung disease VE = 87.2 (63.8 to 95.5) Significant cardiac disease VE = 88.0 (65.9 to 95.8) Severe obesity (BMI >40) VE = 91.4 (81.4 to 96.0) Diabetes VE = 96.2 (87.9 to 98.8) Liver disease VE = 81.0 (−64.8 to 97.8) HIV VE = 100 (NE to 100)	Overall population ≥14 Days to <2 months: VE 91.8% (86.9 to 95.1) 2 months to <4 months: VE 94.0% (91.2 to 96.1) ≥ 4 months: VE 92.4% (84.3 to 96.8)	

*The studies highlighted yellow are part of the same trial, with Polack,[52] publishing initial results, and Thomas[56] updating the Polack paper with longer follow-up time for trial participants.

@Co-morbidities defined as asthma; chronic lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1, type 2, or gestational); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and

(pulmonary) hypertension or high blood pressure; obesity (body mass index (BMI) ≥30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; sleep apnea; Parkinson's disease; seizures; ischemic strokes; Intracranial hemorrhage; Guillain-Barré syndrome; encephalopathy; meningoencephalitis; and participants who live in nursing homes or long-term care facilities.

~The studies highlighted orange are part of the same trial, with El Sahly publishing six month follow-up data of Baden.

£ Data on further comorbidities are available however vaccine effectiveness could not be calculated due to insufficient sample sizes. Further data is available in Appendix C.

$ At risk is defined as having at least one of the Charlson Comorbidity Index categories or obesity

Definition for at risk of severe COVID 19. includes Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma, Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension), Severe obesity (BMI ≥ 40 kg/m^2), Diabetes (Type 1, Type 2 or gestational), Liver disease, HIV infection

€ Obese defined as BMI > 30 kg/m^2

Key: CI – confidence interval, IQR interquartile range, NE – not estimated NR - not reported, PP – per protocol, VE – vaccine efficacy, US – United States.

BNT162b2 (Pfizer/BioNTech)

Polack et al.[52] report on the pivotal placebo-controlled RCT of BNT162b2 (Pfizer/BioNTech) in participants aged 16 years or older. The mean follow-up time in the BNT162b2 (Pfizer/BioNTech) arm was eight weeks. Despite the large sample size, (n=43,448), there were very few events to inform vaccine efficacy (VE) estimates against severe disease or mortality thus, the estimates are associated with substantial uncertainty. For VE for symptomatic disease, there is less uncertainty. The estimated VE for the seronegative population for symptomatic disease, was 95.0% (95% CI 90.3 to 97.6). Polack et al. also reported VE for symptomatic disease for those with an underlying condition associated with a high risk of COVID-19 complications. In this study, 'at risk' was defined as having at least one of the Charlson Comorbidity Index categories[58] (for example, HIV, malignancies, cerebrovascular disease, dementia and diabetes) or obesity (body mass index (BMI) ≥30 kg/m^2). A total of 7,743 (20.5%) participants had at least one Charlson comorbidity. The number of individuals with obesity was not reported. VE for participants at risk was found to be similar to that for participants not at risk (95.3% (95% CI, 87.7 to 98.8) vs. 94.7% (95% CI, 85.9 to 98.6)). VE was also found to be similar for participants with obesity compared with those without obesity (95.4% (95% CI, 86 to 99.1) vs. 94.8% (95% CI, 87.4 to 98.3)). When stratified by age, VE for the symptomatic disease was found to be similar in participants aged between 16 and 64 years who were at risk compared with those who were not at risk (95.9% (95% CI, 87.6 to 99.2) vs. 94.2% (95% CI, 84.4 to 98.5)). Additionally, similar VE estimates were found in participants aged between 16 and 64 with obesity compared with those without obesity (94.9% (95% CI, 84.4 to 99) vs. 95.2% (95% CI, 87.3 to 98.7)).

From December 2020, participants aged 16 years and older had an option for unblinding if they became eligible for COVID-19 vaccination according to national or local recommendations. Unblinded participants were followed in an open-label study (no data available). Thomas et al.[56] present updated results for all participants who were followed in the blinded portion of the trial.

Vaccine efficacy for severe disease (regardless of the previous history of SARS-CoV-2) was 95.7% (95% CI 73.9 to 99.9). Thomas et al.[56] also present information on efficacy data for symptomatic disease for the total seronegative population (≥12 years) both overall and over time. Overall VE against the symptomatic disease was 91.3% (95% CI 89.0 to 93.2). VE was reported, stratified by time since the second dose was administered, at three time intervals: ≥7 days to <2 months, ≥2 months - <4 months, and ≥4 months to data cut-off (six months post-dose 2), with VE of

96.2% (95% CI 93.3 to 98.1), 90.1% (95% CI 86.6-92.2) and 83.7% (95% CI 74.7 to 89.9), respectively.

Thomas et al.[56] also reported vaccine efficacy for symptomatic disease for those with an underlying condition associated with a high risk of COVID-19 complications, using the same definition of 'at risk' adopted by Polack et al..[52] Similar to Polack et al., this updated study found comparable vaccine efficacy for participants at risk and those not at risk (91.6% (95% CI, 88.2 to 94.3) vs. 91.0% (95% CI, 87.6 to 93.6), and when comparing participants with, and without obesity (91.6% (95% CI, 87.6 to 94.6) vs. 91.1% (95% CI, 88.1 to 93.5)). No notable differences in vaccine efficacy were observed when stratified by age, with participants aged between 16 and 64 who were at risk, or those with obesity, found to have similar protection levels against symptomatic disease compared with total population estimates for those who were not at risk or those without obesity. Of note, no age breakdown was provided in this study for those who were not at risk or without obesity.

While the risk of bias for the trial as a whole was considered low, a number of elements of the trial design may have biased the results towards showing a decline in vaccine efficacy over time. Participants who chose to be unblinded and discontinue the trial will have shorter follow-up than those who did not. Many countries prioritised vaccine rollout by age, resulting in older individuals being more likely to have discontinued earlier than younger patients and thus being more likely to have a shorter follow-up. Furthermore, in countries where vaccine rollout was slower, the impact of different prioritisation policies may have been amplified. Participants who remain in the trial may therefore systematically differ from the cohort as a whole which could lead to differences in vaccines efficacy over time. For example, the authors report a subgroup analysis that indicated that vaccine efficacy may differ by region with lower efficacy in Latin America; however, insufficient information is provided to ascertain if there are systematic differences in the characteristics between those who remained in the study and those who discontinued.

Thomas et al.[56] also explicitly report data in relation to the Beta variant. In South Africa, where the Beta variant was dominant, vaccine efficacy was 100% (95% CI 53.5 to 100) for symptomatic disease. No disaggregated data were presented for those with underlying conditions.

mRNA-1273 (Moderna)

Baden et al.[45] report on a phase three, multicentre, observer-blinded placebo-controlled RCT of mRNA-1273 (Moderna) in patients aged 18 years or over with no

known history of SARS-CoV-2 infection living or working in locations or circumstances that put them at an increased risk of severe COVID-19 (n=28,207 per protocol). The median time since the final vaccination dose was nine weeks. Vaccine efficacy for symptomatic infection was estimated at 94.1% (95% CI 89.3 to 96.8). Estimates of vaccine efficacy for severe disease were lower for those aged 65 years or older compared with those aged less than 65 years, but the confidence intervals of the estimates overlap. Baden et al. undertook subgroup analysis in those at risk of severe disease. The 'at risk' category comprised those with chronic lung disease, moderate to severe asthma, significant cardiac disease, severe obesity (body mass index ≥ 40 kg/m^2), diabetes (Type 1, Type 2 or gestational), liver disease and HIV infection. In terms of vaccine efficacy for symptomatic infection, estimates were lower for those at risk of severe disease compared with those who were not at risk, though the confidence intervals overlapped (VE 90.9% (95% CI, 74.7 to 96.7) vs. VE 95.1% (95% CI 85.2 to 96.8)). Estimates of vaccine efficacy were found to be lower in those with two or more risk factors (VE 87.2% (95% CI, -2.7 to 98.4)) compared with those with one risk factor (VE 91.7% (95% CI, 73.0 to 97.4)) which was in turn lower than the estimate for those without any risk factors (VE 95.1% (95% CI, 89.6 to 97.7)). However, the confidence intervals were very wide and overlapping and so caution is required in their interpretation. Among participants aged between 18 and 64 there did not appear to be any reduction in protection against symptomatic infection for those at risk compared with those not at risk (VE 94.4% (95% CI, 76.9 to 98.7) vs. VE 95.9% (95% CI, 90.0 to 98.3)). The trial was not powered to estimate vaccine efficacy for severe disease and no conclusions regarding this outcome can be drawn.

El Sahly et al. published an updated analysis of the mRNA-1273 (Moderna) trial originally published by Baden et al.[45] with a median follow-up of 26 weeks (IQR 24 to 28) after dose two.[47] The mRNA-1273 (Moderna) overall vaccine efficacy estimates were 98.2% (95% CI 92.8 to 99.6) and 93.2% (95% CI 90.9 to 94.8) for severe and symptomatic disease, respectively. When stratified by time since the second dose was administered, there was no evidence of waning efficacy for symptomatic disease, with vaccine efficacy of 91.8% (95% CI 86.9 to 95.1) and 92.4% (95% CI 84.3 to 96.8) for the intervals ≥14 days and < two months and at ≥ four months after dose two, respectively. Overall efficacy for symptomatic disease over the total follow-up period, did not appear to differ for healthcare providers (VE 94.4%, 95% CI 90.3 to 96.8), those in older age groups (VE 91.5%, 83.2 to 95.7) or for those with a chronic lung disease (VE 87.2%, 95% CI 63.8 to 95.5). No apparent differences in VE were observed in any of the other included underlying conditions, though small sample sizes and event rates for some conditions resulted in very wide

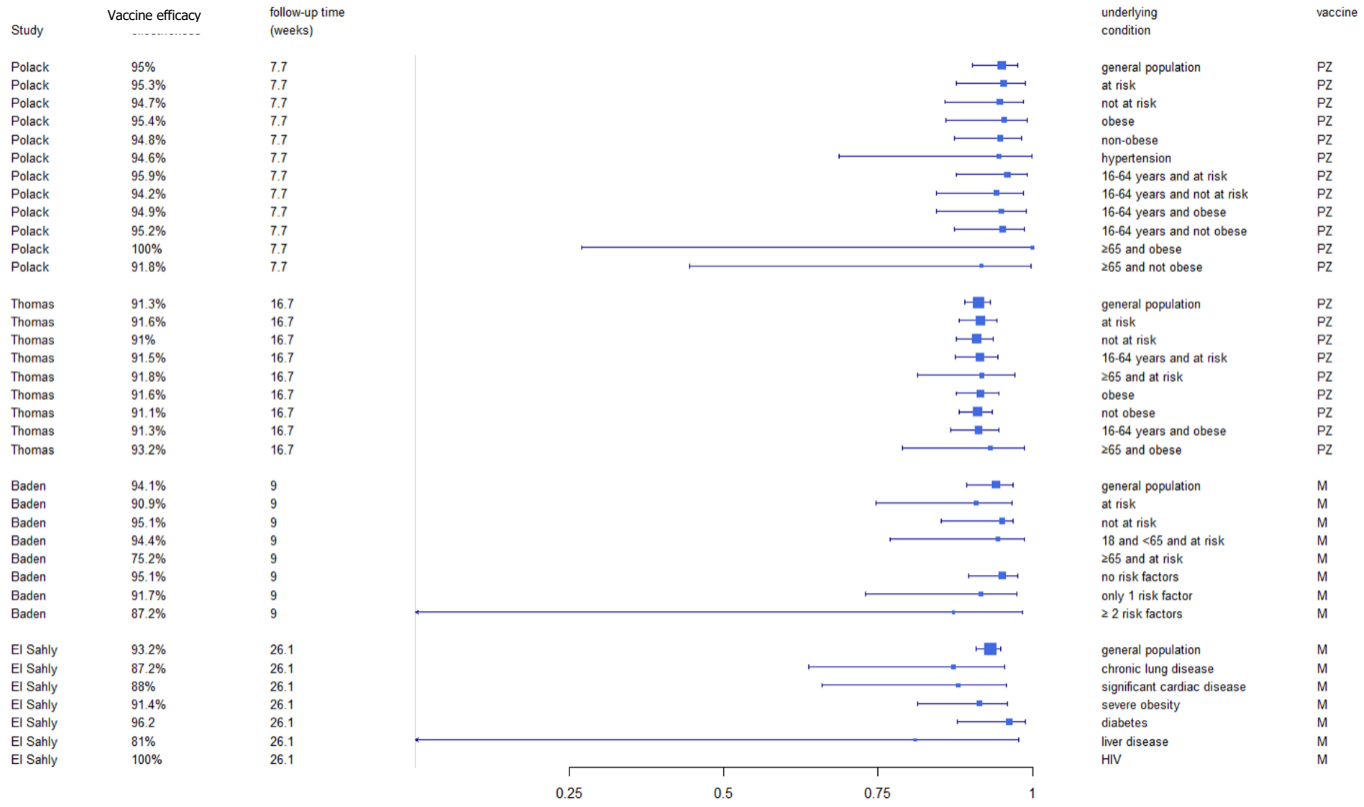
confidence intervals: significant cardiac disease (VE 88% (95% CI, 65.9 to 95.8)), severe obesity (BMI >40) (VE 91.4% (95% CI, 81.4 to 96.0)), diabetes (VE 96.2% (95% CI, 87.9 to 98.8)), liver disease (VE 81% (−64.8 to 97.8)) and HIV (VE 100% (not estimable to 100)).

Summary of vaccine efficacy in those with underlying conditions across RCTs of mRNA vaccines

The mRNA vaccine trials (BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna)), described above, examined efficacy against symptomatic SARS-CoV-2 infection for various underlying conditions and risk categories (Figure 2). In general, vaccine efficacy was high across all underlying conditions and risk categories. The BNT162b2 (Pfizer/BioNTech) report by Polack et al.[52] and the longer term follow-up by Thomas et al.[56] found broadly comparable vaccine efficacy estimates between individuals with and without underlying conditions or risk factors. However, confidence intervals in these subgroups were wide indicating substantial uncertainty. Conversely, the mRNA-1273 (Moderna) report by Baden et al.[45] found lower point estimates in those with two or more risk factors than those with either one or no risk factor. The longer term follow-up mRNA-1273 (Moderna) study by El Sahly et al.[47] found lower point estimates in those with certain conditions such as chronic lung disease, significant cardiac disease, severe obesity and HIV than that found for the general population. Importantly, for both mRNA-1273 (Moderna) reports, the confidence intervals were wide and overlapping, and so caution is required in the interpretation of these estimates.

Figure 2: Vaccine efficacy against symptomatic infection, by underlying condition/risk group, as reported in the published RCTs for BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna)

Vaccine efficacy (95% CI) against symptomatic infection as reported by Polack et al. (27 Jul 2020 – 14 Nov 2020), Thomas et al. (27 Jul 2020 – 13 Mar 2021), Baden et al. (27 Jul 2020 – 21 Nov 2020), and El Sahly et al. (27 Jul 2020 – 26 Mar 2021)



Key: M – mRNA-1273(Moderna), PZ – BNT162b2 (Pfizer/BioNTech)

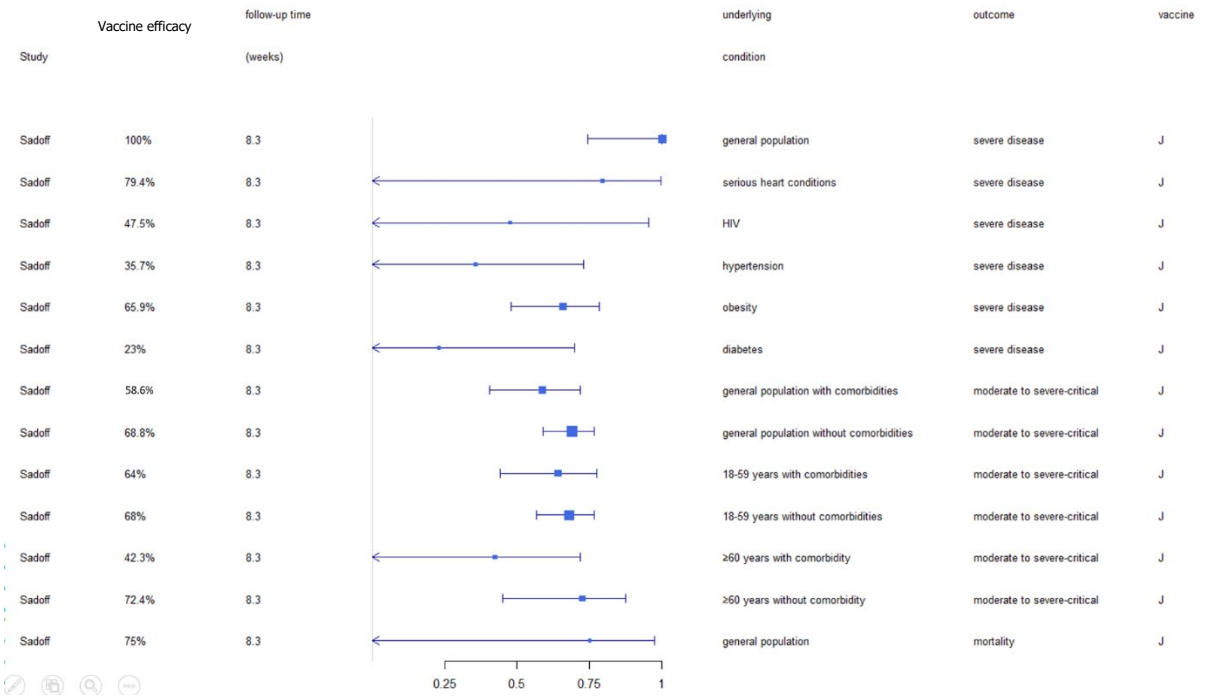
Ad26.COV2.S (Janssen)

Sadoff et al.[38] report on a phase three, multicentre double blind, RCT of the Janssen (Ad26.COV2.S) vaccine versus placebo in patients aged 18 years or older with no known history of SARS-CoV-2 (n=39,321 per protocol).[38] The trial was conducted in two stages. Stage A enrolled patients in good health. Stage B was initiated later and included patients with co-morbidities. The median time since vaccination was 8.3 weeks. Outcomes reported here represent those more than 28 days post vaccination. The trial was not powered to estimate vaccine efficacy for mortality and no conclusions regarding this outcome can be drawn. For the total population: vaccine efficacy for severe disease (COVID-19 related hospitalisation)

and for symptomatic infection was estimated at 100% (95% CI 74.3 to 100) and 66.5% (95% CI 55.5 to 75.1), respectively. There was also some evidence to suggest efficacy against the Beta variant. Despite the high prevalence of the Beta variant in South Africa (94.5% of sequenced cases), efficacy was 64.0% (95% CI 41.2 to 78.7) against moderate to severe–critical disease and 81.7% (95% CI 46.2 to 95.4) against severe–critical disease with onset at ≥28 days post vaccination. Vaccine efficacy for the first occurrence of moderate to severe/critical COVID-19 with onset at least 28 days after vaccination was estimated for an extensive range of conditions (Figure 3). Vaccine efficacy was lower for individuals with comorbid conditions than for those without such conditions (VE 58.6% (95% CI 40.6 to 71.6) vs. VE 68.8% (CI 59.0 to 76.6)), with greater disparity seen in those aged 60 years and older (VE 42.3% (95% CI, -13.1 to 71.6) vs. VE 72.4% (95% CI, 45.0 to 87.3)) compared to those aged 18 to 59 years (VE 64% (95%CI, 44.3 to 77.3) vs VE 68% (95% CI, 56.8 to 76.6) for those with and without a comorbidity, respectively). However, the confidence intervals are wide, and the uncertainty in the point estimate is large, thus limited conclusions can be drawn. Vaccine efficacy estimates for each individual comorbidity were as follows: serious heart conditions (VE 79.4% (95% CI, -83.7 to 99.6), HIV (VE 47.5% (95% CI -266 to 95.3), hypertension (VE 35.7% (-45.6 to 72.8), obesity (VE 65.9% (47.8 to 78.3), type 2 diabetes mellitus (VE 23.0% (-90.1 to 69.8). Given the limited number of events, vaccine efficacy was not estimable specifically for those with asthma, cancer, chronic kidney disease, COPD, immunocompromised from blood transplants, liver disease or those with neurological conditions.

Figure 3: Vaccine efficacy against moderate/severe/critical disease or mortality, by underlying condition, as reported in the published RCT of Ad26.COV2 (Janssen)

Vaccine efficacy (95% CI) against severe disease or mortality as reported by Sadoff et al. (21 Sep 2020 – 5 Feb 2021)



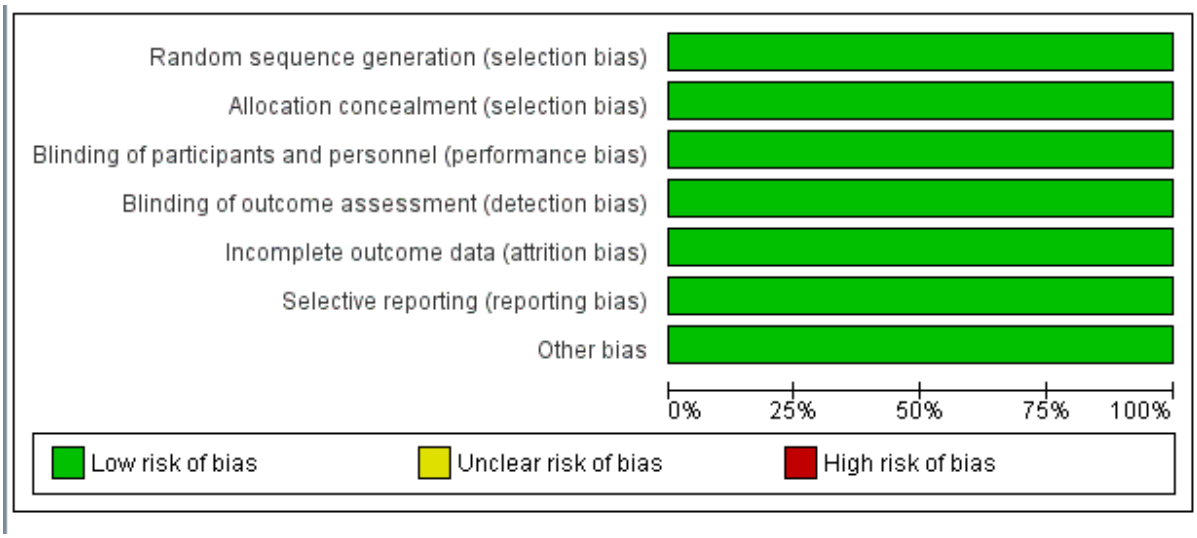
Key: J – Ad26.COV2.S (Janssen)

Sadoff et al.[38] also analysed efficacy over time. The authors report no evidence of waning efficacy among the approximately 30,000 participants who were followed for 11 weeks or among 1,000 participants who were followed for 15 weeks for the moderate to severe-critical COVID-19 endpoint (VE 66.1 (95% CI 55.0 to 74.8)). However, there were little data to inform the analysis after eight weeks and confidence intervals beyond this time are very wide.[38] The onset of efficacy was evident as of 14 days after administration for moderate to severe–critical disease and as of seven days after administration for severe–critical disease. Efficacy continued to increase through approximately eight weeks after administration, especially for severe–critical COVID-19. Vaccine efficacy against moderate to severe–critical cases in participants greater than 60 years of age, with and without comorbidities, had limited follow-up beyond 56 days, and is reflected in CIs around estimated vaccine efficacy beyond that time point.[38]

Risk of bias of randomised controlled trials

The risk of bias assessment of the RCTs included in this evidence summary is presented in Figure 4. Collectively, the three studies were considered at low risk of bias across all the domains examined.[38, 45, 47, 52, 56]

Figure 4: Risk of bias summary across RCTs



Vaccine effectiveness

Characteristics of included studies

Of the 11 observational studies included, six were cohort studies,[35, 46, 48, 50, 53, 54] and five were case-control studies,[41, 44, 49, 51, 55] of which three were a test-negative case-control design (Appendix C).[41, 44, 51] Seven studies examined vaccine effectiveness in the general population,[35, 41, 44, 48, 50, 53, 54] two studies exclusively enrolled healthcare and other frontline workers,[51, 55] and two studies were conducted exclusively in populations with underlying conditions.[46, 59] All 11 studies presented information on individuals with underlying conditions either as subgroups of a larger population,[35, 38, 41, 44, 45, 47, 48, 50-56] or as the sole focus of the study.[46, 49]

Table 4. Summary of primary outcomes (vaccine effectiveness against COVID-19 related severe disease and mortality) and secondary outcomes (vaccine effectiveness against any or symptomatic SAR-CoV-2 infection) for included studies

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
Andrews [44], England Test-negative case-control design	BNT162b2 (Pfizer/ BioNTech)	**N:** 4,774,735 individuals - Of these, AstraZeneca: 38.7% Pfizer: 31.7% Moderna: 2.4%	NR	Delta hospitalisation (VE): Week 1: 99.7 (97.6 to 100) 2-9 weeks: 98.4 (97.9 to 98.8) 10-14 weeks: 96.5 (95.9 to 97.1) 15-19 weeks: 94.4 (93.4 to 95.2) 20+ weeks: 92.7 (90.3 to 94.6) Subgroups: 1. 65+years clinically extremely vulnerable (CEV) Week1: 100 (0 case, 139 con) 2-9 weeks: 94.6 (80.6 to 98.5) 10-14 weeks: 91.7 (84.1 to 95.7)	Delta mortality 2-9 weeks: 98.2 (95.9 to 99.2) 10 to 14 weeks: 95.2 (93.0 to 96.7) 15 to 19 weeks: 93.9 (91.1 to 95.8) 20+ weeks: 90.4 (85.1 to 93.8)	NR	Delta symptomatic infection (VE) Week 1: 92.4 (92.1 to 92.7) 2 to 9 weeks: 89.8 (89.6 to 90.0) 10 to 14 weeks: 80.3 (79.9 to 80.6) 15 to 19 weeks: 73.4 (72.9 to 73.9) 20+ weeks: 69.7 (68.7 to 70.5)	Good

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
				15-19 weeks: 83.4 (70.6 to 90.7) 20+ weeks: 71.4 (40.9 to 86.1) 2. 40-64 years CEV/ clinical risk Week 1: 100 (0 case, 992 con) 2-9 weeks: 98.1 (97 to 98.8) 10-14 weeks: 96.8 (95.6 to 97.8) 15-19 weeks: 95.4 (92.6 to 97.2)				
	ChAdOx1 (AstraZeneca)			Delta hospitalisation (VE): Week 1 93.9 (91.3 to 95.7) 2 to 9 weeks 95.2 94.6 to 95.6) 10 to 14 weeks 91.4 (90.5 to 92.2) 15 to 19 weeks 86.8 (85.1 to 88.4)	Delta mortality 2 to 9 weeks 94.1 (91.8 to 95.8) 10 to 14 weeks 92.4 (89.7 to 94.4) 15 to 19 weeks 89.1 (84.2 to 92.5) 20+ weeks 78.7 (52.7 to 90.4)		Delta symptomatic infection Week 1 62.7 (61.7 to 63.8) 2 to 9 weeks 66.7 (66.3 to 67.0) 10 to 14 weeks 59.3 (58.8 to 59.9) 15 to 19 weeks 52.6 (51.7 to 53.5) 20+ weeks 47.3 (45.0 to 49.6)	

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
				20+ weeks 77.0 (70.3 to 82.3) Subgroups: 1. 65+years CEV Week1: N too small 2-9 weeks: 79.3 (59.2 to 89.5) 10-14 weeks: 78.6 (63.1 to 87.6) 15-19 weeks: 75.1 (56.3 to 85.8) 20+ weeks: 59.4 (14.1 to 80.8) 2. 40-64 years CEV/ clinical risk Week1: 94.3 (86.1 to 97.7) 2-9 weeks: 93.7 (92.3 to 94.8) 10-14 weeks: 90.2 (88.2 to 91.9) 15-19 weeks:				

Author, Country Study Design	Exposure[#]	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
				86.6 (82.2 to 89.9) 20+ weeks: 69.7 (29.7 to 86.9)				
	mRNA-1273 (Moderna)			Delta hospitalisation: Week 1 97.5 (82.3 to 99.7) 2-9 weeks 100 (0 cases, 6,363 controls)	NR	NR	Delta symptomatic infection Week 1 95.2 (94.4 to 95.9) 2-9 weeks 94.5 (94.1 to 95.0) 10-14 weeks 90.3 (67.2 to 97.1)	
Chemaitelly,[(46)] Preprint Qatar Retrospective cohort study with crossover	BNT162b2 (Pfizer/ BioNTech): 93% mRNA-1273 (Moderna): 7%	**N:** 782	Mean 10.5 weeks (max = 24 weeks)	≥14 days VE: 72.3 (0.0 to 90.9). ≥42 days VE: 85.0 (35.7 to 96.5) ≥56 days: VE: 83.8 (31.3 to 96.2)	NR	VE: ≥14 days 46.6 (0.0 to 73.7) 42 days 66.0 (21.3 to 85.3) ≥56 days 73.9 (33.0 to 89.9)	NR	Fair
Liu,[(48)] **Pre-print** **US** **Retrospective cohort study with crossover**	**Exposure**: BNT162b2 (67.5%), mRNA-1273 (32.5%) **Comparator:** No vaccination	**N:** Vax positive 198 Vax negative 14,164 Pre-vax positive (Positive PCR test before vaccination period) 6,462	Mean: 14.4 weeks	NR	NR	Comparing Vax cohort to a matched Pre-Vax cohort before 11 Dec 2020 N (pre-vax/vax) 14,362/14,362 OR 0.115 (0.099-0.134) aOR 0.116 (0.0998-0.135) VE 88.4% (86.5 to 90)	NR	Fair

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
		Pre-vax negative (negative PCR test and without any evidence of SARS-CoV-2 before the vaccination period) 55,580 Un-Vax positive (positive PCR test after entry date and before administration of first vaccine dose, with no evidence of SARS-CoV-2 infection before entry date) 3,902 Un-vax negative (negative PCVR test after entry date and before administration of first vaccine dose, with no evidence if SARS-CoV-2 infection before entry date) 33,850				Comparing Vax cohort to a matched Pre-Vax cohort after 18 Jan 2021 N (pre-vax/vax) 14,362/14,362 IRR 0.42 (0.36-0.49) aIRR 0.41 (0.35 -0.48) <u>Subgroups:</u> Comparing Vax cohort to a matched pre-vax cohort before 11 Dec 2020. Immunocompromised: Prevalence (pre-vax/vax) 642/90 OR 0.127 (0.101-0.159) aOR 0.129 (0.103-0.162) VE 87.1% (83.8 to 89.7) Not immunocompromised: Prevalence (pre-vax/vax) 914/108 OR 0.107 (0.087-0.131) aOR 0.106 (0.086-0.129) VE 89.4% (87.1 to 91.4) Comparing Vax cohort to a matched un-vax cohort after 18 Jan 2021. Immunocompromised:		

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
		Subgroups: Is immune compromised: Pre-vax 5,287 Vax 5,223 Not immune compromised: Pre-vax 9,075 Vax 9,139				Incident rate/1,000 person-days (un-vax/vax) 0.41/0.19 aIRR 1.49 (1.1-2). Incident Rate Ratio (95%CI) 0.47 (0.37-0.59) aIRR 0.43 (0.34-0.55) Not immunocompromised: Incident rate/1000 person-days (un-vax/vax) 0.36/0.14 Incident Rate Ratio (95% CI) 0.38 (0.31-0.47) aIRR 0.38 (0.31-0.46) Risk factors associated with breakthrough case rate compared to not immunocompromised group: Immunocompromised: aIRR 1.48 (1.09-2) Active tumour: aIRR 1.56 (1.1-2.2) CKD: aIRR 1.33 (9.86-2.06) HIV:		

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
						aIRR 1.25 (0.63-2.47) On immunosuppressant therapy: aIRR 1.45 (1.03-2.04) Primary immunodeficiency: aIRR 2.53 (1.4-4.58) Organ transplant: aIRR 1.99 (0.98-3.71)		
McKeigue,[49] **Preprint** **Scotland** **Case-control**	Vaccination with AstraZeneca or mRNA vaccine (Pfizer or Moderna).	N:* 223,742 (53,264 fully vaccinated)	There is at least a median of 9.57 weeks. [IQR = 6 – 12.7 weeks. Max 26 weeks], with an additional 2.3 weeks follow up in the updated report	Severe Disease** No risk condition RR# 0.06 (0.04 to 0.07) VE 94% (93% to 96%) Moderate risk condition RR 0.11 (0.09 to 0.14) VE= 89% (86% to 91%) Condition eligible for shielding RR 0.27 (0.21 to 0.36) VE = 73% (64% to 79%)	Hospitalisation or mortality*** No risk condition RR# 0.14 (0.12 to 0.15) VE = 86% (85 to 88) Moderate risk condition RR 0.17 (0.15 to 0.18) VE = 83% (82 to 85) Condition eligible for shielding RR 0.32 (0.29 to 0.37) VE = 68% (63% to 71%)	NR	NR	Good
	ChAdOx1 (AstraZeneca)			*RR for severe disease:* No risk condition RR# 0.07 (0.05, 0.09)	*RR for hospitalisation or mortality*: No risk condition RR# 0.19 (0.17 to 0.2))			

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
				Moderate risk condition RR 0.13 (0.10, 0.17) Condition eligible for shielding RR 0.28 (0.21, 0.37) VE = (72% (63% to 79%))	Moderate risk condition RR 0.22 (0.2 to 0.25) Condition eligible for shielding RR 0.38 (0.33, 0.43)			
	BNT162b2 (Pfizer/ BioNTech) Or mRNA-1273 (Moderna)			RR for severe disease: No risk condition RR# 0.04 (0.03, 0.06) Moderate risk condition RR 0.07 (0.05, 0.09) Condition eligible for shielding RR 0.27 (0.17, 0.371) VE= 73% (59% to 83%)).	RR for hospitalisation or mortality: No risk condition RR# 0.08 (0.07, 0.09) Moderate risk condition RR 0.09 (0.08, 0.11) Condition eligible for shielding RR 0.23 (0.19, 0.29)			
	Vaccination with AstraZeneca or mRNA vaccine (Pfizer or Moderna) and underlying condition (Solid organ transplant)			RR for severe disease 0.6 (0.24 to 1.51) + *VE 40% (-51% to 76%)*	RR for hospitalisation or mortality 0.6 (0.38 to 0.95) ~ VE 40% (0.05 to 0.62)			
Nordstrom[50] Pre-print	:	N:	Symptomatic Infection	>14 days after second/final dose		NR	Overall population 15-30 days	Fair

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
Sweden Retrospective Cohort Study	ChAdOx1 (AstraZeneca) mRNA-1273 (Moderna) BNT162b2 (Pfizer/BioNTech) **Comparator /Control:** Unvaccinated	Vaccinated – 842,974 Unvaccinated – 842,974 ChAdOx1 – 76,597 mRNA-1273 – 76,880 BNT162b2 – 637,107 BNT162b2/mRNA – 51,766 Co-morbidities/Special Populations: N (%) *Myocardial infarction* Vaccinated - 21,885 (2.6) Unvaccinated – 18,350 (2.2) *Stroke* Vaccinated – 29,493 (3.5) Unvaccinated – 16,808 (2.0)	Mean 16.6 weeks) (Range: 2.1 to 40) Hospitalisations and mortality Mean =16.1 weeks (Range 2.1 to 39.1 weeks))	Overall population Hospitalisation or death Vaccinated (277) vs unvaccinated (825) Day 15 to 30 VE = 89% (83 to 93, P<0.001) Day 121 to 180 VE = 74% (47 to 87, P<0.001) Day 180+ VE = 42%; (-35 to 75, P=0.21) Second matched cohort: Underlying conditions Hospitalisation or death Day 15-30 VE 89 (85-92) Day 31-60 VE 88 (85-90) Day 61-120 VE 88 (86-90) Day 121-180 VE 88 (82-92) Day >180 VE 62 (34-78)			VE = 92 (91 to 93) 31-60 days VE = 89 (88 to 89) 61 -120 days VE = 82 (81 to 83) 121-180 days VE = 48 (41 to 54) 181 – 210 days VE = 32 (19 to 44) >210 days VE = 23 (-2 to 41) Underlying conditions over time *Day 15-30* VE = 86 (84 to 89) Day 31-60 VE = 85 (83 to 86) Day 61-120 VE = 79 (77 to 80) Day 121-180 VE = 55 (42 to 65) Day >180 VE = 15 (-17 to 38) Second matched cohort: Underlying conditions over time Day 15-30	

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
		Diabetes Vaccinated – 91,203 (10.6) Unvaccinated – 62,198 (7.4) *Hypertension* Vaccinated – 262,659 (31.2) Unvaccinated - 207,862 (24.7) *Kidney failure* Vaccinated – 20,027 (2.4) Unvaccinated – 10,317 (1.2) *COPD* Vaccinated – 17,257 (2.0) Unvaccinated – 13,353 (1.6) *Asthma* Vaccinated – 50,341 (6.0) Unvaccinated – 36,671 (4.4)					VE = 86 (84 to 87) <u>Day 31-60</u> VE = 80 (80 to 83) <u>Day 61-120</u> VE = 74 (72 to 75) Day 121-180 VE = 60 (54 to 66) Day 180-210 VE = 41 (24 to 55) Day >210 VE = 1 (-147 to 33)	

Author, Country Study Design	Exposure[#]	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
		Cancer Vaccinated – 48,512 (5.8) Unvaccinated – 37,092 (4.4) Included a second matched cohort (less strict matching criteria) N Vaccinated – 1,983,315 Unvaccinated - 1,983,315						
Pilishvili, [51] **Peer-reviewed** **US** **Test negative case-control**	BNT162b2 (Pfizer/ BioNTech) (Cases: 78%, Controls 79%) mRNA-1273 (Moderna) (Cases: 21%, Controls 20%)	N: Cases – 1,482 Controls – 3,449	Median – 5.98 weeks (range 1 to 23.5 weeks)	Hospitalisation in cases Completely vaccinated: 4 (2%) Partially vaccinated: 1 (1%) Unvaccinated: 21 (3%)	NR	NR	Any COVID vaccine VE: 90.4 (87.0 to 92.9) BNT162b2 VE: 88.8 (84.6 to 91.8) mRNA-1273 VE: 96.3 (91.2 to 98.4) Subgroups: <50 years	Good

Author, Country Study Design	Exposure[#]	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
							VE: 90.3% (86.5% to 93.0%) <u>≥50 years</u> VE: 90.7% (84.2% to 94.6%) <u>Asthma</u> VE: 90.5% (81.9% to 95.0%) <u>Obesity</u> VE: 92.1% (87.6% to 95.0%) <u>Obesity or overweight</u> VE: 91.0% (87.0% to 93.7%) <u>Hypertension</u> VE: 91.8% (83.9% to 95.8%) <u>Diabetes</u> VE: 80.2% (45.8% to 92.7%) <u>Pregnancy (assessed for partial and complete vaccination)[€]</u> VE: 77.1% (32.2% to 92.2%)	

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
							Any immunocompromising condition, (assessed for partial and complete vaccination) VE: 39.1% (−45.0% to 74.4%)	
Polinski, [35] **Preprint** **US** **Matched cohort study with crossover**	Ad26.COV2.S (Janssen)	**N:** 390,517 vaccinated 1,524,153 matched with no record of vaccination	Mean 15.4 weeks Maximum 152 days = 21.7 weeks	VE: 73 (69 to 76) Subgroup: Immunocompromised VE = 54% (35 to 67)	NR	VE: 69 (67 to 71) Subgroup: Immunocompromised VE = 52% (42% to 60%)	NR	Poor
Pouwels,[53] Peer-reviewed UK National longitudinal survey from UK National statistics agency.	BNT162b2 (Pfizer/ BioNTech)	**N**: 743,526 individuals 384,543 (alpha dominant phase) 358,983 (delta dominant phase)	Median (IQR) weeks 8.43 (5 to 12.29)	NR	NR	Overall population BNT162b2 Alpha: 78% (68 to 84) Delta: 80% (77 to 83) ChAdOx1 Alpha: 79% (56 to 90%) Delta: 67% (62 to 71%) Long term health condition BNT162b2 (Delta): 81% (69-89%) ChAdOx1 (Delta): 58% (39 to 71%)	Overall population BNT162b2 Alpha: VE: 97 (96 to 98) Delta: VE: 84 (82 to 86) ChAdOx1 Alpha: 97 (93 to 98) Delta: 71% (66 to 74) Long term health condition BNT162b2 (Delta) VE: 92 (84 to 96) ChAdOx1 (Delta) VE: 64% (44 to 77)	Good

Author, Country Study Design	Exposure[#]	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
Saciuk,[54] preprint preprint Israel Retrospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech)	**N:** 1,650,885	Median: 10.1 weeks 14 weeks (maximum)	VE: 93.4 (91.9 to 94.7) Subgroups: Crude VE - Hypertension: 95. 3 (93.5, 96.7) - Diabetes: 95.1 (93.7, 96.2) - Obesity: 97.6 (96.2, 98.4)	VE: 91.1 (87 to 94) Subgroups: Crude VE against Mortality - Hypertension: 91.7 (85.9, 95.1) - Diabetes: 91.7 (87.1, 94.6) - Obesity: 83.3 (14.1, 96.8*)*	VE: 93% (92.6 to 93.4) Subgroup: Crude VE against any COVID-19 Infection Hypertension: 94 (93.2, 94.7) Diabetes: 94.5 (93.9, 95.0) Obesity: 96.5 (96.2, 96.9) Adjusted VE against any COVID-19 infection: Hypertension: 89.7 (88.6,91.7) Diabetes: 88.9 (87.3-90.2) Obesity: 89.7 (88.6-90.7)	NR	Fair
Tenforde,[55] Published report (CDC) US Case-control	BNT162b2 (Pfizer/ BioNTech) 59% MRNA-1273 (Moderna) 41%	**N:** Cases: 1,194 Controls: 1,895 Immunocompromising condition: Cases 205 (21% of the overall study population) Controls 447	Median 9.3 weeks, (IQR 5.84 to 13.25 weeks)	VE: 86 (82 to 88) Subgroups: Hospitalisation: Those with immunocompromising condition: 63 (44 to 76) Those without immunocompromising conditions: 90 (87% to 92%) VE for immunocompromised patients at: - 2-12 weeks = 64.3 (48.5-79.6)	NR	NR	NR	Fair

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
				-13-24 weeks = 53.6 (12.8 to 77.8)				
Thompson[41] **Peer-reviewed US** **Test negative case-control study**	BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.Cov2.S (Janssen)	Hospitalisations: BNT162b2 (Pfizer/BioNtech) 8,500 mRNA-1273 (Moderna) 6,374 Ad26.COV2.S (Janssen) 707 Unvaccinated 20,406 Subgroups: Hospitalisation: ≥50 years of age with ≥ 1 chronic respiratory condition Fully vaccinated 10,257	Hospitalisation – Median - 53 IQR (33 to 75) 7.6 weeks (4.7-10.7) ICU admission – Median 7.4 weeks (4.9-10.4) ED/ Urgent Care – Median 7.1 weeks (4.4-10.4)	Hospitalisation: BNT162b2 vaccine 87 (85 to 90) mRNA1273 vaccine 91 (89 to 93) Ad26.COV2.S vaccine 68 (50 to 79) ICU admissions: <u>BNT162b2 or mRNA1273 vaccine</u> 90 (86 to 93) ED or urgent care visit: <u>BNT162b2 vaccine</u> 89 (85 to 91) <u>mRNA1273 vaccine</u> 92 (89 to 94) <u>Ad26.COV2.S vaccine</u>	NR	Infection leading to emergency department or urgent care clinic visit: <u>≥50 years of age with ≥ 1 chronic respiratory condition</u> 90 (86 to 93) <u>≥50 years of age with ≥ 1 chronic non-respiratory condition</u> 90 (87 to 92)	NR	Good

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
		Unvaccinated 13,018 ≥50 years of age with ≥ 1 chronic non-respiratory condition Fully vaccinated 13,999 Unvaccinated 18,089 ED or urgent care clinic visit: ≥50 years of age with ≥ 1 chronic respiratory condition Fully vaccinated 2,206 Unvaccinated 3,832 ≥50 years of age with ≥ 1 chronic non-respiratory condition Fully vaccinated		73 (59 to 82) <u>Hospitalisation</u> <u>≥50 years of age with ≥ 1 chronic respiratory condition</u> 90 (88-92) <u>≥50 years of age with ≥ 1 chronic non-respiratory condition</u> 88 (86-90)				

Author, Country Study Design	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up VE % (95% CI)		Secondary Outcomes: overall follow-up VE % (95% CI)		Quality appraisal
				Severe Disease	Mortality	Any infection	Symptomatic infection	
		3,947 Unvaccinated 6,483						

All effectiveness results are ≥ 7 days or ≥ 14 days (except where stated) after the final dose depending on when the individual was defined as being fully vaccinated.

Key: CDC - Centers for Disease Control and Prevention, CEV – Clinically Extremely Vulnerable, CI – confidence interval, ED – Emergency Department, HCW – healthcare worker, IQR - inter-quartile range, LTC – long-term care, sd – standard deviation, NR - not reported, US – United States, Vax – vaccinated, VE – vaccine effectiveness

Table 5 Summary of change in vaccine effectiveness over time for included studies

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
Andrews, [44] **Preprint England Test-negative case-control design**	BNT162b2 (Pfizer/BioNTech)	**N:** 4,774,735 individuals - Of these, AstraZeneca: 38.7% Pfizer: 31.7% Moderna: 2.4%	Up to 20+ weeks	Overall population VE against **mortality** by weeks after second dose (Delta) 2-9 weeks: 98.2% (95.9 to 99.2) 10 to 14 weeks: 95.2% (93.0 to 96.7) 15 to 19 weeks: 93.9% (91.1 to 95.8) 20+ weeks: 90.4% (85.1 to 93.8) VE against **hospitalisation** by weeks after second dose (Delta): 2-9 weeks: 98.4% (97.9 to 98.8) 10-14 weeks: 96.5% (95.9 to 97.1) 15-19 weeks: 94.4% (93.4 to 95.2) 20+ weeks: 92.7% (90.3 to 94.6) VE against **symptomatic infection** by weeks after second dose (Delta) week 1: 92.4 (92.1 to 92.7) 2 to 9 weeks: 89.8 (89.6 to 90.0) 10 to 14 weeks: 80.3 (79.9 to 80.6) 15 to 19 weeks: 73.4 (72.9 to 73.9) 20+ weeks: 69.7 (68.7 to 70.5) Subgroups: VE against **hospitalisation** by weeks after second dose (Delta): Age 65+ years and clinically extremely vulnerable (CEV) 1 week: 100% (0 to 139) 2-9 weeks: 94.6% (80.6 to 98.5) 10-14 weeks: 91.7% (84.1 to 95.7) 15-19 weeks: 83.4% (70.6 to 90.7) 20+ weeks: 71.4% (40.9 to 86.1) Age 65+ years and Not CEV

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
				1 week: 100 (0 case, 769 con) 2-9 weeks: 98.3 (96.2 to 99.3) 10-14 weeks: 96.2 (94.7 to 97.3) 15-19 weeks: 94.6 (92.7 to 96.1) 20+ weeks: 94.6 (90.5 to 97.0) Age 40-64 years and in clinical risk/CEV group 1 week: 100% (0 to 992) 2-9 weeks: 98.1% (97 to 98.8) 10-14 weeks: 96.8% (95.6 to 97.8) 15-19 weeks: 95.5% (92.6 to 97.2) Age 40-64 years and Not in clinical risk/CEV group 1 week: 100 (0 case, 1695 con) 2-9 weeks: 98.7 (97.1 to 99.4) 10-14 weeks: 98.4 (96.4 to 99.3) 15-19 weeks: 97.6 (92.6 to 99.2)
	ChAdOx1 (AstraZeneca)		Up to 20+ weeks	Overall population VE against **mortality** by weeks after second dose (Delta) 2 to 9 weeks: 94.1 (95% CI 91.8 to 95.8) 10 to 14 weeks: 92.4 (95% CI 89.7 to 94.4) 15 to 19 weeks: 89.1 (95% CI 84.2 to 92.5) 20+ weeks: 78.7 (95% CI 52.7 to 90.4) VE against **hospitalisation** by weeks after second dose (Delta): week 1: 93.9 (91.3 to 95.7) 2 to 9 weeks: 95.2 (94.6 to 95.6) 10 to 14 weeks: 91.4 (90.5 to 92.2) 15 to 19 weeks: 86.8 (85.1 to 88.4) 20+ weeks: 77.0 (70.3 to 82.3) VE against **symptomatic infection** by weeks after second dose (Delta) Week 1: 62.7 (61.7 to 63.8)

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
				2 to 9 weeks: 66.7 (66.3 to 67.0) 10 to 14 weeks: 59.3 (58.8 to 59.9) 15 to 19 weeks: 52.6 (51.7 to 53.5) 20+ weeks: 47.3 (45.0 to 49.6) Subgroups: VE against **hospitalisation** by weeks after second dose (Delta): Age 65+ years and CEV 1 week: N to small 2-9 weeks: 79.3% (59.2 to 89.5) 10-14 weeks: 78.6% (63.1 to 87.6) 15-19 weeks: 75.1% (56.3 to 85.8) 20+ weeks: 59.4% (14.1 to 80.8) Age 65+ years and not in clinical risk/CEV group 1 week: 92.5 (43.4 to 99.0) 2-9 weeks: 93.7 (91.0 to 95.6) 10-14 weeks: 91.7 (89.3 to 93.6) 15-19 weeks: 86.5 (82.5 to 89.7) 20+ weeks: 78.4 (65.7 to 86.4) 40-64 years and in clinical risk/CEV group Week1: 94.3 (86.1 to 97.7) 2-9weeks: 93.7 (92.3 to 94.8) 10-14weeks: 90.2 (88.2 to 91.9) 15-19weeks: 86.6 (82.2 to 89.9) 20+ weeks: 69.7 (29.7 to 86.9) 40-64 years and not in clinical risk/CEV group 1 week: 95.3 (92.5 to 97.0) 2-9 weeks: 97.4 (96.9 to 97.8) 10-14 weeks: 94.5 (93.1 to 95.6) 15-19 weeks: 93.0 (87.5 to 96.1)

<table>
<tr><th>Author, Country Study Design</th><th>Exposure#</th><th>Sample Size</th><th>Time since final Vaccination</th><th>Change in vaccine effectiveness over time
VE (95% CI)</th></tr>
<tr><td></td><td>mRNA-1273 (Moderna)</td><td></td><td>Up to 14 weeks</td><td>VE against hospitalisation by weeks after second dose (Delta):
Overall population

Week 1: 97.5 (82.3 to 99.7)
2-9week: 100.0 (0 cases, 6363 con)
10- 14 weeks: NR

VE against symptomatic infection by weeks after second dose (Delta)
Week 1: 95.2 (94.4 to 95.9)
2-9 weeks: 94.5 (94.1 to 95.0)
10-14 weeks: 90.3 (67.2 to 97.1)</td></tr>
<tr><td>Chemaitelly, [46] preprint Qatar, Retrospective cohort study with crossover</td><td>BNT162b2 (Pfizer/BioNTech): 93%
MRNA-1273 (Moderna): 7%</td><td>N: 782</td><td>Mean 10.5 weeks (max = 24 weeks)</td><td>Kidney transplant recipients

VE against any severe critical or fatal disease:
Days after the second dose:

≥14 days VE 72.3% (95% CI: 0.0 to 90.9%).

≥42 days VE 85.0% (95% CI: 35.7 to 96.5%)

≥56 days:
VE 83.8% (95% CI: 31.3 to 96.2%)</td></tr>
<tr><td>Liu,[48] preprint US, Retrospective cohort study (with matching for some analyses)</td><td>BNT162b2 (67.5%), mRNA-1273 (32.5%)</td><td>6 cohorts (some individuals are in multiple cohorts at different times)
1). “Vax positive” (N = 198)
2). “Vax negative” (N = 14,164)</td><td>Mean: 14.4 weeks</td><td>Change of Incidence rate from time to fully vaccination:
<table><tr><td></td><td></td><td colspan="3">Pfizer/BNT162b2</td></tr><tr><td></td><td></td><td colspan="3">Moderna/mRNA-1273</td></tr><tr><td>Time since fully vaccinated</td><td>Total person-days at risk£</td><td>Incidence</td><td>Incident rate / 1,000 person-days</td><td>Incidence</td><td>Incident rate / 1000 person-days</td></tr><tr><td>210-240 days</td><td>443</td><td>1</td><td>2.257</td><td></td><td></td></tr><tr><td>180-210 days
210-240 days</td><td>3,074</td><td>5</td><td>1.952</td><td>5</td><td>0.902</td></tr></table></td></tr>
</table>

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
with crossover		3). "Pre-Vax positive" (N = 6,462) 4). "Pre-Vax negative" (N = 55,580) 5). "Un-Vax positive" (N = 3,902) 6). "Un-Vax negative" (N = 33,850)		180-210 days: 16,811 / 24 / 1.428 150-180 days: 34,847 / 16 / 0.459 120-150 days: 66,486 / 27 / 0.406 90-120 days: 105,697 / 15 / 0.142 60-90 days: 150,864 / 16 / 0.106 30-60 days: 203,392 / 26 / 0.128 0-30 days: 259,596 / 26 / 0.100 [£] Incidence rate / 1,000 person-days were calculated for each time interval relative to the fully vaccinated date 150-180 days: 16,525 / 6 / 0.363 120-150 days: 32,243 / 7 / 0.217 90-120 days: 52,162 / 5 / 0.096 60-90 days: 74,806 / 5 / 0.067 30-60 days: 100,706 / 5 / 0.050 0-30 days: 126,977 / 8 / 0.063
Nordstrom[50]	**Intervention/Exposure**: ChAdOx1 (AstraZeneca) mRNA-1273 (Moderna)	N: Vaccinated – 842,974 Unvaccinated – 842,974	**Time since final vaccination dose:** Symptomatic Infection	**VE against hospitalisation or death** Overall population: primary analysis (any vaccine) Day 15 to 30 VE = 89% (VE = 83 to 93, P<0·001) Day 121 to 180 VE = 74% (47 to 87, P<0·001

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
	BNT162b2 (Pfizer/BioNTech) **Comparator/Control:** Unvaccinated	ChAdOx1 – 76,597 mRNA-1273 – 76,880 BNT162b2 – 637,107 BNT162b2/mRNA – 51,766 Co-morbidities/Special Populations: N (%) *Myocardial infarction* Vaccinated - 21,885 (2.6) Unvaccinated – 18,350 (2.2) *Stroke* Vaccinated – 29,493 (3.5) Unvaccinated – 16,808 (2.0) *Diabetes* Vaccinated – 91,203 (10.6) Unvaccinated – 62,198 (7.4)	Mean 16.6 weeks) (Range: 2.1 to 40) <u>Hospitalisations and mortality</u> Mean =16.1 weeks (Range 2.1 to 39.1 weeks)	Day 180+ VE = 42%; (-35-75, P=0·21) *Second matched cohort: Underlying conditions* Day 15-30 VE 86 (84-87) Day 31-60 VE 87 (85-90) Day 61-120 VE 86 (83-89) Day 121-180 VE 85 (77-90) Day >180 VE 58 (26-77) **<u>VE against symptomatic infection</u>** <u>Overall population: primary analysis (any vaccine)</u> 15-30 days VE = 92 (91-93) 31-60 days VE = 89 (88-89) 61 -120 days VE = 82 (81-83) 121-180 days VE = 48 (41-54)

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
		Hypertension Vaccinated – 262,659 (31.2) Unvaccinated - 207,862 (24.7) *Kidney failure* Vaccinated – 20,027 (2.4) Unvaccinated – 10,317 (1.2) *COPD* Vaccinated – 17,257 (2.0) Unvaccinated – 13,353 (1.6) *Asthma* Vaccinated – 50,341 (6.0) Unvaccinated – 36,671 (4.4) *Cancer* Vaccinated – 48,512 (5.8) Unvaccinated – 37,092 (4.4)		181 – 210 days VE = 32 (19-44) >210 days VE = 23 (-2-41) <u>Underlying conditions: primary analysis</u> *Day 15-30* VE = 86 (84-89) <u>Day 31-60</u> VE = 85 (83-86) <u>Day 61-120</u> VE = 79 (77-80) Day 121-180 VE = 55 (42-65) Day >180 VE = 15 (-17-38) Second matched cohort: Underlying conditions over time *Day 15-30* VE = 86 (84-87) <u>Day 31-60</u> VE = 80 (80-83) <u>Day 61-120</u> VE = 74 (72-75)

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)
		Included a second matched cohort (less strict matching criteria) Vaccinated – 1,983,315 Unvaccinated - 1,983,315		Day 121-180 VE = 60 (54-66) Day 180-210 VE = 41 (24-55) Day >210 VE = 1 (-147-33)
Pilishvili, [51] US Test negative case-control	BNT162b2 (Pfizer/BioNTech) (Cases: 78%, Controls 79%) mRNA-1273 (Moderna) (Cases: 21%, Controls 20%)	N: Cases – 1,482 Controls – 3,449	Median – 5.98 weeks (range 1 to 23.5 weeks	VE against **symptomatic infection** <u>Overall population</u> 1-2 weeks 92.73% (89.1 to 95.03) 3-4 weeks 96.55% (92.73 to 98.47) 5-6 weeks 91.77% (83.56 to 95.98) 7-8 weeks 88.71% (79.92 to 94.07) 9-10 weeks 83.74% (68.26 to 91.59) 11-12 weeks 82.79% (68.45 to 90.44) 13-14 weeks 80.88% (60.99 to 90.44)
Polinski, [35]	Ad26.COV2.S (Janssen)	**N:** 390,517 vaccinated 1,524,153 matched with no record of vaccination	Mean 15.4 weeks Maximum 152 days = 21.7 weeks	The authors concluded there was no decline in effectiveness over time based on plot of Schoenfeld residuals.

<table>
<tr><th>Author, Country Study Design</th><th>Exposure#</th><th>Sample Size</th><th>Time since final Vaccination</th><th>Change in vaccine effectiveness over time VE (95% CI)</th></tr>
<tr><td>Pouwels, [53] peer-reviewed UK National longitudinal survey from UK National statistics agency</td><td>BNT162b2 (Pfizer/BioNTech)</td><td>N: 743,526 individuals
384,543 (alpha dominant phase)
358,983 (delta dominant phase)</td><td>Median (IQR) weeks: 8.4 (5 to 12.3)</td><td>VE over Time

Overall population

<table>
<tr><th>VE 18 – 64 years</th><th>Days since second dose</th><th>BNT162b2 (Pfizer)</th><th>ChAdOx1 (Astra Zeneca)</th></tr>
<tr><td>Any infection</td><td>14</td><td>85% (79–90%)</td><td>68% (61–73%)</td></tr>
<tr><td></td><td>30</td><td>83% (78–88%)</td><td>66% (61–71%)</td></tr>
<tr><td></td><td>60</td><td>80% (76–83%)</td><td>64% (58–69%)</td></tr>
<tr><td></td><td>90</td><td>75% (70–80%)</td><td>61% (53–68%)</td></tr>
<tr><td></td><td>Relative reduction in effectiveness per month from second dose</td><td>22% decline[a] (6% decline to 41% decline)</td><td>7% decline (18% decline to 2% increase)</td></tr>
<tr><td></td><td>Test for evidence of change over time from second dose</td><td>0.007</td><td>0.15</td></tr>
<tr><td>cycle threshold (Ct) value<30</td><td>14</td><td>92% (87–95%)</td><td>69% (61–75%)</td></tr>
<tr><td></td><td>30</td><td>90% (86–93%)</td><td>67% (61–73%)</td></tr>
<tr><td></td><td>60</td><td>85% (81–89%)</td><td>65% (58–70%)</td></tr>
<tr><td></td><td>90</td><td>78% (72–82%)</td><td>61% (52–69%)</td></tr>
<tr><td></td><td>Relative reduction in effectiveness per month from second dose</td><td>52% decline[a] (26% decline to 84% decline)</td><td>9% decline (22% decline to 3% increase)</td></tr>
<tr><td></td><td>Test for evidence of change over time from second dose</td><td>< 0.0001</td><td>0.14</td></tr>
<tr><td>symptomatic infection</td><td>14</td><td>93% (89–96%)</td><td>72% (64–78%)</td></tr>
<tr><td></td><td>30</td><td>92% (87–95%)</td><td>70% (64–76%)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Author, Country Study Design</th><th>Exposure#</th><th>Sample Size</th><th>Time since final Vaccination</th><th>Change in vaccine effectiveness over time VE (95% CI)</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>60</td><td>86% (82–90%)</td><td>67% (60–72%)</td></tr>
<tr><td></td><td>90</td><td>78% (72–82%)</td><td>63% (53–71%)</td></tr>
<tr><td></td><td>Relative reduction in effectiveness per month from second dose</td><td>63% decline[a] (30% decline to 103% decline)</td><td>11% decline (26% decline to 2% increase)</td></tr>
<tr><td></td><td>Test for evidence of change over time from second dose</td><td>< 0.0001</td><td>0.10</td></tr>
</table>

Subgroup:

<u>Long term health condition (LTHC)</u>: VE estimated from interception points in Fig 2 in the report
BNT162b2 - Day 14:
Without LTHC: 86% (80-90%)
With LTHC: 81% (69-89%).
ChAdOx1 – Day 14:
Without LTHC: 69% (62-74%)
With LTHC: 58% (39-71%)

No numerical estimates are given for any later days.</td></tr>
<tr><td></td><td>ChAdOx1 (AstraZeneca)</td><td></td><td>5.86 (3.86 to 8.14)</td><td>(Measure as above)
OR 1.07 0.98-1.18, p=0.15)</td></tr>
<tr><td rowspan="2">Tenforde [55] published report (CDC) US, Case-Control</td><td rowspan="2">BNT162b2 (Pfizer/BioNTech): 59%
MRNA-1273 (Moderna): 41%</td><td><u>Overall population</u>
N: Cases: 1,194
Controls: 1,895</td><td>Median 9.3 weeks, (IQR 5.8 to 13.3 weeks)</td><td><u>VE against hospitalisation</u>
<u>Overall population</u>
Weeks 2-12: VE 86% (82% to 90%)
Weeks 13-24: VE 84% (77% to 90%)</td></tr>
<tr><td><u>Underlying condition</u>
N: Cases: 205
Controls: 447</td><td>Median 9.3 weeks, (IQR 5.8 to 13.3 weeks) in study overall</td><td>VE against hospitalisation

Subgroups:

Immunocompromised</td></tr>
</table>

<table>
<tr><th>Author, Country Study Design</th><th>Exposure#</th><th>Sample Size</th><th>Time since final Vaccination</th><th>Change in vaccine effectiveness over time
VE (95% CI)</th></tr>
<tr><td></td><td></td><td>(21% of the overall study population)</td><td></td><td>2-12 weeks: 64.3 (48.5 to 79.6)
13-24 weeks: 53.6 (12.8 to 77.8)

With multiple morbidities
2-12 weeks: 72.3 (62.2 to 82.2)
13-24 weeks: 70.0 (52.4 to 81.9)

No statistically significant change in VE over a 24-week period was observed within subgroups</td></tr>
<tr><td>Thompson(55)
US

Test negative case-control</td><td>BNT162b2 (Pfizer/BioNTech)
mRNA-1273 (Moderna)
Ad26.Cov2.S (Janssen)</td><td>Hospitalisations:
BNT162b2 (Pfizer/BioNtech)
8,500

mRNA-1273 (Moderna)
6,374

Ad26.COV2.S (Janssen)
707

Unvaccinated
20,406</td><td>Hospitalisation – Median - 53 IQR (33 to 75)
ICU admission – Median - 52 (IQR 34 to 73)
Emergency department/Urgent Care – Median 50 (IQR 31 to 73)</td><td>VE against hospitalisation
Overall population
<table>
<tr><th>Days post dose 2</th><td>Pfizer-BioNTech</td><th>Days post dose 2</th><td>Moderna</td><td>Days post dose</td><td>Janssen</td></tr>
<tr><td>14-27</td><td>87% (80 to 91)</td><td>14-27</td><td>90% (81 to 94)</td><td>14-27</td><td>72% (38 to 88)</td></tr>
<tr><td>28 to 41</td><td>95% (91 to 97)</td><td>28 to 41</td><td>89% (83 to 93)</td><td>28 to 41</td><td>69% (34 to 86)</td></tr>
<tr><td>42-55</td><td>86% (79 to 91)</td><td>42-55</td><td>93% (87 to 97)</td><td>42-55</td><td>68% (18 – 87)</td></tr>
<tr><td>56 to 69</td><td>83 (75 to 89)</td><td>≥ 56 post dose 2</td><td>(91% (85% to 94)</td><td>≥ 56 post dose 2</td><td>79% (48 to 91)</td></tr>
<tr><td>70 to 83</td><td>90% (82 to 94)</td><td>59 to 69</td><td>96%(92 to 98)</td><td></td><td></td></tr>
<tr><td>84 to 97</td><td>87% (76 to 93)</td><td>70-83</td><td>86% (75 to 92)</td><td></td><td></td></tr>
<tr><td>98 to 111</td><td>75% (57 to 85)</td><td>84-97</td><td>93%(82 to 97)</td><td></td><td>-</td></tr>
<tr><td>≥112</td><td>83% (64 to 92)</td><td>≥112</td><td>95% (79 to 99)</td><td></td><td></td></tr>
</table>
VE against emergency department and urgent care (ED/UC) medical events
Overall population</td></tr>
</table>

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)					
				days post dose 2	**Pfizer-BioNTech**	**days post dose 2**	**Moderna**	Days post dose	**Janssen**
				14-27 days	93% (87 to 96)	**14-27**	90% (81 to 95)	**14-27**	67% (30 to 84)
				28 to 41	94% (90 to 97)	**28 to 41**	96% (92 to 98)	**28 to 41**	80% (52 to 92)
				42-55 days	93% (81 to 87)	**42-55**	93% (85-96)	**42-55**	58% (5 to 81)
				56 to 69 days	82% (68 to 90)	**≥ 56 post dose 2**	90% (79-95)	**≥ 56 post dose 2**	87% (71 to 94)
				70 to 83 days	80% (66 to 88)	**59 to 69**	91%(79 – 96)		
				84 to 97 days	91% (82 to 96)	**70-83**	91% (79 – 97)		
				98 to 111 days	78% (61 to 87)	**84-97**	NR - no breakthrough cases		
				≥112 days	83% (64 to 92)	**≥112**	90% (52 to 98)		

Key: aOR – Adjusted Odds Ratio, CDC - Centers for Disease Control and Prevention, CI – confidence interval, HCWs – healthcare workers, ICU – Intensive care unit, IQR inter-quartile range, LTC – long-term care, LTHC – Long term health condition, N – sample size, NR - not reported, US – United States of America, VE – vaccine effectiveness

This section describes 11 included observational studies of vaccine effectiveness in vaccinated compared with unvaccinated individuals. Of the 11 observational studies, five were conducted in the US,[35, 41, 48, 51, 55] three were conducted in the UK,[44, 49, 53] and one each was conducted in Qatar,[46] Sweden[50] and Israel.[54] Studies are described below grouped by country.

US

Thompson et al.[41] is a test-negative case-control study conducted in the US of over 41,000 hospital admissions and 21,000 emergency or urgent care visits in patients aged 50 years or older. The Alpha variant was dominant at the time of the analysis. Vaccine effectiveness was estimated for the BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna) and Ad26.COV.S (Janssen) vaccines for hospitalisation, ICU admission, and emergency or urgent care visit. Results were adjusted with weights based on propensity for vaccination, age, region, calendar time and local virus circulation.

No evidence of a decline in vaccine effectiveness over time was observed for hospitalisation and emergency/urgent care visits. The vaccine effectiveness (mRNA-based vaccines combined) for hospitalisation was 88% (95% CI 84 to 92) and 86% (95% CI 74 to 93) at 14-27 days and ≥112 days after vaccination, respectively. When broken down by vaccine type, similar results were observed with vaccine effectiveness for hospitalisation at ≥112 days post-dose two estimated at 86% (95% CI 74 to 93) and 95% (95% CI 79 to 99) for BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), respectively. Data for Ad26.COV.S (Janssen) were limited to ≥56 days after vaccination (VE 79% (95% CI 48 to 91)). Vaccine effectiveness (mRNA based vaccines combined) for emergency or urgent care visits was 92% (95% CI 88 to 95) and 86% (95% CI 74 to 93) at 14-27 days and ≥112 days after dose two, respectively. The overall vaccine-specific estimates for hospitalisation were estimated at 87% (95% CI 85 to 90), 91% (95% CI 89 to 93) and 68% (95% CI 50 to 79) for BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna) and Ad26.COV2.S (Janssen), respectively. No formal tests for statistical significance between the vaccine-specific estimates or changes in VE over time were reported.

Subgroup analysis over a median follow-up of 12 weeks showed vaccine effectiveness for emergency department or urgent care clinic visits of 84% (95% CI 73 to 91) in patients 85 years of age or older, 90% (95% CI 86 to 93) in those aged ≥ 50 years with one or more chronic respiratory conditions, and 90% (95% CI 87 to 92) in those aged ≥ 50 years with one or more chronic non-respiratory conditions. With regards to VE for hospitalisations, similar high levels of protection among these

subgroups were observed. No difference in effectiveness for these groups was apparent compared to the total cohort for either outcome.

Tenforde et al.[60] is a Centers for Disease Control and Prevention (CDC) case-control study of hospitalised patients from 11 March to 14 July 2021. The dominant variant of concern varied during this period, with the Alpha variant dominant from March to May and Delta dominant from June to July.

Cases (n=1,194) were matched to controls (n=1,895) using admission date, region, age, sex and race. Overall, 141 (11.8%) cases and 988 (52.1%) controls were fully vaccinated (defined as receipt of the second dose of BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) mRNA COVID-19 vaccines ≥14 days before illness onset). Most patients had at least one chronic condition (82%), with 26% and 21% having a history of pulmonary disease or an immunocompromising condition, respectively. A small proportion of patients were long term care (LTC) residents, but subgroup-specific results were not provided for this cohort.

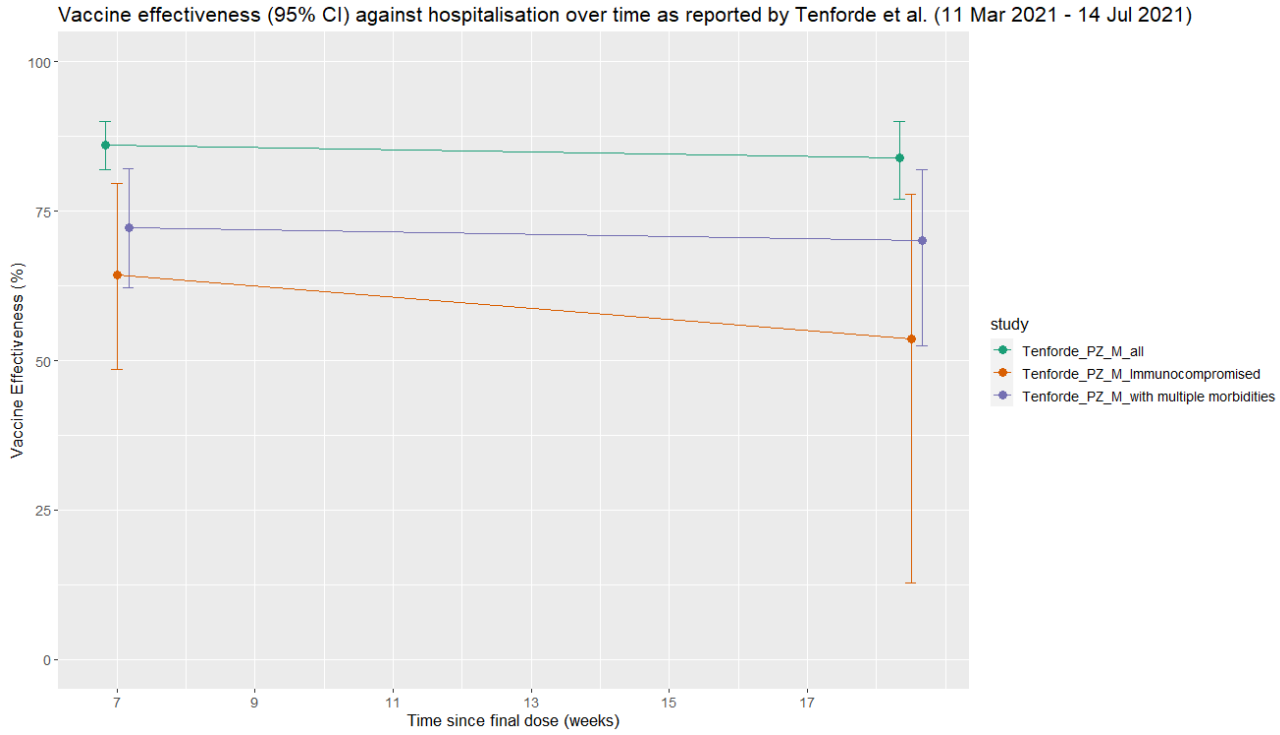
Vaccine effectiveness was estimated using logistic regression adjusted for admission date, region, age group (18-49, 60-64 or ≥65 years), sex and race, with no socioeconomic variables or comorbidities adjustment. Over the total surveillance period (median 53 days (IQR: 33 to 75)), VE against hospitalisation for COVID-19 was 86% (95% CI 82 to 88) with similar effectiveness estimates when assessed for the Alpha and Delta dominant periods separately.

No significant change in vaccine effectiveness was observed over time. Vaccine effectiveness for hospitalisation was 86% (95% CI 82 to 90) and 84% (95% CI 77 to 90) for the periods 2–12 weeks and 13–24 weeks after the second dose, respectively. Sensitivity analysis using alternative statistical models for time were consistent with the primary analysis. The authors report no statistically significant change in vaccine effectiveness over time for those aged 65 years or older or for those with multiple morbidities. Results were only presented graphically, but data suggest vaccine effectiveness for those aged over 65 years was 86.7% (95% CI 81.7 to 91.1) and 80.1% (95% CI 70.0 to 88.1) for the periods 2–12 weeks and 13–24 weeks after the second dose, respectively. For those with multiple morbidities, vaccine effectiveness was estimated at 72.3% (95% CI 62.2 to 82.2) and 70.0% (95% CI 52.4 to 81.9) at the equivalent time points.

Vaccine effectiveness for hospitalisation associated with COVID-19 was lower for those with an immunocompromising condition (VE 63%, 95% CI 44 to 76) compared to those without (VE 90%, 95% CI 87 to 92). No formal interaction tests are reported, but the confidence intervals do not overlap. The authors report that no

statistically significant change in vaccine effectiveness over time was observed within the subgroup of people with immunocompromising conditions, but further numerical results were not presented. Results derived by digitising the corresponding graph show that estimates of effectiveness were 64.3% (95% CI 48.5 to 79.6) and 53.6% (95% CI 12.8 to 77.8) at 2-12 weeks and at 12-24 weeks, respectively after the second dose. Figure 5 graphically depicts the changes in vaccine effectiveness against hospitalisation over time in the total population (green line), in those with multiple morbidities (purple line) and in those with immunocompromising conditions (red line).

Figure 5: Vaccine effectiveness against hospitalisation over time, by underlying condition, as reported by Tenforde et al.



Key: M – mRNA-1273 (Moderna), PZ – BNT162b2 (Pfizer/BioNTech).

Polinski et al. examined the effectiveness of the Ad26.COV2.S (Janssen) vaccine in a matched cohort study with cross over.[35] Vaccinated individuals were matched with to up to ten controls by age, sex, date location, comorbidity index, plus 17 COVID-19 risk factors via propensity score matching. The mean time since vaccination was 15 weeks. The authors assumed that 40% of participants in the unvaccinated cohort were actually vaccinated and applied a correction factor to all vaccine effectiveness estimates which increased the vaccine effectiveness results presented. For example, the authors estimated vaccine effectiveness of 79% (95% CI 79 to 80) for any

infection with the correction factor versus 69% (95% CI 57% to 71%) without. As insufficient justification was given for application of this correction factor, remaining results are presented without the correction factor. For COVID-19 related hospitalisation, vaccine effectiveness was estimated at 81% (95% CI 79% to 84%). Vaccine effectiveness for COVID-19 related hospitalisation was lower for those aged 60 years and older compared to those aged less than 60 years with effectiveness of 68% (95% CI 63 to 73) compared with 79% (95% CI 74 to 84). Vaccine effectiveness was lower for those with immunocompromising conditions with estimates of 54% (95% CI 35 to 67) and 52% (95% CI 42 to 60%) for COVID-19-related hospitalisation and symptomatic disease, respectively. In the general study population, the authors report that no difference in effectiveness for either hospitalisation or any infection was observed over time. However, the vaccine effectiveness over time was not analysed by subgroup in this study.

Pilishvili et al. conducted a test negative case-control study to examine the effectiveness of mRNA vaccines in HCW across 25 US states.[51] Cases (n=1,482) were defined as positive PCR or antigen-based tests for SARS-CoV-2 and the presence of at least one COVID-19 like symptom. Controls (n=3,449) were defined on the basis of a negative PCR test for SARS-CoV-2 regardless of symptoms and were matched by week of test date and site. Results were adjusted for sociodemographics, underlying conditions and exposure to a person with COVID-19. The median time since final vaccination dose was six weeks (range 1 to 24). Vaccine effectiveness for symptomatic infection more than seven days after dose two were presented for mRNA vaccines combined (VE 90.4%; 95% CI 87 to 92.9), for BNT162b2 (Pfizer/BioNTech) (VE 88.8%; 95% CI 84.6 to 91.8), and for mRNA-1273 (Moderna) (VE 96.3%; 95% CI 91.3 to 98.4). Multiple subgroup analysis were presented for the mRNA combined analysis. Vaccine effectiveness, did not differ by age (<50 versus ≥50 years), for people with asthma, obesity, obesity or overweight, hypertension, or for those with underlying conditions or risk factors for severe COVID-19. Vaccine effectiveness was found to be numerically lower in those with diabetes (VE 80.2% (95% CI 45.8% to 92.7%)) compared with those with no underlying risk factor (VE 91.1% (95% CI 85.5% to 94.6%)), however the confidence intervals were wide and overlapping, and no statistical tests were reported to determine if differences observed between subgroups were statistically significant.

Vaccine effectiveness by time was presented up to 14 weeks after receipt of dose two. While effectiveness estimates during weeks nine through 14 were lower than the maximum vaccine effectiveness observed during weeks three and four, the authors considered that wide and overlapping confidence intervals did not support a

conclusion of waning immunity, but suggested that the data warrant longer-term monitoring of vaccine effects. Digitised estimates taken from the figure presented in the publication estimate the effectiveness as 96.6% (95% CI 92.7 to 98.5) and 80.9% (95% CI 61.0 to 90.4) at 3-4 weeks and 13-14 weeks after dose two, respectively.

Liu et al.[48] conducted a retrospective matched cohort study with crossover based on electronic health records (EHRs) of Columbia University Irving Medical Center/New York Presbyterian (CUIMC/NYP) up to 21 September 2021. Adults 18 years or older residing in New York State who received routine clinical care from this healthcare system were included. The aim of this study was to assess the association between breakthrough infection rate in vaccinated individuals (two doses of BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna), with a mean of 14.4 weeks of follow-up since final dose) and multiple risk factors. In a separate analysis, logistic regression was used to assess the association between vaccine administration and infection rate by comparing a vaccinated cohort to a historically matched cohort in the period before vaccines were available. Infection incident rates were also compared between vaccinated individuals and longitudinally matched unvaccinated individuals. Matching was based on previous visit counts, observational days, demographics, underlying immune conditions and the incidence of SARS-CoV-2 at the PCR test date.

Vaccine effectiveness for SARS-CoV-2 infection was estimated to be 88.4% (95% CI, 86.5 to 90) in a vaccinated cohort compared with a historically matched cohort (n=14,362 pairs) recruited before 11 December 2020. Vaccine effectiveness did not appear to differ by age (≤65 versus >65 years), sex, or for those with immunocompromising conditions, though no statistical tests were reported to determine if differences observed between subgroups were statistically significant. Vaccine effectiveness for SARS-CoV-2 infection was also estimated comparing a matched vaccinated and unvaccinated cohort (n=10,283 pairs) recruited since 18 January 2021. For this analysis, the authors estimated effectiveness in terms of adjusted incident rate ratio (aIRR) using incident rates per 1,000 person-days and are thus, the estimates are not directly comparable to VE estimated using odds ratios, hazard ratios or rate ratios. In this cohort, the aIRR was estimated at 0.41 (95% CI, 0.35 to 0.48). As above, vaccine effectiveness did not appear to differ by age (≤65 versus >65 years), sex, or for those with immunocompromising conditions, though no statistical tests were reported to determine if differences observed between subgroups were statistically significant.

The authors reported an increase in breakthrough infections over time, with a notable rise in the incident rate observed after 120 days post final vaccination for

BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines. For example, with regards to BNT162b2 (Pfizer/BioNTech), the incident rate per 1,000 person-days increased from 0.1 to 0.41 up to 1.95 for the periods 0-30 days, 120-150 days, and 210-240 days post final dose, respectively. A similar pattern was observed for mRNA-1273 (Moderna).

The authors examined risk factors associated with breakthrough infections in those who were fully vaccinated by comparing incidence rates between vaccinated individuals who experienced breakthrough infections (n=198) and vaccinated individuals who remained infection-free (n=14,164). Compared with those who were not immunocompromised, individuals who were immunocompromised (IRR 1.48 (95% CI, 1.09 to 2.0)), had an active tumour (IRR 1.56 (95% CI, 1.1 to 2.2)), were on immunosuppressive therapies (IRR 1.45 (95% CI, 1.03-2.04) or who had a primary immunodeficiency disorder (IRR 2.53 (95% CI, 1.4 to 4.58)) were found to be at a significantly increased risk of breakthrough infections. However, compared with those who were not immunocompromised, those who had chronic kidney disease (IRR 1.33 (95% CI, 0.86 to 2.06)), HIV (IRR 1.25 (95% CI, 0.63 to 2.47) or an organ transplant (IRR 1.9 (95% CI, 0.98 to 3.71) had a higher IRR but were not found to be at a significantly increased risk of breakthrough infections, which may be as a result of the small sample sizes.

The authors also examined the association between individual drugs/conditions and breakthrough infection. The individual conditions that were most statistically significantly associated with breakthrough infections (ranked by p-value) were as follows:

- chronic pulmonary heart disease (IRR 4.07 (95% CI, 2.07 to 7.99) p<0.001)
- asteatosis cutis (xerosis) (IRR 2.6 (95% CI, 1.56 to 4.33) p<0.001)
- immunodeficiency disorder (IRR 3.62 (95% CI, 1.81 to 7.22) p<0.001)
- post-inflammatory pulmonary fibrosis (IRR 3.34 (95% CI 1.69 to 6.59) p<0.001)
- tubulointerstitial nephritis (IRR 3.84 (95% CI, 1.78 to 8.28) p=0.001)
- Alzheimer's disease (IRR 3.5 (95% CI, 1.68 to 7.28) p=0.001)
- bacterial pneumonia (IRR 2.97 (95% CI, 1.5 to 5.87) p=0.002)
- epidermoid cyst (IRR 2.45 (95% CI, 1.39 to 4.32) p=0.002)
- peripheral circulatory disorder due to type 2 diabetes mellitus (IRR 2.78 (95% CI, 1.45 to 5.36) p=0.002)
- acute deep venous thrombosis of femoral vein (IRR 3.62 (95% CI, 1.58 to 8.27) p=0.002).

The drugs that were statistically significantly associated with breakthrough infections were those that are used to treat and manage the above listed conditions (for example, valganciclovir to prevent viral infections in those with immunocompromising conditions, donepezil for individuals with Alzheimer's disease, and salbutamol for those with respiratory conditions). There is no link necessarily between the use of these drugs and an increased risk of breakthrough infections.

Some caution is required in the interpretation of the findings of this study given the use of historical controls for some of the analysis, the comparator populations were affected by different variants of SARS-CoV-2. In additional, it is unclear whether all key confounders were controlled for in this retrospective analysis. Statistical tests are not adjusted for multiplicity, and therefore the possibility of spurious associations should be considered when interpreting the results of the analysis.

UK

Three UK studies, from Public Health England,[44] Public Health Scotland,[49] and the UK Office for National Statistics/Oxford[53] provide important information for the review question.

Public Health England

In a preprint, Andrews et al.[44] describe a national test-negative case-control study of vaccine effectiveness conducted by Public Health England using linked data from national registries and databases. Vaccine effectiveness was adjusted for a wide range of potential confounders including calendar time, clinical risk group status, health and social care worker status and a wide range of sociodemographic and socioeconomic variables.

Vaccine effectiveness over time for both the Alpha and Delta dominant periods was presented for three outcomes (symptomatic disease, hospitalisation and death). Results were stratified by vaccine, age and clinical risk group status. Results from the Delta period are summarised here. No statistical tests were reported to determine if differences observed between vaccines types, subgroups or over time were statistically significant. Confidence intervals for some of the analyses were wide and overlapping. Therefore, no firm conclusions can be drawn from these analyses.

The analysis estimated the vaccine effectiveness for the BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) vaccines with up to 20 weeks of follow-up after the second dose.

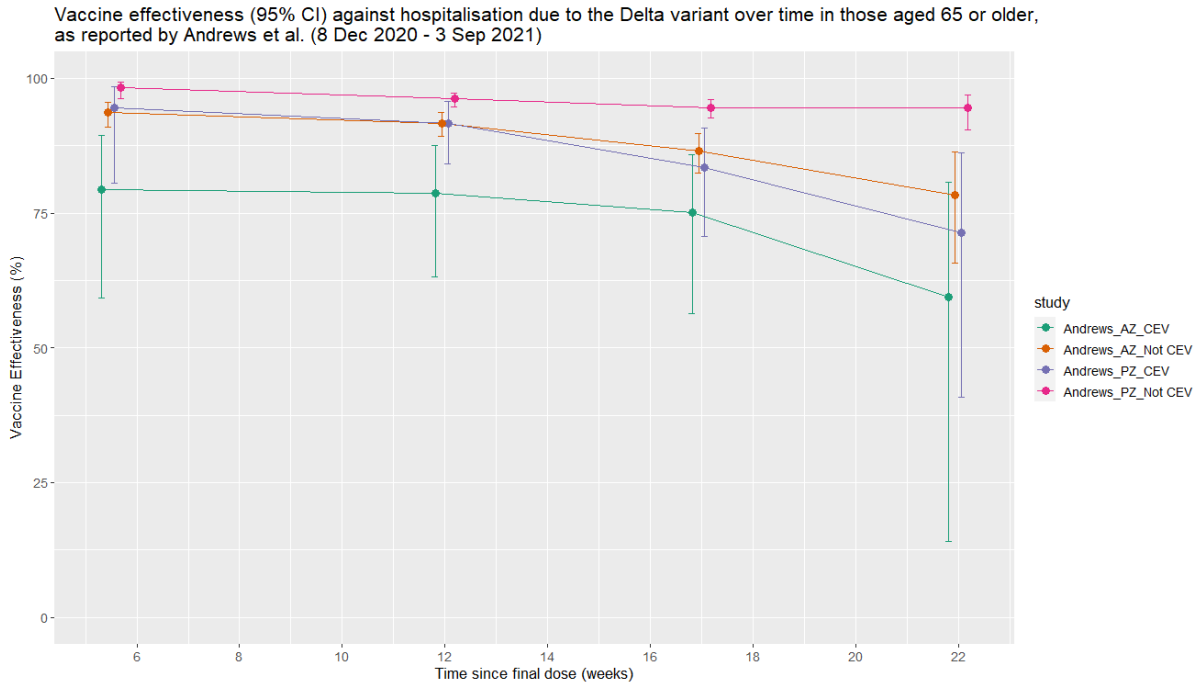
In the population, aged 16 years and over, BNT162b2 (Pfizer/BioNTech) vaccine effectiveness for mortality ranged from 98.2% (95% CI 95.9 to 99.2) to 90.4%

(95% CI 85.1 to 93.8) for the periods 2-9 weeks and ≥20 weeks after the second dose, respectively. For the ChAdOx1 (AstraZeneca) vaccine, VE for these two intervals ranged from 94.1% (95% CI 91.8 to 95.8) to 78.7% (95% CI 52.7 to 90.4), respectively. Results for those aged 65 years or older were similar to the primary analysis.

Similar patterns were observed for hospitalisations for both vaccines. For the BNT162b2 (Pfizer/BioNTech) vaccine, vaccine effectiveness remained at 92.7% (95% CI 90.3 to 94.6) and 90.7% (95% CI 86.0 to 93.8) ≥20 weeks after the second dose for those aged ≥16 years and ≥65 years, respectively. For the ChAdOx1 (AstraZeneca) vaccine, VE for those aged 16 years or older declined from 95.2% (95% CI 94.6 to 95.6) to 77% (95% 70.3 to 82.3) over the periods from 2-9 weeks to ≥20 weeks after the second dose. When limited to the subgroup aged 65 years or older, VE ranged from 92.2% (95% CI 89.4 to 94.3) to 76.3% (95% CI 65.3 to 83.8) over the same periods.

Vaccine effectiveness against hospitalisation over time, in the context of Delta dominance, in those aged 65 years and older, stratified by risk category is illustrated in Figure 6. For BNT162b2 (Pfizer/BioNTech), vaccine effectiveness for hospitalisation was 71.4% (95% CI 40.9 to 86.1) in adults aged 65 years or older in a clinically extremely vulnerable group at ≥20 weeks after dose two (purple line).[44] This is in contrast to VE of 94.6% (95% CI, 90.5 to 97) in adults aged 65 years or older not in a clinically extremely vulnerable group beyond 20 weeks after dose two (pink line). For ChAdOx1 (AstraZeneca), effectiveness for hospitalisation (in the context of Delta as the dominant variant) in those aged 65 years or older in the clinically extremely vulnerable group[61] was estimated as 59.4% (95% CI 14.1 to 80.8) at ≥20 weeks after dose two (green line). In contrast, a VE of 78.4% (95% CI, 65.7 to 86.4) was observed in adults aged 65 years or older not in a clinically extremely vulnerable group beyond 20 weeks after dose two (orange line).

Figure 6: Vaccine effectiveness against Delta hospitalisation over time, in those aged 65 years and older by risk category, as reported by Andrews et al.

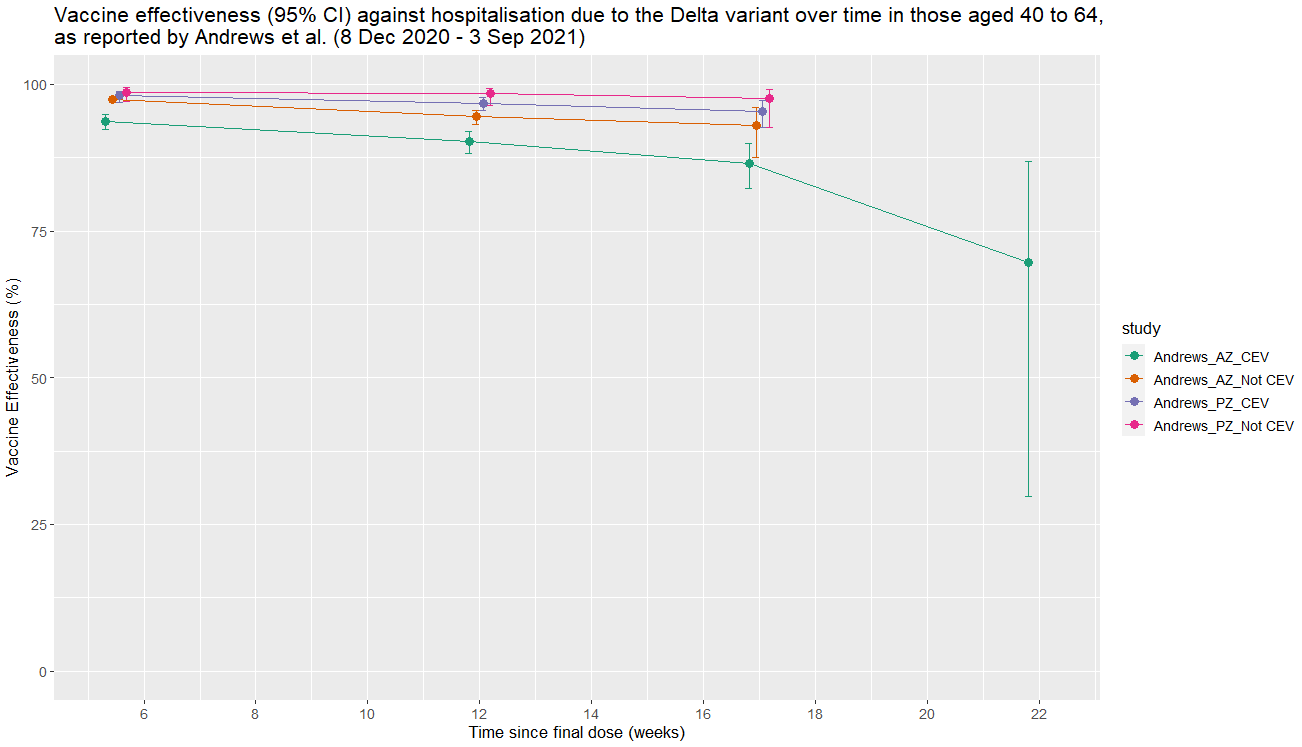


Key: AZ – ChAdOx1 (Astra Zeneca), hosp – hospitalisation, CEV – Clinically Extremely Vulnerable, PZ – BNT162b2 (Pfizer/BioNTech).

Vaccine effectiveness against hospitalisation over time, in the context of Delta dominance, in those aged 40 to 64, stratified by risk category is illustrated in Figure 7. For BNT162b2 (Pfizer/BioNTech), effectiveness for hospitalisation was 95.4% (95% CI 92.6 to 97.2) at weeks 15-19 in adults aged 40 to 64 in a clinically extremely vulnerable group (purple line). This is broadly similar to VE of 97.6% (95% CI, 92.6 to 99.2) in adults aged 40 to 64 not in a clinically extremely vulnerable group 15 to 19 weeks after dose two (of note, data were not reported beyond week 20) (pink line). Vaccine effectiveness for hospitalisation for the ChAdOx1 (AstraZeneca) vaccine in those aged 40 to 64 years in either a clinical risk group or in the clinically extremely vulnerable risk group was 86.6% (95% CI, 82.2 to 89.9) and 69.7% (95% CI 29.7 to 86.9) at 15-19 weeks and ≥20 weeks, respectively (green line). This is broadly similar to the effectiveness of 93% (95% CI, 87.5 to 96.1) in adults aged 40 to 64 not in a clinically extremely vulnerable group 15 to 19 weeks after dose two (of note, equivalent data are not presented beyond week 20) (orange line). These findings are suggestive of a potential reduction in vaccine effectiveness for those in clinical risk groups aged 65 years and older, but not necessarily those aged between 40 and 64 compared with the general

population. However, the confidence intervals were wide and overlapping and so caution is required in the interpretation of these data.

Figure 7: Vaccine effectiveness against Delta hospitalisation over time, in those aged 40-64, by risk category, as reported by Andrews et al.



Key: Abbreviations: AZ – ChAdOx1 (Astra Zeneca), hosp – hospitalisation, CEV – clinically extremely vulnerable, PZ – BNT162b2 (Pfizer/BioNTech).

In relation to the total population, in the context of Delta dominance, greater variation over time was observed for the symptomatic disease endpoints. ChAdOx1 (AstraZeneca) effectiveness ranged from 66.7% (95% CI 66.3 to 67.0) 2-9 weeks after the second dose to 47.3% (95% CI 45.0 to 49.6) ≥20 weeks after the second dose. BNT162b2 (Pfizer/BioNTech) effectiveness ranged from 80.1% (95% CI 77.5 to 82.4) to 55.3% (95% CI 50.2 to 60.0) for the time periods 2-9 weeks and ≥20 weeks after the second dose, respectively. There was shorter follow-up for those who received the mRNA-1273 (Moderna) vaccine, the estimated VE was 90.3% (95% CI 67.2 to 97.1) 10-14 weeks after the second dose with no longer term data presented.

The authors reported that the results suggest greater waning with the ChAdOx1 (AstraZeneca) compared with the BNT162b2 (Pfizer/BioNTech) vaccine, but

cautioned that there were differences in the groups who received the different vaccines.

REACT-SCOT – Public Health Scotland.

REACT-SCOT (McKeigue et al.)[49] is an ongoing matched case-control study by Public Health Scotland. Data from 1 December 2020 to 8 September 2021 were examined to estimate the effectiveness of ChAdOx1 (AstraZeneca) and mRNA vaccines (BNT162b2 (Pfizer/BioNTech) or mRNA-1273 Moderna) for severe disease and for a composite outcome of hospitalisation or fatal COVID-19.[62] Potential cofounders were accounted for by matching each case (severe disease n = 5,644; hospitalisation/fatal disease n= 21,671) to ten controls by matching on some co-variates (age, sex, primary care practice and calendar time) and by adjusting for others (risk category, number of non-CV drug classes and recent hospital stay). Effectiveness was reported as rate ratios with lower rate ratios indicating higher vaccine effectiveness (vaccine effectiveness = 1 – rate ratio). Over the total cohort, the median time since vaccination was 10 weeks with a maximum of 26 weeks. In the Delta dominant period, the estimated overall rate ratios for the composite outcome of hospitalisation or COVID-19 mortality for ChAdOx1 (AstraZeneca) and mRNA vaccines, were 0.19 (95% CI 0.17 to 0.2) and 0.08 (95% CI 0.07 to 0.09), respectively.

Vaccine effectiveness over time was also reported up to approximately 26 weeks after the second dose. Vaccine effectiveness was seen to decrease (increasing log rate ratio) for both the severe disease and hospitalisation/fatal disease outcomes, over the first two months after the second dose for both the ChAdOx1 (AstraZeneca) and mRNA vaccines, plateauing after that. While the mRNA vaccines were initially more effective for the severe disease outcome than ChAdOx1 (AstraZeneca), this difference diminished over time.

Further analyses were undertaken to model the rate of waning for the three vaccines combined.[49] Two types of model were compared: (1) a "waning to zero efficacy" model in which the effect of vaccination on the scale of log rate ratio decays exponentially to zero with time since second dose; (2) a "waning to constant efficacy" model in which the effect of vaccination is the sum of two terms: a time-invariant effect and a waning effect that decays exponentially with time since second dose. The "waning to constant efficacy" was the best fitting model for both the hospitalised or fatal COVID-19 (p = 0.001) and the severe disease outcomes (p=0.05), with a calculated waning effect half-life of 17 (95% CI 9 to 39) days and 27 (95% CI 14 to 143) days, respectively, and reaching a constant effectiveness of 83% and 82% for these outcomes, respectively. Limitations of this study include a

lack of information about the models used to examine waning of efficacy with no explanation as to how these were chosen, or what alternatives may have also fitted the data. While the relative fit of the two models was compared, goodness-of-fit was not reported separately for each model limiting the ability to ascertain whether either model is a good fit for the data.

The authors report effectiveness for severe disease of 94% (95% CI 93 to 96) in those without risk conditions, 86% (95% CI 86 to 91) in those with moderate risk conditions, and 73% (95% CI 64% to 79%) in the clinically extremely vulnerable (CEV) category (eligible for shielding).[61] Effectiveness against hospitalisation or mortality was also lower at 68% (95% CI 63% to 71%) in the CEV group than in the other two risk categories (VE 86% (95% CI, 85 to 88) in those without any risk condition and VE 83% (95% CI, 82 to 85) in those with moderate risk conditions. Results by CEV subgroups (solid organ transplant, specific cancers, severe respiratory, rare diseases, on immunosuppressants, additional conditions) were presented in the form of rate ratios compared to unvaccinated matched controls, but confidence intervals were too wide for comparison of effectiveness between groups. Point estimates (RR) for severe disease ranged from 0.1 (95% CI 0.03 to 0.28) for rare diseases to 0.6 (95% CI 0.24 to 1.51) for solid organ transplant recipients, and for the composite of hospitalisation and mortality, these estimates ranged from 0.28 (95% CI, 0.24 to 0.33) for severe respiratory disease to 0.6 (95% CI, 0.38 to 0.95) for solid organ transplant recipients.

Results by risk condition and vaccine type (ChAdOx1 (AstraZeneca), any mRNA – BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) were also presented. Effectiveness of two doses against severe COVID-19 in the CEV group were lower for those who received the ChAdOx1 (AstraZeneca) vaccine (VE 72%; 95 CI 63% to 79%) and the mRNA vaccines (VE 73%; 95% CI 59% to 83%), compared with those without any risk conditions, ((VE 93%; 95% CI 91 to 95%) and VE 96% (95% CI, 94 to 97)), respectively. Similar reductions in effectiveness for those in the CEV group were observed in relation to the composite outcome of hospitalisation and mortality. Vaccine effectiveness over time was not examined for this clinically vulnerable cohort.

Pouwels et al.

One general population study by Pouwels et al.[53] using data from the UK Office for National Statistics COVID-19 infection survey was identified. This peer-reviewed study is an analysis of the effectiveness of BNT162b2(Pfizer/BioNTech) and ChAdOx1(AstraZeneca). They examined differences in effectiveness by subgroup (age, self-reported long term health condition and evidence of prior infection), time since second vaccination, and the interaction by time and subgroup. This is a large community-based survey of randomly selected households providing a representative sample across the UK with data linked to administrative records from the UK National Immunisation Management Service. Individuals had follow-up visits every week for the first month after enrolment, then monthly for 12 months from enrolment. To minimise potential bias from differences in test-seeking behaviour between vaccinated and unvaccinated participants, all enrolled individuals had monthly reverse transcriptase polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 infection. At each visit, a person's vaccination and previous infection status was updated, therefore each person could contribute visits attributed to vaccinated and unvaccinated cohorts over the time frame of the analysis.

Participants aged 18 years or older were included with results reported separately for the Alpha and Delta dominant phases (1 December 2020 to 17 May 2021 and 17 May 2021 to 1 August 2021, respectively). In the Alpha dominant phase, 384,543 individuals contributed a median of seven visits per person while in the Delta dominant phase 358,983 participants provided a median of two visits per person.

Vaccine effectiveness estimates for those fully vaccinated (that is, ≥ 14 days after the second dose) with either the BNT162b2 (Pfizer/BioNTech) or ChAdOx1 (AstraZeneca) vaccines were calculated versus unvaccinated participants (>21 days before vaccination) with no prior positive SARS-COV-2 result. As participants with a history of infection were excluded from the unvaccinated, but not the vaccinated groups, vaccine effectiveness estimates may be biased upwards. Results were adjusted for a wide range of potential confounders including socio-demographic and occupation variables. Primary outcomes of interest to this review (severe disease or mortality) were not reported, and only data related to the secondary review outcomes of RT-PCR-confirmed infections were presented.

The median time since the final vaccination dose at each visit was longer for BNT162b2 (Pfizer/BioNTech) (8 weeks) compared with ChAdOx1 (AstraZeneca) (6 weeks). The overall results are summarised here, with full details presented in the data extraction tables (Appendix C). Statistical tests are not adjusted for multiplicity

and therefore the possibility of spurious associations should be considered when interpreting the results of the analysis.

In patients aged 18 years or older, vaccine effectiveness (VE) for BNT162b2 (Pfizer/BioNTech) for symptomatic infection (PCR positive, self-reported symptoms) differed significantly between the Alpha and Delta dominant phases with vaccine estimates of 97% (95% CI 96 to 98) and 84% (95% CI 82 to 86), respectively (heterogeneity p<0.0001). Similar findings were observed for cases with a cycle threshold (Ct) <30 (reflecting higher viral load) with estimates of 94% (95% CI 91 to 96) and 84% (95% CI 82 to 86) for the Alpha and Delta dominant phases, respectively. Lower estimates of VE were observed for any infection, with no difference between the Alpha and Delta dominant phases (VE 78% (95% CI 68 to 84) and VE 80% (95% CI 77 to 83), respectively).

For the ChAdOX1 (AstraZeneca) vaccine, VE estimates were similar to those observed for BNT162b2 (Pfizer/BioNTech) in the Alpha dominant phase for symptomatic infection and cases with a Ct<30 (VE estimates of 97% (95% CI 93 to 98) and 86% (95% CI 71 to 93), respectively). However, effectiveness for symptomatic infection and cases with a Ct<30 in the Delta phase (VE of 71% (95% CI 66 to 74) and 70% (95% CI 65 to 73), respectively) were significantly lower compared with either the Alpha phase (p = 0.04) or the equivalent Delta phase for BNT162b2 (Pfizer/BioNTech) (p<0.0001).

Lower estimates of effectiveness were observed for ChAdOX1 (AstraZeneca) against any infection with an estimated VE of 79% (95% CI 56 to 90) and 67% (95% CI 62 to 71) for the Alpha and Delta dominant phases, respectively. These estimates were noted to be significantly lower than those observed for BNT162b2 in the Delta phase (p<0.001).

As noted, Pouwels et al.[53] also examined differences in VE by subgroup (age, self-reported long term health condition and evidence of prior infection), time since second vaccination, and the interaction by time and subgroup. These analyses were limited to patients aged 18 to 64 years in the Delta dominant period only due to a decreasing number of visits in the unvaccinated reference group over time in the Alpha dominant period, particularly for older individuals.[53]

Vaccine effectiveness estimates were lower for those with a self-reported long term health condition compared with those without (range 81-92% vs. 86-94% and 58-65% vs. 69-73% for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca), respectively), but differences were not statistically significant. As the interaction

effect between long term health condition and age was not accounted for, these results should be interpreted with caution.

Vaccine effectiveness was significantly lower for those aged 35 to 64 compared to those aged 18 to 34, irrespective of the outcome (symptomatic infection, Ct<30, any infection) or the vaccine type (BNT162b2 (Pfizer/BioNTech), ChAdOx1 (AstraZeneca)). In those aged 18 to 34 years, VE ranged from 90-96% and from 73-76% for the BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) vaccines, respectively. In those aged 35 to 64 years, VE ranged from 77-88% and from 54-57% for the BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) vaccines, respectively.

For both vaccine types, vaccine effectiveness estimates were significantly higher for those with a history of a prior infection (range 93-99% vs. 85-93% and 88-94% vs. 68-72% for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca), respectively).

In those aged 18 to 64 years, there was evidence of a reduction in effectiveness over time against new RT-PCR-positive infections (OR 1.22, 95% CI 1.06 to 1.41, p=0.007; and OR 1.07, 95% CI 0.98 to 1.18, p=0.15 for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) vaccines, respectively). For those with a Ct<30, there was a significant difference (p=0.003) in the performance of the two vaccines with a declining effectiveness observed for the BNT162b2 (Pfizer/BioNTech) (OR 1.52, 95% CI 1.26 to 1.84, p<0.0001), but not the ChAdOx1 (AstraZeneca) vaccine (OR 1.09, 95% CI 0.97 to 1.22, p=0.14). The authors concluded that the study provided evidence that the effectiveness of BNT162b2 (Pfizer/BioNTech) against symptomatic infection and infection with Ct<30 declined faster than for ChAdOx1.

Pouwels et al.[53] further investigated evidence of vaccine waning over time for both BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) vaccines for each of the outcomes (symptomatic infection, infection with a higher viral load (Ct<30), and any infection) for a range of subgroups (age, self-reported long term health conditions, prior infection, dosing interval), though for the current review the focus is on the long term health conditions subgroup. Data were presented graphically with no interpretation of subgroup interaction effects. Estimates were reported at day 14, but numerical results were not reported for any subsequent time points, or for the subgroups. Furthermore confidence intervals are wide and formal statistical tests are not reported, hence descriptions of the graphs should be interpreted with caution as to the direction of point estimates only.

In the first analysis, the protection against all new PCR-positive episodes over time from second dose, by presence or absence of self-reported long term health condition in those 18-64 years in the Delta-dominant period is graphically illustrated. It is difficult to ascertain from the graph whether there is an interaction between the rate of treatment waning and evidence of a long term health condition. The estimated vaccine effectiveness for BNT162b2 (Pfizer/BioNTech) at day 14 was 81% (95% CI, 69-89%) and 86% (95% CI, 80-90%) and for those with and without long term health conditions, (interception points) (p=0.31). The estimated effectiveness for ChAdOx1 (AstraZeneca) at day 14 was 58% (95% CI, 39-71%) and 69% (95% CI, 62-74%) for those with and without long term health conditions, respectively, (interception points) (p=0.1). In alternative analyses (measuring VE against cases with Ct<30), there does not appear to be an interaction between the rate of treatment waning and evidence of a long term health condition for either BNT162b2 (Pfizer/BioNTech) or ChAdOx1 (AstraZeneca). However in a third analysis (measuring VE against cases with reported symptoms), it appears that there may be faster treatment waning for those with a long term health condition compared with those without in the Pfizer treatment group; though there does not appear to be an interaction between the rate of treatment waning and evidence of a long term health condition in the ChAdOx1 (AstraZeneca) treatment group.

While there may be some evidence of faster waning in those with long term health conditions, limited conclusions can be drawn from this study as it is not possible to interpret these graphs as evidence of an effect.

Sweden

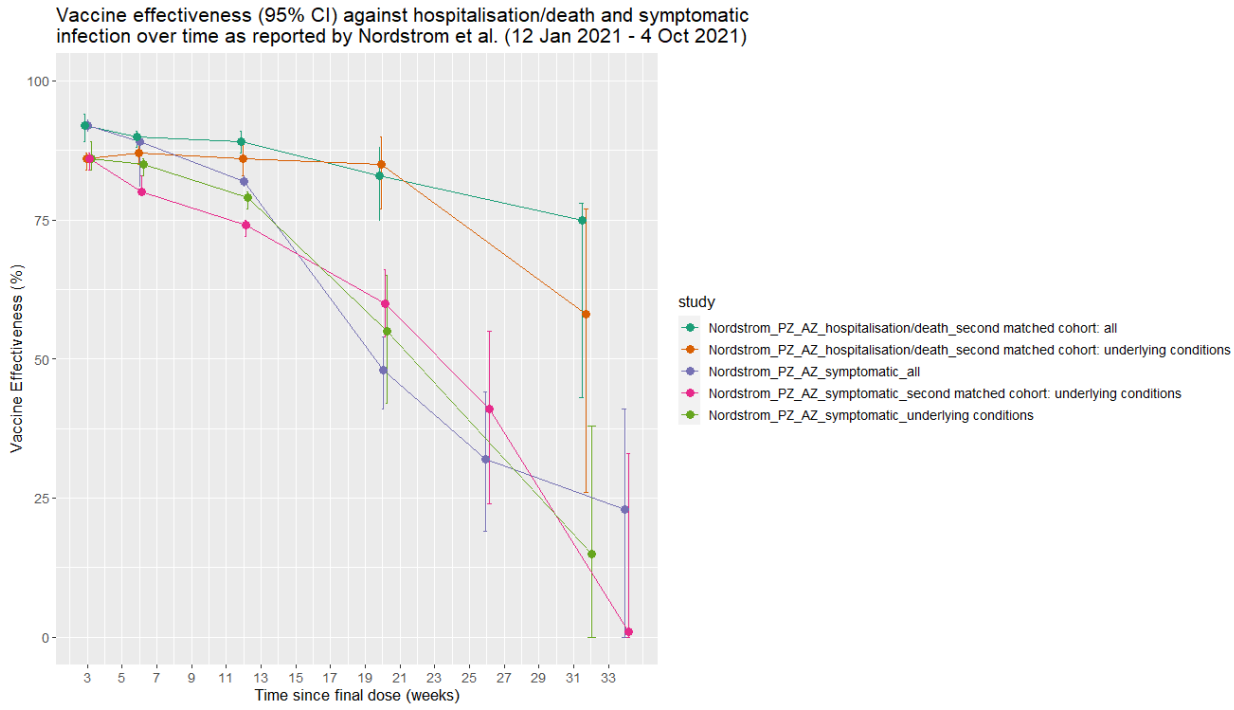
A retrospective cohort study was conducted by Nordström et al. using Swedish nationwide registries.[50] In this study which is currently available as a preprint, the cohort comprised 842,974 pairs (N=1,684,958), including individuals vaccinated with two doses of ChAdOx1 nCoV-19 (AstraZeneca), mRNA-1273 (Moderna), or BNT162b2 (Pfizer), and matched unvaccinated individuals. Cases of symptomatic infection and severe COVID-19 (hospitalisation or 30-day mortality after confirmed infection) were collected from 12 January to 4 October 2021. The mean follow-up was 16.6 weeks (range 2.1 to 40) and 16.1 weeks (range 2.1 to 39.1) post final vaccination dose for symptomatic infection and severe COVID-19 outcomes, respectively, with a maximum follow-up of nine months. Fully vaccinated (two doses) individuals were matched 1:1 (based on birth year and sex) to randomly sampled unvaccinated individuals. Baseline date was set to the date of second dose of vaccine. Matched unvaccinated individuals were excluded if they received a first

dose of vaccine or died within 14 days of baseline, and a new individual sourced from the remaining total cohort.

A significant waning in vaccine protection against symptomatic infection across all subgroups up to nine months was observed. Vaccine effectiveness of BNT162b2 (Pfizer/BioNTech) against symptomatic infection waned progressively from 92% (95% CI, 92 to 93) to 47% (95% CI, 39 to 55) for the periods 15-30 days and 121-180 days post-final dose, respectively and from day 211 onwards no effectiveness could be detected (23% 95% CI, -2 to 41). The effectiveness waned slightly slower for mRNA-1273 (Moderna), with VE estimated at 88% (95% CI, 88 to 90) at 15-30 days post final dose reducing to 59% (95% CI, 18 to 79) from day 181 onwards. In contrast, effectiveness of ChAdOx1 (Astra Zeneca) was generally lower and waned faster, with VE estimated at 44% (95% CI, 36 to 52) at 15-30 days post final dose, with no protection against infection observed from day 121 onwards (-19%, 95% CI, -97 to 28). However VE from heterologous ChAdOx1 (AstraZeneca)/ mRNA-1273 (Moderna) vaccination, which was initially 89% (95% CI, 79 to 94) at 15-30 days post final dose was maintained from 121 days and onwards (66%; 95% CI, 41 to 80).

The change in vaccine effectiveness against severe disease and infection outcomes observed in this study is illustrated in Figure 8. Vaccine effectiveness against symptomatic infection was found to decrease substantially over time both in the total study population and in individuals with underlying conditions at baseline (myocardial infarction, stroke, diabetes, hypertension, kidney failure, COPD, asthma or cancer). In those with underlying conditions, vaccine effectiveness (any vaccine) reduced from 86% (95% CI, 84 to 89) at 15-30 days post-final vaccination to 15% (95% CI, 17 to 38) from day 181 onwards. A secondary analysis using less restrictive matching criteria, but a larger cohort (1,983,315 pairs; N=3,966,630 in total) also found that VE for symptomatic infection waned in those with underlying conditions, from 86% (95% CI, 84 to 87) at 15-30 days to 1% (95% CI, -147 to 33) with uncertainty increasing over time. Additionally, notable waning of vaccine effectiveness against symptomatic infection was observed among men and older individuals (≥ 65 years). In Figure 8, the purple line represents vaccine effectiveness against symptomatic infection in the total study population in the primary analysis, whereas the lime green and pink lines represent vaccine effectiveness against symptomatic infection in those with underlying conditions in the primary and secondary analyses, respectively. Of note, directly comparable data were not provided in all cases and hence only the available relevant data are plotted in Figure 8.

Figure 8: Vaccine effectiveness against severe disease and symptomatic infection over time, by underlying condition, as reported by Nordstrom et al.



Key: AZ – ChAdOx1 (AstraZeneca), PZ – BNT162b2 (Pfizer/BioNTech).

Effectiveness appeared to be more durable against severe COVID-19 than against symptomatic infection, however protection still waned over time (Figure 8). Vaccine effectiveness (any vaccine) reduced from 89% (95% CI, 83 to 93) at day 15-30 to 74% (95% CI, 47-87) by day 121-180 and to 42% (95% CI, -35 to 75) from day 181 and onwards, with sensitivity analyses showing notable waning among men, older frail individuals, and individuals with underlying conditions. In a sensitivity analysis, individuals >80 years old were excluded resulting in VE against severe disease being 80% (95% CI, 41 to 93), from day 181 onwards, potentially indicating the strong influence of age on waning protection. The secondary analysis, using a less stringently matched, but larger cohort (1,983,315 pairs; N=3,966,630 in total) supported the finding of reduced effectiveness against severe COVID-19 over time especially for older, frail individuals, men and individuals with underlying conditions. The aqua green and orange lines in Figure 8 represent vaccine effectiveness against hospitalisation or death in the secondary analysis, in the total study population and in those with underlying conditions, respectively.

There are certain limitations associated with this study. The first of which is related to outcome ascertainment bias specifically for symptomatic infection, as individuals

who were already vaccinated may not have sought a test for COVID-19 if they believed that they were immune, which may overestimate effectiveness for this outcome. Secondly, certain important confounders such as socioeconomic factors were not taken into account and therefore the possibility of residual and unmeasured confounding cannot be excluded; the impact of this limitation has an unclear impact on results. Of note there is considerable uncertainty in the estimates generated in this study, particularly beyond 150 days.

Israel

One study was identified from Israel where, to date, the immunisation programme has primarily been based on the BNT162b2 (Pfizer/BioNTech) vaccine.[54]

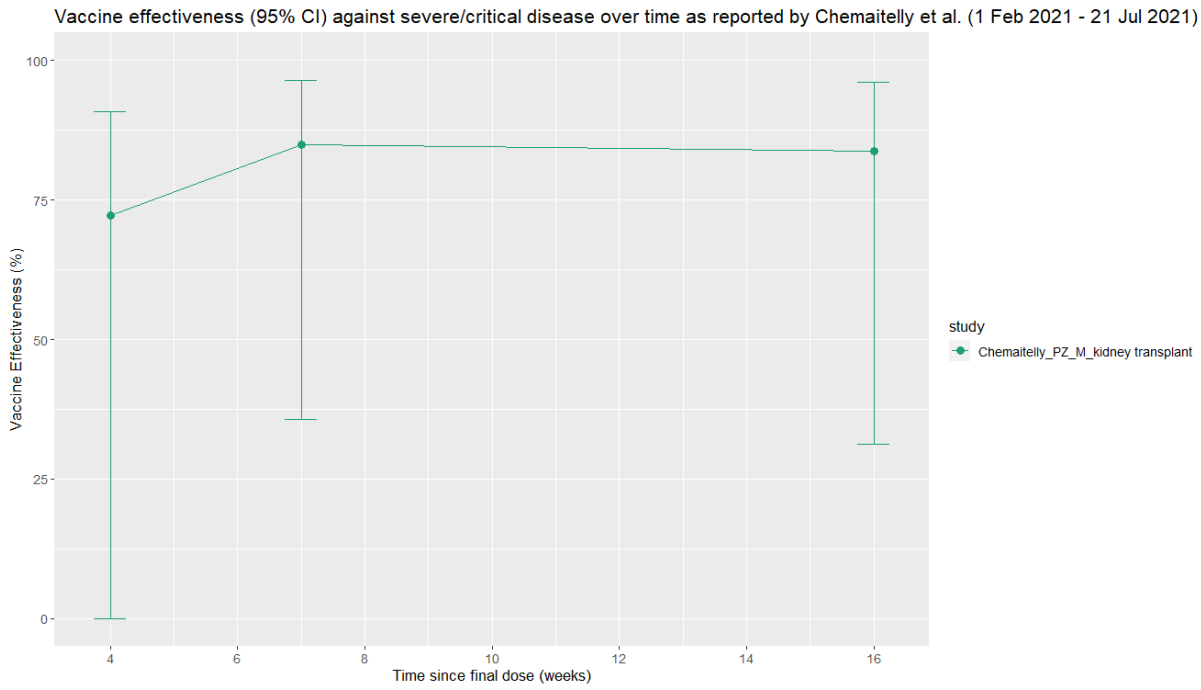
Saciuk et al.[54] examined the effectiveness of BNT162b2 (Pfizer/BioNTech) in a large retrospective study (N=1,650,885) in a period of high Alpha prevalence from 18 January to 25 April 2021. Crossover between groups was permitted. The median time since final vaccination dose was ten weeks. Effectiveness estimates were adjusted for gender, age, co-morbidity, geographical statistical area and calendar week. Vaccine effectiveness estimates were 93.4% (95% CI 91.9 to 94.7) and 91.1% (95% CI 86.7 to 94.1) for hospitalisation and COVID-19 related mortality, respectively. VE versus any infection was 93% (95% CI 92.6 to 93.4). VE point estimates for hospitalisation and mortality among those with hypertension, diabetes or obesity were not appreciably different from that of the overall population, with no significant differences observed, though the adjusted estimates are not reported. However, adjusted VE rates for infection were lower for study participants with hypertension (89.7%, CI: 88.6 to 91.7), diabetes (88.9%, CI: 87.3 to 90.2) and obesity (89.7%, 88.6 to 90.7) than total population VE for infection (93%, CI: 92.6 to 93.4), and this difference was found to be significant given the non-overlapping 95% confidence intervals.

Qatar

In a preprint, Chemaitelly et al.[46] reported on vaccine effectiveness estimates from Qatar in a retrospective cohort study of prior kidney transplant recipients receiving immunosuppressants with no prior RT-PCR confirmed infection. Out of 782 recipients, 506 were fully vaccinated at the index date or crossed over during the study period. The mean time since vaccination was ten weeks. The study was conducted during a period dominated by the Alpha and Beta variants. VE estimates were adjusted for age, sex, nationality group and competing risks. The observed VE

for severe disease was 72.3% (95% CI 0.0 to 90.9) and 83.8% (95% CI 31.3 to 96.2) at ≥14 and ≥56 days after the second dose, respectively (Figure 9). For any confirmed SARS-CoV-2 infection, VE was 46.6% (95% CI 0.0 to 73.7) and 73.9% (95% CI 33.0 to 89.9) at ≥14 and ≥56 days after the second dose, respectively. No COVID-19 deaths occurred. The authors note that the build-up of vaccine protection mirrored the slow development of antibodies in transplant recipients that has been previously reported.[46] However care must be taken when interpreting the analysis as there were limited adjustments for potential confounders, such as calendar time.

Figure 9: Vaccine effectiveness against severe/critical/fatal disease over time, as reported by Chemaitelly et al.



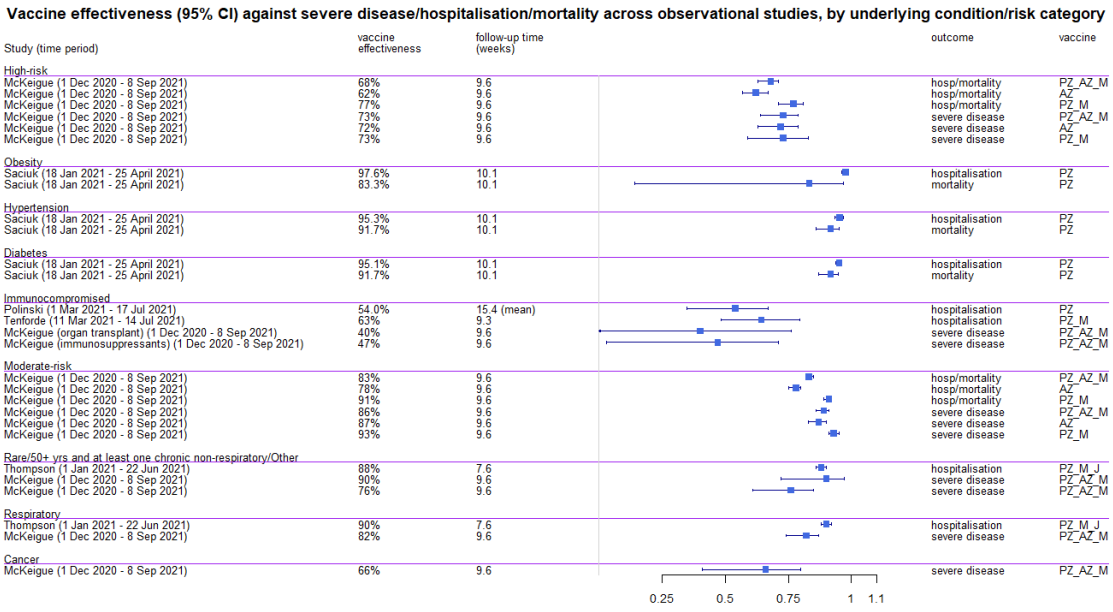
Key: M – mRNA-1273 (Moderna), PZ – BNT162b2 (Pfizer/BioNTech).

Summary of vaccine effectiveness in those with underlying conditions across observational studies

Five of the included observational studies reported outcomes for cumulative vaccine effectiveness against severe disease, hospitalisation or mortality specifically in those with underlying conditions or in risk categories (Figure 10).[35, 41, 49, 54, 55] Comparisons across observational studies are challenging given the differences in populations, analytical methods and vaccines, as well as the limited number of studies for each individual condition. In addition, the confidence intervals are wide and overlapping indicating a large degree of uncertainty. However, certain trends

can be observed, such as the consistently lower vaccine effectiveness against all outcomes (hospitalisation/mortality and severe disease) for all examined vaccines (BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) and or ChAdOx1 (AstraZeneca)) in high-risk compared with moderate-risk groups as reported by McKeigue et al..[49] Of note, across studies, those with immunocompromising conditions were found to have consistently lower vaccine effectiveness against hospitalisation[35, 55] or severe disease.[49]

Figure 10: Cumulative vaccine effectiveness against severe disease, hospitalisation or mortality, by underlying condition/risk category, across observational studies

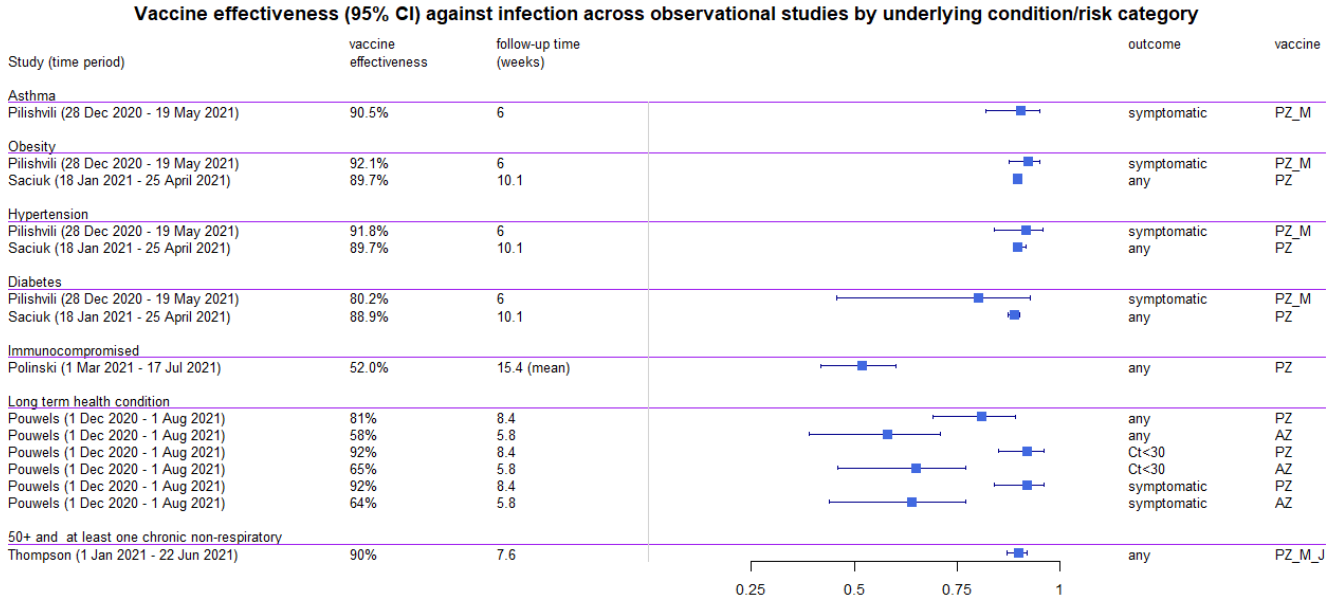


Key: AZ – ChAdOx1 (Astra Zeneca), hosp – hospitalisation, M – mRNA-1273(Moderna), PZ – BNT162b2 (Pfizer/BioNTech).

Five studies reported outcomes for cumulative vaccine effectiveness against SARS-CoV-2 infection, specifically in those with underlying conditions or in risk categories (Figure 11).[35, 41, 51, 53, 54] Limited inferences about individual conditions can be made from this forest plot given the issues relating to the heterogeneity of the studies as outlined above. However, substantially lower vaccine effectiveness against any SARS-CoV-2 infection is apparent among those with immunocompromising conditions.[35] Results from the study by Pouwels et al., which reported effectiveness in those with a range of long term health conditions, suggest lower vaccine effectiveness with the ChAdOx1 (AstraZeneca) vaccine compared with the BNT162b2 (Pfizer/BioNTech) vaccine against all three SARS-CoV-2 infection outcomes (any

infection, Ct value <30 or symptomatic infection).[53] However, there were differences in the populations who received the different vaccines.

Figure 11: Cumulative vaccine effectiveness against SARS-CoV-2 infection, by underlying condition/risk category, across observational studies



Key: AZ – ChAdOx1 (Astra Zeneca), Ct – Cycle Threshold, J – Ad26.COV2.S, M – mRNA-1273(Moderna), PZ – BNT162b2 (Pfizer/BioNTech).

Quality of included effectiveness studies

Quality appraisal was conducted using the NIH Quality Assessment Tools[26]

The quality appraisal of the six cohort studies,[35, 46, 48, 50, 53, 54] and the five case-control studies,[41, 44, 49, 51, 55] are described in Appendix B (Tables App.B1 and App.B2). Of the 11 observational studies, five were rated as good quality,[41, 44, 49, 51, 53] five were appraised as being of fair quality[46, 48, 50, 54, 55] and one of poor quality.[35]

The primary reasons for downgrading studies were for issues relating to measurement of the outcome (leading to outcome ascertainment bias) and confounding.

Outcome ascertainment bias can be a concern in studies of vaccine effectiveness as individuals aware of their vaccinated status may alter their testing behaviour. Routine testing regardless of vaccination or symptom status (such as that described in the study by Pouwels et al.[53]) reduces the likelihood of this bias. Outcome ascertainment bias is less of a concern for outcomes such as COVID-19 associated hospitalisation and death, thus studies were not automatically downgraded unless there were additional concerns.

Other concerns for which studies were downgraded related to unclear process for selecting the study population,[48] and inadequate controlling for confounders.[46, 48, 50]

Seven of the 11 observational studies are currently published as preprints,[35, 44, 46, 48-50, 54] and have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.

Discussion

Summary of findings

This review identified 18 reports describing 14 unique studies that examined vaccine efficacy or effectiveness in those with underlying conditions. Three of these studies were RCTs,[20, 21, 38, 45, 52, 56, 57] and the remaining 11 were observational study designs.[35, 41, 44, 46, 48-51, 53-55] All four currently licensed vaccines in Ireland were examined in the included studies, though the BNT162b2 (Pfizer/BioNTech) vaccine was the most commonly investigated in 12 of the 18 reports.[41, 44, 46, 48-56]

The aim of this review was to examine the change in efficacy and effectiveness of COVID-19 vaccination over time specifically in individuals with underlying health conditions. Overall, there was limited and inconsistent evidence regarding vaccine efficacy and effectiveness in those with underlying conditions. Across both primary (that is, severe disease and mortality) and secondary outcomes (that is, SARS-CoV-2 infection), overall vaccine efficacy or effectiveness in those with underlying conditions was found to be comparable to[41, 47, 48, 51, 52, 56] or lower than[35, 38, 44-46, 49, 53, 55] that in the general population. Additionally, there was considerable uncertainty in the estimates with often wide and overlapping confidence intervals. There were also nuances in the data. For example, when stratified by age, any significant reduction in protection against severe disease or mortality in those with underlying conditions was limited to older adults (either >60 or ≥ 65 years), with protection in younger age groups with underlying conditions found to be largely comparable to that observed in the general population.[38, 44] Where those with immunocompromising conditions were analysed as a subgroup, vaccine effectiveness against both primary and secondary outcomes was found to be reduced.[35, 55] Hence it is unclear whether any reduction in vaccine efficacy or effectiveness in those with underlying conditions is driven by age or is specific to those with immunocompromising conditions.

There was some evidence that vaccine effectiveness, particularly against infection, waned over time in those with underlying conditions.[35, 44, 50, 53, 55] However, it is unclear whether this waning occurs any faster than in the general population. Based on data from Swedish nationwide registries, Nordstrom et al. who had up to nine months follow-up, reported greater reductions in vaccine effectiveness, particularly against infection, in those with underlying conditions, compared with the general population.[50] In a Public Health England study, greater reductions in vaccine effectiveness against hospitalisation were observed in those in a clinical risk group, compared with those not in a clinical risk group, but only in those who were 65 years and older. In the same study, the ChAdOx1 (AstraZeneca) vaccine was

associated with lower protection compared with BNT162b2 (Pfizer/BioNTech) vaccine across all age groups, particularly for those in clinical risk groups.[44] Similarly, a study by the CDC only found significant differences in the rate of waning in those with immunocompromising conditions.[55] In contrast, among a population of immunosuppressed kidney transplant recipients in Qatar, Chemaitelly et al. reported an initially low, but increasing protection over time, against severe, critical, or fatal COVID-19 disease, reaching 83.8% (95% CI, 31.3 to 96.2) eight weeks after the second dose of either BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) vaccine.[46] The authors noted that most vaccine breakthrough infections occurred in the first few weeks after receiving the first and or second dose.

Findings in context

The World Health Organization (WHO) have recommended that the primary goal of immunisation in the COVID-19 pandemic remains to protect against hospitalisation, severe disease and death.[63] Individuals with underlying conditions are at greater risk of severe disease outcomes following infection with SARS-CoV-2, and they constitute a larger proportion of the critical and hospitalised cases. Irish data from the Health Protection Surveillance Centre (HPSC) reports that 75% (n=195) of all COVID-19 cases admitted to intensive care units (ICU) in Ireland between 27 June and 2 October 2021 had an underlying condition.[64] An Irish study by Bennett et al. using HPSC data found chronic heart disease, a BMI ≥40kg/m^2 and male sex were associated with a significantly higher risk of mortality, hospitalisation and ICU admission. Additionally, diagnosis of a chronic neurological condition (OR 1.41; 95% CI: 1.17 to 1.69), chronic kidney disease (OR 1.74; 95% CI:1.35 to 2.24) and cancer (OR 2.77; 95% CI:2.21 to 3.47) were significantly associated with a higher risk of mortality among all cases, with similar patterns of association observed for mortality among hospitalised cases.[65] In the Scottish study outlined by McKeigue et al., those with designated risk conditions or in a clinically extremely vulnerable group accounted for 88% of critical cases and 77% of hospitalised cases.[59]

Studies suggest that immunocompromised individuals who receive COVID-19 vaccination might not be as protected against severe COVID-19 outcomes as immunocompetent individuals.[66] A study by Di Fusco et al. evaluated COVID-19 breakthrough infections among immunocompromised individuals.[67] Of 1,277,747 individuals aged 16 years or older included in this study who received two BNT162b2 doses, a total of 225,796 (17.7%) were identified as immunocompromised. The proportion of breakthrough infections was three times higher in the immunocompromised cohort compared to the non-immunocompromised cohort

(N=374 (0.18%) vs. N=604 (0.06%); unadjusted incidence rates were 0.89 and 0.34 per 100 person-years, respectively). Organ transplant recipients had the highest incidence rate; those with greater than one immunocompromising conditions, antimetabolite medication usage, primary immunodeficiencies, and haematologic malignancies also had higher incidence rates compared to the overall immunocompromised cohort. Incidence rates in older (≥65 years old) immunocompromised individuals were generally higher than younger immunocompromised individuals (<65 years).

Individuals with a compromised immune system, as well as all those aged 60 years and above, were eligible for an additional or booster dose of the COVID-19 vaccine in Ireland, respectively, at the time of this review (4 November 2021).[68] Evidence was found to suggest that reductions in effectiveness seen in those with underlying health conditions may largely be driven by older age or specifically those with immunocompromising conditions. Therefore, it is unclear if effectiveness is reduced in younger cohorts with non-immunocompromising underlying conditions. However, given the significant burden of SARS-CoV-2 infection on individuals with underlying conditions, any small decrease in protection is likely to have a substantial outsized impact in this population.

Five of the included observational studies stated that they were conducted when the Delta variant was dominant.[35, 44, 49, 50, 53] Two of these studies found that vaccine effectiveness was reduced with the Delta variant in comparison to the Alpha variant,[44, 53] two reported high levels of vaccine waning when Delta was the dominant variant,[49, 50] and one study reported high levels of protection despite widespread circulation of the Delta variant.[35] However, it is uncertain whether this apparent reduction in vaccine effectiveness was due to waning vaccine-induced immunity over time, immune evasion properties of the Delta variant, or residual confounding in these observational studies. Of note, all of the RCTs were conducted prior to the emergence of the Delta variant.

Strengths and Limitations

The main strength of the review is that it examines clinical outcomes in preference to biochemical outcomes such as antibody titres which do not necessarily predict reductions in effect over time.[69] In this way, primacy is given to outcomes that are of greater relevance to the public and policymakers. Another strength is the comprehensiveness of the evidence collated with regulatory reports examined to provide supplementary efficacy data on subgroups and mortality endpoints not available in the pivotal RCT publications.

This review is subject to several important limitations. These relate to the type of review conducted ('rapid review'), which was limited by the time constraints associated, and the biases considered likely to be present in the studies included in this review. Although efforts have been made to identify all available evidence from peer-reviewed and preprint publications, it is important to note that evidence is rapidly emerging in this area and that the conclusions of the review may change as further longer term studies are published.

Seven of the 11 observational studies are currently published as preprints.[46, 54, 70-81] Therefore, they have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication. For preprints, it has been highlighted that while some of the details may change prior to formal publication and that there is a selective emphasis on particular results, preprint reports such as those identified in this review provide a partial and useful snapshot of the emerging literature.[69]

As it was beyond the scope of this review to conduct an analysis of the comparative efficacy and effectiveness of the COVID-19 vaccines, any differences observed between the vaccines need to be interpreted with caution. Differences in populations and study design can lead to differences in the estimated efficacy and effectiveness across studies.

Observational studies are prone to bias from lack of adjustment for known and unknown confounders. For example, vaccination status may lead to different behaviours between vaccinated and unvaccinated individuals and therefore different levels of exposure to the virus. Vaccinated individuals may have greater levels of socialisation and increased exposure to SARS-CoV-2 compared to the unvaccinated group due to perceived lower levels of risk after vaccination or because of differences in the local restrictions that apply. For example, in Israel only vaccinated individuals could obtain a green pass to attend large events and certain public spaces.[82] Conversely, individuals who choose not to be vaccinated may also have lower adherence to other COVID-19 mitigations measures such as the wearing of face masks. None of the studies identified were able to control for differences in behaviours that may lead to differences in the levels of exposure to the virus between groups. Test-negative designs such as that applied by Public health England[44] and Thompson et al., (US study)[83] which compare the vaccination status of people who tested positive and those who tested negative, seek to reduce confounding due to health-seeking behaviour. However, they do not prevent distortion of results due to collider bias, as the probability that individuals who have a mild infection will be tested may be influenced by their vaccination status.[69]

Estimating changes in effectiveness over time in real-world observational studies is difficult for several reasons. The comprehensive rollout of COVID-19 vaccines during the conduct of all the included observational studies led to low numbers in the unvaccinated group, making any comparison between groups less certain over time. Furthermore, the vaccine rollout schedule varied by country, with typically those at highest risk either due to high risk of exposure (healthcare workers) or risk of severe disease outcomes offered vaccination earlier than those deemed to be at lower risk. It is also important to consider the potential impact of the emergence of new variants or the prevalence of existing variants of concern on estimates of the duration of vaccine effectiveness. Changing levels of societal restrictions may also impact on the estimates of vaccine effectiveness over time. A relaxation of restrictions potentially increases the likelihood of exposure to SARS-CoV-2, whereas the implementation of stricter guidance may limit exposure. Where restrictions are applied differently to vaccinated and unvaccinated individuals, this may lead to a lack of comparable exposure levels between groups and thus bias the estimates. Additionally, the time-dependent nature of restrictions and their interaction with the level of the virus circulating in the community, will also have an impact when estimating the duration of effectiveness, as the exposure levels between groups may change over time.

Specifically in relation to examining vaccine efficacy and effectiveness in those with underlying conditions, a particular limitation is the smaller sample size of these subgroups. As a result, substantial uncertainty in the estimates was observed, with wide and overlapping confidence intervals noted, particularly as the length of follow-up increased, or the size of the group decreased. Longer follow-up of larger cohorts are required to provide better information regarding long term vaccine effectiveness in those with underlying conditions.

Evidence gaps

The following were the main evidence gaps identified on this topic:

- vaccine efficacy or effectiveness in those with underlying conditions (combined and as individual conditions) beyond six months
- comparative effectiveness between different vaccines in those with underlying conditions
- the impact of new variants of concern on vaccine efficacy or effectiveness.

Conclusion

Overall, the evidence suggests that vaccination against COVID-19 continues to provide robust protection against severe disease and mortality for at least six months post-vaccination. However, there are data to suggest potential waning of vaccine effectiveness for severe disease, mortality and any infection in individuals with underlying conditions, particularly for those aged 65 years and older, and in those with immunocompromising conditions. National and international data support a higher risk of severe disease outcomes in older individuals and those with underlying health conditions. Given this, and the noted lower initial vaccine efficacy and effectiveness for these populations in many of the included studies, any additional reduction in effect would be of concern. Generally, there is ongoing uncertainty regarding a number of factors including the durability of protective immunity beyond six months, the comparative effectiveness of the vaccines and the impact of new variants of concern. It is important to note that evidence is rapidly emerging in this area and that the conclusions of this review may change as longer-term studies are published.

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Appendix A Excluded studies with reasons

Table App.A6.1 (Original version 30 September 2021, n=406 studies)

Study	Title	DOI	Reason for exclusion
Abe 2021	Neutralizing antibody responses to SARS-CoV-2 variants in vaccinated Ontario long-term care home residents and workers	10.1101/2021.08.06.21261721	Exclusion reason: Wrong outcomes;
Abu-Raddad 2021	Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants	10.1056/NEJMc2104974	Exclusion reason: Opinion piece;
Achiron 2021	COVID-19 vaccination in patients with multiple sclerosis: What we have learnt by February 2021	http://dx.doi.org/10.1177/13524585211003476	Exclusion reason: Insufficient follow-up;
Addeo 2021	Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer	http://dx.doi.org/10.1016/j.ccell.2021.06.009	Exclusion reason: Wrong outcomes;
Adhikari 2021	COVID-19 Vaccination in Pregnant and Lactating Women	http://dx.doi.org/10.1001/jama.2021.1658	Exclusion reason: Wrong study design;
Akova 2021	A randomized, double-blind, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of SARS-CoV-2 vaccine (inactivated, Vero cell): a structured summary of a study protocol for a randomised controlled trial	http://dx.doi.org/10.1186/s13063-021-05180-1	Exclusion reason: Wrong intervention;
Aleem 2021	Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19)		Exclusion reason: Opinion piece;
Alharbi 2021	Effectiveness of COVID-19 Vaccines: Eight Months Post Single Dose Vaccination	10.1101/2021.09.18.21263262	Exclusion reason: Wrong intervention AZD1222 vaccines

			between 19th December 2020 and 14th April 2021;
Ali 2021	Previous COVID-19 infection and antibody levels after vaccination	10.1101/2021.09.04.21263121	Exclusion reason: Wrong outcomes;
Alikhani 2021	Efficacy of new treatment modalities in patients with covid-19, qaemshahar razi hospital 2020		Exclusion reason: Wrong intervention;
AlKaabi 2021	Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial	http://dx.doi.org/10.1001/jama.2021.8565	Exclusion reason: Wrong intervention;
Alkhafaji 2021	The Impact of COVID-19 Vaccine on Rate of Hospitalization and Outcome of COVID-19 Infection in a Single Center in the Eastern Province of Saudi Arabia	10.21203/rs.3.rs-903562/v1	Exclusion reason: Insufficient Sample Size;
Almasri 2021	Assessing Vaccine Protection for Older Adults with Diabetes: A Systematic Review	http://dx.doi.org/10.1177/01939459211005710	Exclusion reason:
AlQahtani 2021	Morbidity and mortality from COVID-19 post-vaccination breakthrough infections in association with vaccines and the emergence of variants in Bahrain		Exclusion reason:
Al-Qerem 2021	COVID-19 Vaccination Acceptance and Its Associated Factors Among a Middle Eastern Population	http://dx.doi.org/10.3389/fpubh.2021.632914	Exclusion reason: Wrong outcomes;
Amodio 2021	Antibodies responses to sars-cov-2 in a large cohort of vaccinated subjects and seropositive patients	http://dx.doi.org/10.3390/vaccines9070714	Exclusion reason: Insufficient follow-up;
Andrejko 2021	Prevention of COVID-19 by mRNA-based vaccines within the general population of California	10.1101/2021.04.08.21255135	Exclusion reason: Insufficient follow-up;
Angel 2021	Association between Vaccination with BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections among Healthcare Workers	http://dx.doi.org/10.1001/jama.2021.7152	Exclusion reason: Insufficient follow-up;

Anonymous 2020	Experts Discuss COVID-19: Vaccine Allocation, Placebo Groups, and More	http://dx.doi.org/10.1001/jama.2020.24075	Exclusion reason: Wrong study design;
Anonymous 2021	Correction to Lancet Infect Dis 2021; published online June 23. https://doi.org/10.1016/ S1473-3099(21)00330-3 (The Lancet Infectious Diseases, (S1473309921003303), (10.1016/S1473-3099(21)00330-3))	http://dx.doi.org/10.1016/S1473-3099%2821%2900397-2	Exclusion reason: Wrong intervention;
Antonelli 2021	Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study	http://dx.doi.org/10.1016/S1473-3099%2821%2900460-6	Exclusion reason: Insufficient follow-up;
Antrim 2021	Patients receiving nucleoside reverse transcriptase inhibitors at lower risk of COVID-19		Exclusion reason: Wrong intervention;
Aran 2021	Estimating real-world COVID-19 vaccine effectiveness in Israel using aggregated counts	10.1101/2021.02.05.21251139	Exclusion reason: Wrong comparator;
Armstrong 2021	Repeat positive SARS-CoV-2 RNA testing in nursing home residents during the initial 9 months of the COVID-19 pandemic: an observational retrospective analysis	10.1016/j.lana.2021.100054	Exclusion reason: Wrong intervention;
Azamgarhi 2021	BNT162b2 vaccine uptake and effectiveness in UK healthcare workers - a single centre cohort study	http://dx.doi.org/10.1038/s41467-021-23927-x	Exclusion reason: Wrong intervention;
Baden 2021	Covid-19 in the Phase 3 Trial of mRNA-1273 During the Delta-variant Surge	10.1101/2021.09.17.21263624	Exclusion reason: Wrong intervention;
Bahl 2021	Vaccination reduces need for emergency care in breakthrough COVID-19 infections: A multicenter cohort study	10.1016/j.lana.2021.100065	Exclusion reason: Time since vaccination unclear;
Balicer 2021	Effectiveness of the BNT162b2 mRNA COVID-19 Vaccine in Pregnancy	10.21203/rs.3.rs-665725/v1	Exclusion reason: Insufficient follow-up;

BaniHani 2021	Medical students and risk of COVID-19 infection: A descriptive cross-sectional study from the University of Jordan	http://dx.doi.org/10.1016/j.amsu.2021.102775	Exclusion reason: Wrong intervention;
Barbeau 2021	Comparative analysis of human immune responses following SARS-CoV-2 vaccination with BNT162b2, mRNA-1273, or Ad26.COV2.S	10.1101/2021.09.21.21262927	Exclusion reason: Wrong outcomes;
Barlow 2021	Effectiveness of COVID-19 Vaccines Against SARS-CoV-2 Infection During a Delta Variant Epidemic Surge in Multnomah County, Oregon, July 2021	10.1101/2021.08.30.21262446	Exclusion reason: Time since vaccination unclear;
Bar-On 2021	BNT162b2 vaccine booster dose protection: A nationwide study from Israel	10.1101/2021.08.27.21262679	Exclusion reason: Wrong intervention;
Baum 2021	Effectiveness of vaccination against SARS-CoV-2 infection and Covid-19 hospitalization among Finnish elderly and chronically ill â€“ An interim analysis of a nationwide cohort study	10.1101/2021.06.21.21258686	Exclusion reason: Time since vaccination unclear;
Bayart 2021	Waning of IgG, total and neutralizing antibodies 6 months post-vaccination with BNT162b2 in healthcare workers	10.21203/rs.3.rs-862966/v1	Exclusion reason: Wrong outcomes;
Bergman 2021	Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial	10.1101/2021.09.07.21263206	Exclusion reason: Wrong outcomes;
Bermingham 2021	Estimating the effectiveness of first dose of COVID-19 vaccine against mortality in England: a quasi-experimental study	10.1101/2021.07.12.21260385	Exclusion reason: Wrong intervention;
Bernal 2021	Effectiveness of COVID-19 vaccines against the B.1.617.2 variant	10.1101/2021.05.22.21257658	Exclusion reason: Time since vaccination unclear;

Bernal 2021	Effectiveness of BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on mortality following COVID-19	10.1101/2021.05.14.21257218	Exclusion reason: Time since vaccination unclear;
Bernal 2021	Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England	10.1101/2021.03.01.21252652	Exclusion reason: Insufficient follow-up;
Bertrand 2021	Antibody and t cell response to sars-cov-2 messenger rna bnt162b2 vaccine in kidney transplant recipients and hemodialysis patients	http://dx.doi.org/10.1681/ASN.2021040480	Exclusion reason: Wrong outcomes;
Bhattacharya 2021	Evaluation of the dose-effect association between the number of doses and duration since the last dose of COVID-19 vaccine, and its efficacy in preventing the disease and reducing disease severity: A single centre, cross-sectional analytical study from In	http://dx.doi.org/10.1016/j.dsx.2021.102238	Exclusion reason: Insufficient Sample Size;
Bianchi 2021	BNT162b2 mRNA COVID-19 Vaccine Effectiveness in the Prevention of SARS-CoV-2 Infection: A Preliminary Report	10.1093/infdis/jiab262	Exclusion reason: Time since vaccination unclear;
BjÃ¶rk 2021	Effectiveness of the BNT162b2 vaccine in preventing COVID-19 in the working age population â€“ first results from a cohort study in Southern Sweden	10.1101/2021.04.20.21254636	Exclusion reason: Insufficient follow-up;
Blain 2021	Prior Covid-19 and high RBD-IgG levels correlate with protection against VOC-Î´ SARS-CoV-2 infection in vaccinated nursing home residents	10.1101/2021.09.21.21263880	Exclusion reason: Wrong outcomes;
Blain 2021	Antibody response after one and two jabs of the BNT162b2 vaccine in nursing home residents: The CONsort-19 study	http://dx.doi.org/10.1111/all.15007	Exclusion reason: Wrong outcomes;
Blaiszik 2021	The Delta Variant Had Negligible Impact on COVID-19 Vaccine Effectiveness in the USA	10.1101/2021.09.18.21263783	Exclusion reason: Time since vaccination unclear;

Breznik 2021	Antibody Responses 3-5 Months Post-Vaccination with mRNA-1273 or BNT163b2 in Nursing Home Residents	10.1101/2021.08.17.21262152	Exclusion reason: Wrong outcomes;
Britton 2021	Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks - Connecticut, December 2020-February 2021	http://dx.doi.org/10.15585/mmwr.mm7011e3	Exclusion reason: Insufficient follow-up;
Brillany 2021	Seroprevalence of antibody to S1 spike protein following vaccination against COVID-19 in patients receiving hemodialysis: a call to arms	http://dx.doi.org/10.1016/j.kint.2021.04.008	Exclusion reason: Insufficient Sample Size;
Broseta 2021	Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-CoV-2 Vaccines Administered to Hemodialysis Patients	http://dx.doi.org/10.1053/j.ajkd.2021.06.002	Exclusion reason: Wrong outcomes;
Brosh-Nissimov 2021	BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel	http://dx.doi.org/10.1016/j.cmi.2021.06.036	Exclusion reason: Insufficient follow-up;
Bukhari 2021	Real-World Effectiveness of COVID-19 Vaccines: the Diverging Pattern of COVID-19 Cases and Deaths in Countries with High Vaccination Rates	10.2139/ssrn.3863750	Exclusion reason: Wrong comparator;
Butsch 2021	COVID-19 Vaccines are Effective in People with Obesity: A Position Statement from The Obesity Society	http://dx.doi.org/10.1002/oby.23251	Exclusion reason: Time since vaccination unclear;
Butt 2021	Effectiveness of the SARS-CoV-2 mRNA Vaccines in Pregnant Women	10.21203/rs.3.rs-622782/v1	Exclusion reason: Time since vaccination unclear;
Butt 2021	SARS-CoV-2 Vaccine Effectiveness in a High-Risk National Population in a Real-World Setting	10.7326/M21-1577	Exclusion reason: Insufficient follow-up;
Cabezas 2021	Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study	10.1136/bmj.n1868	Exclusion reason: Wrong comparator;

Cabreira 2021	Multiple sclerosis, disease-modifying therapies and COVID-19: A systematic review on immune response and vaccination recommendations	http://dx.doi.org/10.3390/vaccines9070773	Exclusion reason: Wrong study design;
Cai 2021	A comprehensive analysis of the efficacy and safety of COVID-19 vaccines	10.1016/j.ymthe.2021.08.001	Exclusion reason: Wrong study design;
Canaday 2021	Significant reduction in humoral immunity among healthcare workers and nursing home residents 6 months after COVID-19 BNT162b2 mRNA vaccination	10.1101/2021.08.15.21262067	Exclusion reason: Wrong outcomes;
Cao 2021	Genetic mismatch explains sizable variation of COVID-19 vaccine efficacy in clinical trials	10.1101/2021.04.22.21254079	Exclusion reason: Wrong outcomes;
Carazo 2021	Single-dose mRNA vaccine effectiveness against SARS-CoV-2 in healthcare workers extending 16 weeks post-vaccination: a test-negative design from Quebec, Canada	10.1101/2021.07.19.21260445	Exclusion reason: Wrong intervention;
Carr 2021	COVID-19 Vaccines: Preparing for Vaccination in the Context of Clinical Oncology Care	http://dx.doi.org/10.1188/21.CJON.76-84	Exclusion reason: Wrong study design;
CDC 2021	COVID-19 Vaccine Breakthrough Infections Reported to CDC - United States, January 1-April 30, 2021	10.15585/mmwr.mm7021e3	Exclusion reason: Wrong comparator;
Cekauskiene 2021	Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study	http://dx.doi.org/10.1016/S2352-3026%2821%2900169-1	Exclusion reason: Wrong outcomes;
Cerqueira-Silva 2021	Influence of age on the effectiveness and duration of protection in Vaxzevria and CoronaVac vaccines	10.1101/2021.08.21.21261501	Exclusion reason: Wrong comparator;
Chambers 2021	Influenza vaccination and interruption of methotrexate in adult patients in the COVID-19 era: an ongoing dilemma	http://dx.doi.org/10.1016/S2665-9913%2820%2930392-1	Exclusion reason: Wrong intervention;

Chandrashekar 2021	Immunogenicity of the Ad26.COV2.S Vaccine for COVID-19	http://dx.doi.org/10.1001/jama.2021.3645	Exclusion reason: Insufficient Sample Size;
Charmetant 2021	Comparison of the immune responses of renal transplant recipients after COVID-19 versus SARS-CoV2 vaccination	http://dx.doi.org/10.1111/tri.13944	Exclusion reason: Wrong outcomes;
Chawla 2021	Comparative Analysis of Susceptibility and Severity of COVID-19 in Countries from the Eastern and the Western World Till March '21	http://dx.doi.org/10.1177/11786361211041367	Exclusion reason: Wrong study design;
Chemaitelly 2021	mRNA-1273 COVID-19 vaccine effectiveness against the B.1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar	http://dx.doi.org/10.1038/s41591-021-01446-y	Exclusion reason: Time since vaccination unclear;
Chen 2021	Differential antibody dynamics to SARS-CoV-2 infection and vaccination	10.1101/2021.09.09.459504	Exclusion reason: Wrong outcomes;
Chen 2021	Prediction of long-term kinetics of vaccine-elicited neutralizing antibody and time-varying vaccine-specific efficacy against the SARS-CoV-2 Delta variant by clinical endpoint	10.1101/2021.09.23.21263715	Exclusion reason: Wrong outcomes;
Chen 2021	Prediction of vaccine efficacy of the Delta variant	10.1101/2021.08.26.21262699	Exclusion reason: Wrong outcomes;
Cherian 2021	Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey	http://dx.doi.org/10.1007/s00296-021-04917-0	Exclusion reason: Wrong outcomes;
Chin 2021	Effectiveness of COVID-19 Vaccines among Incarcerated People in California State Prisons: A Retrospective Cohort Study	10.1101/2021.08.16.21262149	Exclusion reason: Insufficient follow-up;
Chodick 2021	The Effectiveness of the First Dose of BNT162b2 Vaccine in Reducing SARS-CoV-2 Infection: Real-World Evidence	10.2139/ssrn.3769977	Exclusion reason: Insufficient follow-up;

Chodick 2021	The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence	10.1101/2021.01.27.21250612	Exclusion reason: Insufficient follow-up;
Chu 2021	A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine	http://dx.doi.org/10.1016/j.vaccine.2021.02.007	Exclusion reason: Wrong outcomes;
Chung 2021	Effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes in Ontario, Canada: a test-negative design study	10.1101/2021.05.24.21257744	Exclusion reason: Duplicate;
Chung 2021	Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines Against Symptomatic SARS-CoV-2 Infection and Severe COVID-19 Outcomes in Ontario, Canada	10.2139/ssrn.3845993	Exclusion reason: Insufficient follow-up;
Clemens 2021	Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil; an exploratory analysis of a randomised controlled trial	10.21203/rs.3.rs-654257/v1	Exclusion reason: Time since vaccination unclear;
Committee for Medicinal Products for Human Use (CHMP)	European Medicines Agency. European Public Assessment Report: Pfizer/BioNTech (22 July 2021)	https://www.ema.europa.eu/en/documents/variation-report/comirnaty-h-c-5735-ii-0030-epar-assessment-report-variation_en.pdf	Exclusion reason: Insufficient follow-up;
Committee for Medicinal Products for Human Use (CHMP)	European Medicines Agency. European Public Assessment Report: Pfizer/BioNTech (19 February 2021)	https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf	Exclusion reason: Insufficient follow-up;

Committee for Medicinal Products for Human Use (CHMP)	CHMP extension of indication variation assessment report: SpikeVax	https://www.ema.europa.eu/en/documents/variation-report/spikevax-previously-covid-19-vaccine-moderna-epar-chmp-extension-indication-variation-assessment_en.pdf	Exclusion reason: Insufficient follow-up;
Committee for Medicinal Products for Human Use (CHMP)	European Medicines Agency. European Public Assessment Report: COVID-19 Vaccine Janssen	https://www.ema.europa.eu/en/documents/assessment-report/covid-19-vaccine-janssen-epar-public-assessment-report_en.pdf	Exclusion reason: Insufficient follow-up;
Committee for Medicinal Products for Human Use (CHMP)	European Medicines Agency. European Public Assessment Report: COVID-19 Vaccine AstraZeneca	https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf	Exclusion reason: Insufficient follow-up;
Consortium 2021	Association of COVID-19 vaccines ChAdOx1 and BNT162b2 with major venous, arterial, and	10.1101/2021.08.18.21262222	Exclusion reason: Wrong outcomes;

	thrombocytopenic events: whole population cohort study in 46 million adults in England		
Corchado-Garcia 2021	Real-World Effectiveness of Ad26.COV2.S Adenoviral Vector Vaccine for COVID-19	10.2139/ssrn.3835737	Exclusion reason: Insufficient follow-up;
Cornberg 2021	EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients	http://dx.doi.org/10.1016/j.jhep.2021.01.032	Exclusion reason: Wrong outcomes;
COVID-19 National Incident Room Surveillance Team (Australia) 2021	COVID-19 Australia: Epidemiology Report 44: Reporting period ending 20 June 2021	http://dx.doi.org/10.33321/cdi.2021.45.34	Exclusion reason: Wrong study design;
COVID-19 National Incident Room Surveillance Team (Australia) 2021	COVID-19 Australia: Epidemiology Report 43 Reporting period ending 6 June 2021 - Reporting period ending 6 June 2021	http://dx.doi.org/10.33321/cdi.2021.45.33	Exclusion reason: Wrong study design;
COVID-19 National Incident Room Surveillance Team (Australia) 2021	COVID-19 Australia: Epidemiology Report 42 Reporting period ending 23 May 2021	http://dx.doi.org/10.33321/cdi.2021.45.30	Exclusion reason: Wrong study design;
COVID-19 National Incident Room Surveillance Team (Australia) 2021	COVID-19 Australia: Epidemiology Report 41: Reporting period ending 9 May 2021	http://dx.doi.org/10.33321/cdi.2021.45.26	Exclusion reason: Wrong study design;
COVID-19 National Incident Room Surveillance Team (Australia) 2021	COVID-19 Australia: Epidemiology Report 40: Reporting period ending 25 April 2021	http://dx.doi.org/10.33321/cdi.2021.45.25	Exclusion reason: Wrong study design;
COVID-19 National Incident Room	COVID-19 Australia: Epidemiology Report 38 Reporting period ending 28 March 2021	http://dx.doi.org/10.33321/cdi.2021.45.19	Exclusion reason: Insufficient follow-up;

Surveillance Team (Australia) 2021			
Cox 2021	An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status	http://dx.doi.org/10.1093/cid/ciab608	Exclusion reason: Insufficient follow-up;
Cromer 2021	SARS-CoV-2 variants: levels of neutralisation required for protective immunity	10.1101/2021.08.11.21261876	Exclusion reason: Wrong outcomes;
Cuesta-Lazaro 2021	Vaccinations or Non-Pharmaceutical Interventions: Safe Reopening of Schools in England	10.1101/2021.09.07.21263223	Exclusion reason: Wrong outcomes;
Cupaiolo 2021	Six-month interim analysis of ongoing immunogenicity surveillance of the mRNA-1273 vaccine in healthcare workers: A third dose is expected	http://dx.doi.org/10.1016/j.jinf.2021.08.031	Exclusion reason: Wrong outcomes;
Daghfal 2021	The initial impact of a national BNT162b2 mRNA COVID-19 vaccine rollout	http://dx.doi.org/10.1016/j.ijid.2021.05.021	Exclusion reason: Insufficient follow-up;
D'Agostini 2021	What is the probability that a vaccinated person is shielded from Covid-19? A Bayesian MCMC based reanalysis of published data with emphasis on what should be reported as `efficacy'		Exclusion reason: Wrong study design;
Dailey 2021	Antibody Responses to SARS-CoV-2 after Infection or Vaccination in Children and Young Adults with Inflammatory Bowel Disease	10.1101/2021.06.12.21258810	Exclusion reason: Wrong outcomes;
Dal-Re 2021	Being fair to participants in placebo-controlled COVID-19 vaccine trials	http://dx.doi.org/10.1038/s41591-021-01338-1	Exclusion reason: Wrong study design;
Damasceno 2021	The impact of Vaccination worldwide on SARS-CoV-2 infection: A Review on Vaccine Mechanisms, Results of Clinical Trials, Vaccinal Coverage and Interactions with Novel Variants	http://dx.doi.org/10.2174/0929867328666210902094254	Exclusion reason: Wrong study design;
Dean 2021	Hospital admissions due to COVID-19 in Scotland after one dose of vaccine	10.1016/S0140-6736(21)00765-0	Exclusion reason: Opinion piece;

Debrabant 2021	The Cost-Effectiveness of a COVID-19 Vaccine in a Danish Context	10.2139/ssrn.3773381	Exclusion reason: Wrong outcomes;
deCellÃ¨s 2021	Immunological heterogeneity informs estimation of the durability of COVID-19 vaccine protection		Exclusion reason: Wrong study design;
Deepak 2021	Effect of Immunosuppression on the Immunogenicity of mRNA Vaccines to SARS-CoV-2 : A Prospective Cohort Study	http://dx.doi.org/10.7326/M21-1757	Exclusion reason: Wrong outcomes;
DeLeo 2021	Effectiveness of the mRNA BNT162b2 vaccine against SARS-CoV-2 severe infections in the Israeli over 60 population: a temporal analysis done by using the national surveillance data	10.1101/2021.09.27.21264130	Exclusion reason: Wrong study design;
Dispinseri 2021	Seasonal betacoronavirus antibodies expansion post BNT161b2 vaccination associates with reduced SARS-CoV-2 VoCs neutralization	10.1101/2021.08.15.21262000	Exclusion reason: Wrong outcomes;
Dispinseri 2021	Neutralizing antibody responses to SARS-CoV-2 in symptomatic COVID-19 is persistent and critical for survival	10.1038/s41467-021-22958-8	Exclusion reason: Wrong outcomes;
Domi 2021	The BNT162b2 vaccine is associated with lower new COVID-19 cases in nursing home residents and staff	10.1111/jgs.17224	Exclusion reason: Wrong intervention;
Donzelli 2021	Comparison of hospitalizations and deaths from COVID-19 2021 versus 2020 in Italy: surprises and implications	10.12688/f1000research.73132.1	Exclusion reason: Wrong study design;
Doti 2021	The Impact of Vaccinations on COVID-19 Case Rates at the State Level	10.2139/ssrn.3927364	Exclusion reason: Wrong study design;
Duncan 2020	Covid-19 vaccine: We are sleepwalking into a massive prospective cohort study	http://dx.doi.org/10.1136/bmj.m4568	Exclusion reason: Wrong study design;
Edara 2021	Neutralizing Antibodies against SARS-CoV-2 Variants after Infection and Vaccination	http://dx.doi.org/10.1001/jama.2021.4388	Exclusion reason: Wrong outcomes;
Ella 2021	Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind,	http://dx.doi.org/10.1016/S1473-	Exclusion reason: Wrong outcomes;

	randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial	3099%2821%2900070-0	
Ella 2021	Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial	http://dx.doi.org/10.1016/S1473-3099%2820%2930942-7	Exclusion reason: Wrong outcomes;
Elliott 2021	REACT-1 round 13 final report: exponential growth, high prevalence of SARS-CoV-2 and vaccine effectiveness associated with Delta variant in England during May to July 2021	10.1101/2021.09.02.21262979	Exclusion reason: Wrong study design;
Emary 2021	Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial	http://dx.doi.org/10.1016/S0140-6736%2821%2900628-0	Exclusion reason: Time since vaccination unclear;
Emary 2021	Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine Against SARS-CoV-2 VOC 202012/01 (B.1.1.7)	10.2139/ssrn.3779160	Exclusion reason: Insufficient follow-up;
Eyre 2021	The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission	10.1101/2021.09.28.21264260	Exclusion reason: Wrong study design;
Fabiani 2021	Risk of SARS-CoV-2 infection and subsequent hospital admission and death at different time intervals since first dose of COVID-19 vaccine administration, Italy, 27 December 2020 to mid-April 2021	http://dx.doi.org/10.2807/1560-7917.ES.2021.26.25.2100507	Exclusion reason: Wrong intervention;
Favresse 2021	Antibody titers decline 3-month post-vaccination with BNT612b2		Exclusion reason: Wrong outcomes;
Feng 2021	Safety and Immunogenicity of Inactivated SARS-CoV-2 Vaccine in High-Risk Occupational Population: a randomized, parallel, controlled clinical trial	10.1101/2021.08.06.21261696	Exclusion reason: Wrong intervention;
Fiolet 2021	Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern		Exclusion reason: Wrong study design; Heather Eames (2021-

			10-06 02:38:51)(Select): nice ideas for graphs;
Fiori 2021	SARS-CoV-2 epidemic in the South American Southern cone: can combined immunity from vaccination and infection prevent the spread of Gamma and Lambda variants while easing restrictions?	10.1101/2021.09.16.21263701	Exclusion reason: Wrong study design;
Flacco 2021	Interim estimates of covid-19 vaccine effectiveness in a mass vaccination setting: Data from an italian province	http://dx.doi.org/10.3390/vaccines9060628	Exclusion reason: Time since vaccination unclear;
Flannery 2021	Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios	10.1001/jamapediatrics.2021.0038	Exclusion reason: Wrong outcomes;
Fleming 2021	COVID-19 vaccine trials: The use of active controls and non-inferiority studies	http://dx.doi.org/10.1177/1740774520988244	Exclusion reason: Wrong study design;
Follmann 2020	Assessing Durability of Vaccine Effect Following Blinded Crossover in COVID-19 Vaccine Efficacy Trials	10.1101/2020.12.14.20248137	Exclusion reason: Wrong study design;
Follmann 2021	A Deferred-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group Is Vaccinated	10.7326/M20-8149	Exclusion reason: Wrong study design;
Follmann 2021	Estimation of Vaccine Efficacy for Variants that Emerge After the Placebo Group Is Vaccinated	10.1101/2021.08.31.21262908	Exclusion reason: Wrong study design;
Food and Drug Administration (US)	Pfizer-BioNTech COVID-19 Vaccine EUA Amendment Review Memorandum (10 May 2021)	https://www.fda.gov/media/148542/download	Exclusion reason: No previously unidentified outcomes
Food and Drug Administration (US)	Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum (Pfizer/BioNTech) (11 December 2020)	https://www.fda.gov/media/144416/download	Exclusion reason: Insufficient follow-up;

Food and Drug Administration (US)	Emergency Use Authorization (EUA) for an Unapproved Product Review Memorandum (Moderna)	https://www.fda.gov/media/144673/download	Exclusion reason: Insufficient follow-up;
Foulkes 2021	COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study	http://dx.doi.org/10.1016/S0140-6736%2821%29007 90-X	Exclusion reason: Insufficient follow-up;
Fujigaki 2021	Antibody responses to BNT162b2 vaccination in Japan: Monitoring vaccine efficacy by measuring IgG antibodies against the receptor binding domain of SARS-CoV-2	10.1101/2021.07.19 .21260728	Exclusion reason: Wrong outcomes;
Fukutani 2021	Correlation Between SARS-Cov-2 Vaccination, COVID-19 Incidence and Mortality: Tracking the Effect of Vaccination on Population Protection in Real Time	http://dx.doi.org/10.3389/fgene.2021.67 9485	Exclusion reason: Wrong study design;
Furer 2021	Immunogenicity and safety of the BNT162B2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and general population: A multicenter study	http://dx.doi.org/10.1136/annrheumdis-2021-eular.5096	Exclusion reason: Time since vaccination unclear;
Gallais 2021	Evolution of antibody responses up to 13 months after SARS-CoV-2 infection and risk of reinfection	10.1016/j.ebiom.20 21.103561	Exclusion reason: Wrong outcomes;
Gazit 2021	BNT162b2 mRNA Vaccine Effectiveness Given Confirmed Exposure; Analysis of Household Members of COVID-19 Patients	10.1101/2021.06.29 .21259579	Exclusion reason: Time since vaccination unclear;
Ge 2021	Outcomes of SARS-CoV-2 Infection in Patients With Chronic Liver Disease and Cirrhosis: A National COVID Cohort Collaborative Study	10.1053/j.gastro.20 21.07.010	Exclusion reason: Wrong intervention;
Ghazy 2021	Efficacy and Effectiveness of SARS-CoV-2 vaccine: A systematic review and a meta-analysis		Exclusion reason: Wrong study design;
Ghorbani 2021	Epidemiologic characteristics of cases with re-infection, recurrence and hospital readmission due to COVID-19: a systematic review and meta-analysis	10.1002/jmv.27281	Exclusion reason: Wrong study design;

Gilbert 2021	Immune Correlates Analysis of the mRNA-1273 COVID-19 Vaccine Efficacy Trial	10.1101/2021.08.09.21261290	Exclusion reason: Wrong outcomes;
Gill 2021	COVID-19, community trials, and inclusion	http://dx.doi.org/10.1016/S0140-6736%2821%2900661-9	Exclusion reason: Wrong study design;
Glampson 2021	North West London Covid-19 Vaccination Programme: Real-world evidence for Vaccine uptake and effectiveness	10.1101/2021.04.08.21254580	Exclusion reason: Insufficient follow-up;
Glampson 2021	North West London Covid-19 Vaccination Programme: Real-world evidence for Vaccine uptake and effectiveness: Retrospective Cohort Study	http://dx.doi.org/10.2196/30010	Exclusion reason: Wrong outcomes;
Glatman-Freedman 2021	The BNT162b2 vaccine effectiveness against new COVID-19 cases and complications of breakthrough cases: A nation-wide retrospective longitudinal multiple cohort analysis using individualised data	10.1016/j.ebiom.2021.103574	Exclusion reason: Insufficient follow-up;
Gluck 2021	Immunity after COVID-19 and vaccination: follow-up study over 1 year among medical personnel	http://dx.doi.org/10.1007/s15010-021-01703-9	Exclusion reason: Wrong outcomes;
Gobbato 2020	Caratteristiche cliniche, demografiche e ricovero di 3.010 pazienti affetti da Covid-19 in Friuli Venezia Giulia. Analisi statistica multivariata su base di popolazione, Clinical, demographical characteristics and hospitalisation of 3,010 patients with Co	http://dx.doi.org/10.19191/EP20.5-6.S2.122	Exclusion reason: Wrong intervention;
Gomes 2021	Is the BioNTech-Pfizer COVID-19 vaccination effective in elderly populations? Results from population data from Bavaria, Germany	10.1101/2021.08.19.21262266	Exclusion reason: Insufficient follow-up;
Gounant 2021	Efficacy of SARS-CoV-2 vaccine in thoracic cancer patients: a prospective study supporting a third dose in	10.1101/2021.08.12.21261806	Exclusion reason: Insufficient follow-up;

	patients with minimal serologic response after two vaccine doses		
Gower 2021	Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study	http://dx.doi.org/10.1136/bmj.n1088	Exclusion reason: Insufficient follow-up;
Gram 2021	Vaccine effectiveness when combining the ChAdOx1 vaccine as the first dose with an mRNA COVID-19 vaccine as the second dose	10.1101/2021.07.26.21261130	Exclusion reason: Insufficient follow-up;
Gras-Valenti 2021	Effectiveness of the first dose of BNT162b2 vaccine to preventing covid-19 in healthcare personnel		Exclusion reason: Wrong intervention;
Greco 2021	SARS-CoV-2 infection and H1N1 vaccination: Does a relationship between the two factors really exist? A retrospective analysis of a territorial cohort in Ferrara, Italy	http://dx.doi.org/10.26355/eurrev_202103_25441	Exclusion reason: Wrong intervention;
Grupper 2021	Humoral response to the pfizer bnt162b2 vaccine in patients undergoing maintenance hemodialysis	http://dx.doi.org/10.2215/CJN.03500321	Exclusion reason: Wrong comparator;
Guerrera 2021	The BNT162b2 mRNA vaccine induces polyfunctional T cell responses with features of longevity	10.1101/2021.09.27.462006	Exclusion reason: Wrong outcomes;
Guijarro 2021	SARS-CoV-2 new infections among health-care workers after the first dose of the BNT162b2 mRNA COVID-19 vaccine. A hospital-wide cohort study	http://dx.doi.org/10.1016/j.cmi.2021.06.026	Exclusion reason: Wrong comparator;
Gurion 2021	Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD2O antibodies	10.3324/haematol.2021.279216	Exclusion reason: Wrong outcomes;
Haas 2021	Infections, hospitalisations, and deaths averted via a nationwide vaccination campaign using the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel: a retrospective surveillance study	10.1016/S1473-3099(21)00566-1	Exclusion reason: Wrong study design;

Hadar 2021	Coronavirus disease and vaccination during pregnancy and childbirth: a review of the Israeli perspective and experience	http://dx.doi.org/10.1080/14767058.2021.1937110	Exclusion reason: Wrong study design;
Hadjadj 2021	Immunogenicity of BNT162b2 vaccine Against the Alpha and Delta Variants in Immunocompromised Patients	10.1101/2021.08.08.21261766	Exclusion reason: Insufficient Sample Size;
Haghpanah 2021	Analysis of the Potential Efficacy and Timing of COVID-19 Vaccine on Morbidity and Mortality	10.2139/ssrn.3745195	Exclusion reason: Wrong outcomes;
Hall 2021	Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study)	10.2139/ssrn.3790399	Exclusion reason: Time since vaccination unclear;
Hall 2021	Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients	http://dx.doi.org/10.1111/ajt.16766	Exclusion reason: Insufficient follow-up;
Hamed 2021	Clinical characteristics of 51,815 patients presenting with positive and negative SARS-CoV-2 swab results in primary healthcare settings: Priority populations for vaccination	http://dx.doi.org/10.1016/j.jinf.2020.11.014	Exclusion reason: Wrong study design;
Harder 2021	Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: interim results of a living systematic review, 1 January to 14 May 2021	http://dx.doi.org/10.2807/1560-7917.ES.2021.26.28.2100563	Exclusion reason: Wrong study design;
Harris 2021	COVID-19 Incidence and Hospitalization Rates are Inversely Related to Vaccination Coverage Among the 112 Most Populous Counties in the United States	10.1101/2021.08.17.21262195	Exclusion reason: Time since vaccination unclear;
Havers 2021	COVID-19-associated hospitalizations among vaccinated and unvaccinated adults â‰¥18 years â€“ COVID-NET, 13 states, January 1 â€“ July 24, 2021	10.1101/2021.08.27.21262356	Exclusion reason: Time since vaccination unclear;

Havers 2021	Hospitalization of Adolescents Aged 12-17 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1, 2020-April 24, 2021	http://dx.doi.org/10.15585/mmwr.mm7023e1	Exclusion reason: Wrong outcomes;
Haynes 2021	A new vaccine to battle COVID-19	http://dx.doi.org/10.1056/NEJMe2035557	Exclusion reason: Wrong study design;
Higdon 2021	A systematic review of COVID-19 vaccine efficacy and effectiveness against SARS-CoV-2 infection and disease	10.1101/2021.09.17.21263549	Exclusion reason: Wrong study design;
Hilty 2021	Near real-time observation reveals increased prevalence of young patients in the ICU during the emerging third SARS-CoV-2 wave in Switzerland	10.4414/smw.2021.20553	Exclusion reason: Wrong outcomes;
Hitchings 2021	Effectiveness of the ChAdOx1 vaccine in the elderly during SARS-CoV-2 Gamma variant transmission in Brazil	10.1101/2021.07.19.21260802	Exclusion reason: Insufficient follow-up;
Hitchings 2021	Use of recently vaccinated individuals to detect bias in test-negative case-control studies of COVID-19 vaccine effectiveness	10.1101/2021.06.23.21259415	Exclusion reason: Wrong study design;
Hoque 2021	Serial evaluation of anti-SARS-CoV-2 IgG antibody and breakthrough infections in BNT162b2 Vaccinated migrant workers from Bangladesh	10.1101/2021.09.07.21263221	Exclusion reason: Insufficient Sample Size;
Hsu 2021	Seroresponse to SARS-CoV-2 vaccines among maintenance dialysis patients	10.1101/2021.08.19.21262292	Exclusion reason: Wrong outcomes;
Hu 2021	Population Vaccine Effectiveness and its Implication for Control of the Spread of COVID-19 in the US	10.1101/2021.04.30.21256228	Exclusion reason: Wrong study design;
Hu 2021	Effectiveness of inactive COVID-19 vaccines against severe illness in B.1.617.2 (Delta) variant-infected patients in Jiangsu, China	10.1101/2021.09.02.21263010	Exclusion reason: Time since vaccination unclear;
Hunter 2021	Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a	10.1101/2021.02.01.21250957	Exclusion reason: Wrong intervention;

	study of â€˜real-worldâ€™ vaccination outcomes from Israel		
Hyams 2021	Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study	10.2139/ssrn.3796835	Exclusion reason: Wrong intervention;
Hyams 2021	Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study	http://dx.doi.org/10.1016/S1473-3099%2821%2900330-3	Exclusion reason: Wrong intervention;
Iliaki 2021	COVID-19 Vaccine Efficacy in a Diverse Urban Healthcare Worker Population	10.1101/2021.09.02.21263038	Exclusion reason: Time since vaccination unclear;
Imai 2021	Interpreting estimates of coronavirus disease 2019 (COVID-19) vaccine efficacy and effectiveness to inform simulation studies of vaccine impact: a systematic review	10.12688/wellcomeopenres.16992.1	Exclusion reason: Wrong study design;
Ireland 2021	Emergence of SARS-CoV-2 Alpha (B.1.1.7) variant, infection rates, antibody seroconversion and seroprevalence rates in secondary school students and staff: Active prospective surveillance, December 2020 to March 2021, England	http://dx.doi.org/10.1016/j.jinf.2021.08.019	Exclusion reason: Wrong intervention;
Israel 2021	Large-scale study of antibody titer decay following BNT162b2 mRNA vaccine or SARS-CoV-2 infection	10.1101/2021.08.19.21262111	Exclusion reason: Wrong comparator;
John 2021	Association of BNT162b2 mRNA and mRNA-1273 Vaccines with COVID-19 Infection and Hospitalization among Patients with Cirrhosis	http://dx.doi.org/10.1001/jamainternmed.2021.4325	Exclusion reason: Time since vaccination unclear;
Jon 2021	Incidence of COVID-19 recurrence among large cohort of healthcare employees	http://dx.doi.org/10.1016/j.annepidem.2021.04.005	Exclusion reason: Wrong intervention;

Kadali 2021	Non-life-threatening adverse effects with COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms	http://dx.doi.org/10.1002/jmv.26996	Exclusion reason: Wrong outcomes;
Kahlmann 2021	COVID-19 infection in patients with sarcoidosis: susceptibility and clinical outcomes	10.1183/13993003.00048-2021.	Exclusion reason: Wrong intervention;
Kahn 2021	Interpreting vaccine efficacy trial results for infection and transmission	http://dx.doi.org/10.1016/j.vaccine.2021.06.011	Exclusion reason: Opinion piece;
Kai 2021	Efficacy and safety of COVID-19 vaccines: A systematic review	http://dx.doi.org/10.7499/j.issn.1008-8830.2101133	Exclusion reason: Wrong study design;
Kamal 2021	Adverse events following ChAdOx1 nCoV-19 Vaccine (COVISHIELD) amongst healthcare workers: A prospective observational study	http://dx.doi.org/10.1016/j.mjafi.2021.06.014	Exclusion reason: Wrong outcomes;
Kang 2021	Effectiveness of Inactivated COVID-19 Vaccines Against COVID-19 Pneumonia and Severe Illness Caused by the B.1.617.2 (Delta) Variant: Evidence from an Outbreak in Guangdong, China	10.2139/ssrn.3895639	Exclusion reason: Wrong intervention;
Kato 2021	Antibody titers against the Alpha, Beta, Gamma, and Delta variants of SARS-CoV-2 induced by BNT162b2 vaccination measured using automated chemiluminescent enzyme immunoassay	10.1101/2021.09.23.21263927	Exclusion reason: Wrong outcomes;
Kaur 2021	A prospective observational safety study on ChAdOx1 nCoV-19 corona virus vaccine (recombinant) use in healthcare workers- first results from India	http://dx.doi.org/10.1016/j.eclinm.2021.101038	Exclusion reason: Wrong outcomes;
Kaur 2021	Occurrence of COVID-19 in priority groups receiving ChAdOx1 nCoV-19 coronavirus vaccine (recombinant): A preliminary analysis from north India	10.1002/jmv.27320	Exclusion reason: Wrong comparator;

Ke 2021	Longitudinal analysis of SARS-CoV-2 vaccine breakthrough infections reveal limited infectious virus shedding and restricted tissue distribution	10.1101/2021.08.30.21262701	Exclusion reason: Wrong outcomes;
Kearns 2021	Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacityâ€"The OCTAVE Trial		Exclusion reason: Wrong outcomes;
Keegan 2021	Progress of the Delta variant and erosion of vaccine effectiveness, a warning from Utah	10.1101/2021.08.09.21261554	Exclusion reason: Time since vaccination unclear;
Kepten 2021	BNT162B2 mRNA covid-19 vaccine in a nationwide mass vaccination setting	http://dx.doi.org/10.1056/NEJMoa2101765	Exclusion reason: Insufficient follow-up;
Khan 2021	Effectiveness of SARS-CoV-2 Vaccination in a Veterans Affairs Cohort of Patients With Inflammatory Bowel Disease With Diverse Exposure to Immunosuppressive Medications	http://dx.doi.org/10.1053/j.gastro.2021.05.044	Exclusion reason: Insufficient follow-up;
Kho 2021	The RECOVAC IR study: the immune response and safety of the mRNA-1273 COVID-19 vaccine in patients with chronic kidney disease, on dialysis or living with a kidney transplant	10.1093/ndt/gfab186	Exclusion reason: Wrong outcomes;
Kim 2021	mRNA Vaccine Effectiveness against COVID-19 among Symptomatic Outpatients Aged â‰¥16 Years in the United States, February â€" May 2021	10.1101/2021.07.20.21260647	Exclusion reason: Time since vaccination unclear;
Kim 2021	Vaccination strategies and transmission of COVID-19: evidence across leading countries		Exclusion reason: Wrong study design;
Kislaya 2021	Delta variant and mRNA Covid-19 vaccines effectiveness: higher odds of vaccine infection breakthroughs	10.1101/2021.08.14.21262020	Exclusion reason: Time since vaccination unclear;

Klineova 2021	Outcomes of COVID-19 infection in multiple sclerosis and related conditions: One-year pandemic experience of the multicenter New York COVID-19 Neuroimmunology Consortium (NYCNIC)	http://dx.doi.org/10.1016/j.msard.2021.103153	Exclusion reason: Wrong intervention;
Koch 2021	Correlates of vaccine-induced protection against sars-cov-2	http://dx.doi.org/10.3390/vaccines9030238	Exclusion reason: Wrong study design;
Kontopoulou 2021	Evolution of Antibody Titers Up to 6 Months Post-Immunization With the BNT162b2 Pfizer/BioNTech Vaccine in Greece	10.2139/ssrn.3922311	Exclusion reason: Wrong outcomes;
Kontopoulou 2021	Antibody Titers 3-Months Post-Vaccination with the Pfizer/Biontech Vaccine in Greece	10.2139/ssrn.3899094	Exclusion reason: Wrong outcomes;
Korang 2020	Vaccines to prevent COVID-19: a protocol for a living systematic review with network meta-analysis including individual patient data (The LIVING VACCINE Project)	http://dx.doi.org/10.1186/s13643-020-01516-1	Exclusion reason: Wrong study design;
Kornek 2021	Distinct Patterns of Humoral and Cellular Immune Responses Following SARS-CoV-2 mRNA Vaccination in Patients With Immune-Mediated Neurological Disorders on Anti-CD20 Therapy: A Prospective Cohort Study	10.2139/ssrn.3924204	Exclusion reason: Wrong outcomes;
Kosiorek 2021	Systemic COVID-19 vaccination also enhances the humoral immune response after SARS CoV-2 infection. An approach to criteria for COVID-19 re-immunization is needed. Do we need a third dose?	10.21203/rs.3.rs-858160/v2	Exclusion reason: Wrong outcomes;
Kou 2021	Social and Clinical Impact of COVID-19 on Patients with Fibrodysplasia Ossificans Progressiva	10.21203/rs.3.rs-885603/v1	Exclusion reason: Wrong study design;
Kow 2021	Real-world effectiveness of BNT162b2 mRNA vaccine: a meta-analysis of large observational studies	http://dx.doi.org/10.1007/s10787-021-00839-2	Exclusion reason: Wrong study design;

Kroidl 2021	Vaccine breakthrough infection and onward transmission of SARS-CoV-2 Beta (B.1.351) variant, Bavaria, Germany, February to March 2021	http://dx.doi.org/10.2807/1560-7917.ES.2021.26.30.2100673	Exclusion reason: Wrong study design;
Kumar 2021	Effectiveness of the Covid-19 vaccines in preventing infection in dental practitioners â€" results of a cross-sectional â€˜questionnaire-basedâ€™ survey	10.1101/2021.05.28.21257967	Exclusion reason: Wrong outcomes;
Kurita 2021	Estimating Vaccination Effects and Variant Strains on COVID-19 outbreak course in Japan, as of August, 2021	10.1101/2021.06.20.21259209	Exclusion reason: Wrong outcomes;
Laha 2021	Country specific mutational profile of SARS-CoV-2 in pre- and post-international travel ban: Effect on vaccine efficacy	10.1101/2021.02.08.21251359	Exclusion reason: Wrong study design;
Laing 2021	Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) study: an observational cohort study of SARS-CoV-2 infection and vaccination in healthcare workers	http://dx.doi.org/10.1186/s12879-021-06233-1	Exclusion reason: Wrong outcomes;
Lasagna 2021	A snapshot of the immunogenicity, efficacy and safety of a full course of BNT162b2 anti-SARS-CoV-2 vaccine in cancer patients treated with PD-1/PD-L1 inhibitors: a longitudinal cohort study	10.1016/j.esmoop.2021.100272	Exclusion reason: Wrong outcomes;
Lau 2021	PIN5 Immunogenicity and Safety of the COVID-19 Vaccines Compared to Controls in Healthy Adults: A Systematic Review	http://dx.doi.org/10.1016/j.jval.2021.04.565	Exclusion reason: Wrong study design;
Lee 2021	Immune transcriptomes from hospitalized patients infected with the SARS-CoV-2 variants B.1.1.7 and B.1.1.7 carrying the E484K escape mutation	10.1101/2021.05.27.21257952	Exclusion reason: Wrong outcomes;
Lee 2021	Efficacy of COVID-19 vaccines in immunocompromised patients: A systematic review and meta-analysis	10.1101/2021.09.28.21264126	Exclusion reason: Wrong study design;
Lee 2021	Robust immune response to the BNT162b mRNA vaccine in an elderly population vaccinated 15 months after recovery from COVID-19	10.1101/2021.09.08.21263284	Exclusion reason: Wrong outcomes;

Leong 2021	Risk mitigation in Crohn's disease and ulcerative colitis: Session four summary	http://dx.doi.org/10.1111/jgh.15456	Exclusion reason: Wrong intervention;
Li 2021	Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study	http://dx.doi.org/10.1080/22221751.2021.1969291	Exclusion reason: Insufficient Sample Size;
Li 2021	Phased implementation of COVID-19 vaccination: rapid assessment of policy adoption, reach and effectiveness to protect the most vulnerable in the US	10.1101/2021.02.19.21252118	Exclusion reason: Wrong comparator;
Li 2021	Self-assessment of COVID-19 vaccination efficacy using a lateral flow tests for SARS-CoV-2 S1 protein antibody	10.1101/2021.06.27.21258591	Exclusion reason: Wrong intervention;
Li 2021	Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study	http://dx.doi.org/10.1038/s41591-021-01330-9	Exclusion reason: Insufficient Sample Size;
Liang 2021	COVID-19 vaccinations are associated with reduced fatality rates: Evidence from cross-county quasi-experiments	10.7189/jogh.11.05019	Exclusion reason: Wrong outcomes;
Lijeskic 2021	Prospective cohort study of the kinetics of specific antibodies to sars-cov-2 infection and to four sars-cov-2 vaccines available in serbia, and vaccine effectiveness: A 3-month interim report	http://dx.doi.org/10.3390/vaccines9091031	Exclusion reason: Wrong outcomes;
Lin 2021	Evaluating the Long-Term Efficacy of COVID-19 Vaccines	http://dx.doi.org/10.1093/cid/ciab226	Exclusion reason: Opinion piece;
Lin 2021	Evaluating Vaccine Efficacy Against SARS-CoV-2 Infection	http://dx.doi.org/10.1093/cid/ciab630	Exclusion reason: Wrong study design;
Ling 2021	Safety and effectiveness of SARS-CoV-2 vaccines: A systematic review and meta-analysis	http://dx.doi.org/10.1002/jmv.27203	Exclusion reason: Wrong study design;
Linsenmeyer 2021	Cryptic Transmission of the Delta Variant AY.3 Sublineage of SARS-CoV-2 among Fully Vaccinated Patients on an Inpatient Ward	10.1101/2021.08.05.21261562	Exclusion reason: Wrong outcomes;

Liu 2021	Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial	10.1016/S0140-6736(21)01694-9	Exclusion reason: Insufficient follow-up;
Liu 2021	The Lambda variant of SARS-CoV-2 has a better chance than the Delta variant to escape vaccines	10.1101/2021.08.25.457692	Exclusion reason: Wrong outcomes;
LopezBernal 2021	Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant	http://dx.doi.org/10.1056/NEJMoa2108891	Exclusion reason: Insufficient follow-up;
Lustig 2021	BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers	http://dx.doi.org/10.1016/S2213-2600%2821%2900220-4	Exclusion reason: Insufficient follow-up;
Lv 2021	Safety, Immunogenicity, and Efficacy of COVID-19 Vaccine in Children and Adolescents: A Systematic Review	10.1101/2021.09.11.21262855	Exclusion reason: Wrong study design;
Madhi 2021	Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa	10.1101/2021.02.10.21251247	Exclusion reason: Preprint - subsequently published. ;
Malhotra 2021	Epidemiological profiles and associated risk factors of SARS-CoV-2 positive patients based on a high-throughput testing facility in India	http://dx.doi.org/10.1098/rsob.200288	Exclusion reason: Wrong outcomes;
Malinis 2021	Effectiveness of SARS-CoV-2 vaccination in fully vaccinated solid organ transplant recipients	http://dx.doi.org/10.1111/ajt.16713	Exclusion reason: Time since vaccination unclear;
Malipiero 2021	Assessment of humoral and cellular immunity induced by the BNT162b2 SARS-CoV-2 vaccine in healthcare workers, elderly people, and immunosuppressed patients with autoimmune disease	http://dx.doi.org/10.1007/s12026-021-09226-z	Exclusion reason: Wrong outcomes;

Mardani 2020	Should cancer patients be prioritized for covid-19 vaccination?	http://dx.doi.org/10.5812/archcid.113263	Exclusion reason: Opinion piece;
Martinez-Baz 2021	Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection and hospitalisation, Navarre, Spain, January to April 2021	http://dx.doi.org/10.2807/1560-7917.ES.2021.26.21.2100438	Exclusion reason: Insufficient follow-up;
Mason 2021	Lupus, vaccinations and COVID-19: What we know now	http://dx.doi.org/10.1177/0961203321102435 5	Exclusion reason: Wrong outcomes;
Massarweh 2021	Evaluation of Seropositivity following BNT162b2 Messenger RNA Vaccination for SARS-CoV-2 in Patients Undergoing Treatment for Cancer	http://dx.doi.org/10.1001/jamaoncol.2021.2155	Exclusion reason: Wrong outcomes;
McCaughan 2021	COVID-19 vaccination in haematology patients: an Australian and New Zealand consensus position statement	10.1111/imj.15247	Exclusion reason: Wrong study design;
McDougle 2021	Serving as Trusted Messengers about COVID-19 Vaccines and Therapeutics	http://dx.doi.org/10.1016/j.jnma.2021.01.003	Exclusion reason: Opinion piece;
McEvoy 2021	Real-world Effectiveness of 2-dose SARS-CoV-2 Vaccination in Kidney Transplant Recipients	10.1101/2021.09.21.21263457	Exclusion reason: Wrong comparator;
McKeigue 2021	Efficacy of COVID-19 vaccination in individuals designated as clinically extremely vulnerable in Scotland	10.12688/f1000research.53812.1	Exclusion reason: Wrong intervention;
Meggiolaro 2021	Effectiveness of vaccination against symptomatic and asymptomatic SARS-CoV-2 infection: a systematic review and meta-analysis	10.1101/2021.08.25.21262529	Exclusion reason: Wrong study design;
Menni 2021	Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study	http://dx.doi.org/10.1016/S1473-3099%2821%29002 24-3	Exclusion reason: Insufficient follow-up;

Meyer 2021	Two doses of the mRNA BNT162b2 vaccine reduce severe outcomes, viral load and secondary attack rate: evidence from a SARS-CoV-2 Alpha outbreak in a nursing home in Germany, January-March 2021	10.1101/2021.09.13.21262519	Exclusion reason: Insufficient follow-up;
Miles 2021	How fast should social restrictions be eased in England as COVID-19 vaccinations are rolled out?	http://dx.doi.org/10.1111/ijcp.14191	Exclusion reason: Wrong study design;
Milman 2021	Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals	http://dx.doi.org/10.1038/s41591-021-01407-5	Exclusion reason: Wrong outcomes;
Miron 2021	Effectiveness of COVID-19 Vaccines BNT162b2 and mRNA-1273 by Days from Vaccination: A Reanalysis of Clinical Trial Data	10.2139/ssrn.3791560	Exclusion reason: Duplicate;
Miyakawa 2021	Neutralizing efficacy of vaccines against the SARS-CoV-2 Mu variant	10.1101/2021.09.23.21264014	Exclusion reason: Wrong outcomes;
Mohammad 2021	Immune response scenario and vaccine development for SARS-CoV-2 infection	10.1016/j.intimp.2021.107439	Exclusion reason: Wrong outcomes;
Monge 2021	Direct and indirect effectiveness of mRNA vaccination against SARS-CoV-2 infection in long-term care facilities in Spain	10.1101/2021.04.08.21255055	Exclusion reason: Time since vaccination unclear;
Monge 2021	Direct and Indirect Effectiveness of mRNA Vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 in Long-Term Care Facilities, Spain	http://dx.doi.org/10.3201/eid2710.211184	Exclusion reason: Time since vaccination unclear;
Monin 2021	Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study	10.1016/S1470-2045(21)00213-8	Exclusion reason: Wrong outcomes;
Monin-Aldama 2021	Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines	10.1101/2021.03.17.21253131	Exclusion reason: Wrong outcomes;

Mor 2021	BNT162b2 Vaccination Efficacy is Marginally Affected by the SARS-CoV-2 B.1.351 Variant in Fully Vaccinated Individuals	10.2139/ssrn.3878825	Exclusion reason: Wrong study design;
Moustsen-Helms 2021	Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers â€“ a Danish cohort study	10.1101/2021.03.08.21252200	Exclusion reason: Insufficient follow-up;
Muik 2020	COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses	http://dx.doi.org/10.1038/s41586-020-2814-7	Exclusion reason: Insufficient Sample Size;
Mukherjee 2021	What is mRNA COVID 19 Vaccine and What is the safety and Efficacy of mRNA COVID 19 Vaccine?		Exclusion reason: Full Text Not Available;
Murillo-Zamora 2021	Effectiveness of BNT162b2 COVID-19 Vaccine in Preventing Severe Symptomatic Infection among Healthcare Workers	http://dx.doi.org/10.3390/medicina57080746	Exclusion reason: Time since vaccination unclear;
Murugesan 2021	Protective Effect Conferred by Prior Infection and Vaccination on COVID-19 in a Healthcare Worker Cohort in South India	10.2139/ssrn.3914633	Exclusion reason: Time since vaccination unclear;
Mushtaq 2021	Outcomes with COVID-19 in hematopoietic stem cell transplant and cellular therapy patients	http://dx.doi.org/10.1200/JCO.2021.39.15_suppl.7033	Exclusion reason: Insufficient Sample Size;
Mushtaq 2021	Impact of SARS-CoV-2 in Hematopoietic Stem Cell Transplantation and Chimeric Antigen Receptor T Cell Therapy Recipients	http://dx.doi.org/10.1016/j.jtct.2021.07.005	Exclusion reason: Wrong outcomes;
Muthukrishnan 2021	Vaccination status and COVID-19 related mortality: A hospital based cross sectional study	http://dx.doi.org/10.1016/j.mjafi.2021.06.034	Exclusion reason: Time since vaccination unclear;
NÃºÃ±ezLÃ³pez 2021	Untitled	10.1016/j.eimc.2021.06.021	Exclusion reason: Duplicate;

NÃºÃ±ezLÃ³pez 2021	Effectiveness of the BNT162b2 mRNA Covid-19 vaccine in Spanish healthcare workers	10.1016/j.eimc.2021.06.021	Exclusion reason: Wrong outcomes;
Nasreen 2021	Effectiveness of COVID-19 vaccines against variants of concern in Ontario, Canada	10.1101/2021.06.28.21259420	Exclusion reason:
Nassar 2021	Current systematic reviews and meta-analyses of COVID-19	10.5501/wjv.v10.i4.182	Exclusion reason: Wrong study design;
Nasser 2020	Outbreak of sars-cov-2 among migrant farm workers in north florida	http://dx.doi.org/10.1093/ofid/ofaa439.1797	Exclusion reason: Wrong intervention;
Nioi 2020	COVID-19 and Italian Healthcare Workers From the Initial Sacrifice to the mRNA Vaccine: Pandemic Chrono-History, Epidemiological Data, Ethical Dilemmas, and Future Challenges	http://dx.doi.org/10.3389/fpubh.2020.591900	Exclusion reason: Wrong study design;
Nowakowska 2021	SARS-COV-2 mutations and variations and how COVID-19 vaccines work against the variants	http://dx.doi.org/10.32383/APPDR/139673	Exclusion reason: Wrong study design;
Nunes 2021	mRNA vaccines effectiveness against COVID-19 hospitalizations and deaths in older adults: a cohort study based on data-linkage of national health registries in Portugal	10.1101/2021.08.27.21262731	Exclusion reason: Duplicate;
Ogbe 2021	Durability of ChAdOx1 nCov-19 (AZD1222) vaccination in people living with HIV - responses to SARS-CoV-2, variants of concern and circulating coronaviruses	10.1101/2021.09.28.21264207	Exclusion reason: Wrong comparator;
O'Hare 2021	Age differences in the association of comorbid burden with adverse outcomes in SARS-CoV-2	10.1186/s12877-021-02340-5	Exclusion reason: Wrong outcomes;
On 2021	The importance of time post-vaccination in determining the decrease in vaccine efficacy against SARS-CoV-2 variants of concern	10.1101/2021.06.06.21258429	Exclusion reason: Wrong study design;

Ong 2021	Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta)	10.1093/cid/ciab721	Exclusion reason: Insufficient Sample Size;
Oreja-Guevara 2021	COVID-19 infection and vaccination in patients with multiple sclerosis during COVID pandemic	http://dx.doi.org/10.1111/ene.14975	Exclusion reason: Insufficient follow-up;
Pajon 2021	Initial Analysis of Viral Dynamics and Circulating Viral Variants During the mRNA-1273 Phase 3 COVE Trial	10.1101/2021.09.28.21264252	Exclusion reason: Wrong outcomes;
Paris 2021	Effectiveness of mRNA-BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 vaccines against COVID-19 in healthcare workers: an observational study using surveillance data	http://dx.doi.org/10.1016/j.cmi.2021.06.043	Exclusion reason: Wrong intervention;
Park 2021	Emergency Department Utilization by In-hospital Healthcare Workers after COVID-19 Vaccination	http://dx.doi.org/10.3346/jkms.2021.36.e196	Exclusion reason: Wrong intervention;
Passalacqua 2021	1646TiP Efficacy of SARS-CoV-2 vaccination in cancer patients during treatment: A prospective observational study (ANTICOV trial)	http://dx.doi.org/10.1016/j.annonc.2021.08.1639	Exclusion reason: Full Text Not Available;
Passos 2021	Higher mortality during the COVID-19 pandemic in socially vulnerable areas in Belo Horizonte: implications for vaccine prioritization	http://dx.doi.org/10.1590/1980-549720210025	Exclusion reason: Wrong outcomes;
Patalon 2021	Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine	10.1101/2021.08.29.21262792	Exclusion reason: Wrong comparator;
Patel 2021	COVID-19 Outcomes Among Users of CD20 Inhibitors for Immune-Mediated Diseases: A Comparative Cohort Study	10.1101/2021.08.05.21261643	Exclusion reason: Wrong outcomes;
Pawlowski 2021	FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system	10.1101/2021.02.15.21251623	Exclusion reason: Preprint - subsequently published. ;

Perry 2021	Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study	10.1016/S0140-6736(21)01608-1	Exclusion reason: Wrong outcomes;
Pilishvili 2021	Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Healthcare Personnel - 33 U.S. Sites, January-March 2021	http://dx.doi.org/10.15585/mmwr.mm7020e2	Exclusion reason: Time since vaccination unclear;
Pormohammad 2021	Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials	10.2139/ssrn.3812422	Exclusion reason: Wrong study design;
Pradenas 2021	Stable neutralizing antibody levels 6Â months after mild and severe COVID-19 episodes	10.1016/j.medj.2021.01.005	Exclusion reason: Wrong intervention;
Pramod 2021	Effectiveness of Covishield vaccine in preventing Covid-19 â€“ A test-negative case-control study	10.1101/2021.07.19.21260693	Exclusion reason: Time since vaccination unclear;
Prasad 2021	COVID-19 Vaccination Associated with Reduced Post-Operative SARS-CoV-2 Infection and Morbidity	10.1097/SLA.0000000000005176	Exclusion reason: Time since vaccination unclear;
Pritchard 2021	Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom	http://dx.doi.org/10.1038/s41591-021-01410-w	Exclusion reason: Insufficient follow-up;
Pundi 2020	Characteristics and Strength of Evidence of COVID-19 Studies Registered on ClinicalTrials.gov	http://dx.doi.org/10.1001/jamainternmed.2020.2904	Exclusion reason: Insufficient follow-up;
Puro 2021	Impact of prior influenza and pneumoccocal vaccines on humoral and cellular response to sars-cov-2 bnt162b2 vaccination	http://dx.doi.org/10.3390/vaccines9060615	Exclusion reason: Wrong outcomes;
Ramasamy 2020	Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial	http://dx.doi.org/10.1016/S0140-6736%2820%2932466-1	Exclusion reason: Wrong outcomes;

Regev 2021	Short-term outcome of pregnant women vaccinated by BNT162b2 mRNA COVID-19 vaccine	http://dx.doi.org/10.1002/uog.23729	Exclusion reason: Wrong outcomes;
Revon-Riviere 2021	The BNT162b2 mRNA COVID-19 vaccine in adolescents and young adults with cancer: A monocentric experience	10.1016/j.ejca.2021.06.002	Exclusion reason: Insufficient Sample Size;
Riemersma 2021	Shedding of Infectious SARS-CoV-2 Despite Vaccination	10.1101/2021.07.31.21261387	Exclusion reason: Wrong outcomes;
Roesch 2021	Prognostic value of preinfectionroutine laboratory parameters for COVID-19 mortality in tumor patients: Results of the ADHOK Coronavirus Tumor Registry	http://dx.doi.org/10.1200/JCO.2021.39.15-suppl.10571	Exclusion reason: Wrong intervention;
Rogliani 2021	Sars-cov-2 neutralizing antibodies: A network meta-analysis across vaccines	http://dx.doi.org/10.3390/vaccines9030227	Exclusion reason: Insufficient Sample Size;
Rosenberg 2021	New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status - New York, May 3-July 25, 2021	10.15585/mmwr.mm7037a7	Exclusion reason: Time since vaccination unclear;
Rossman 2021	COVID-19 dynamics after a national immunization program in Israel	http://dx.doi.org/10.1038/s41591-021-01337-2	Exclusion reason: Insufficient follow-up;
Ruban 2021	Effectiveness of vaccination in preventing severe SARS CoV-2 infection in South India-a hospital-based cross-sectional study	10.1101/2021.09.17.21263670	Exclusion reason: Time since vaccination unclear;
Sadoff 2021	Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late boosting	10.1101/2021.08.25.21262569	Exclusion reason: Wrong outcomes;
Safari 2021	Identifying the Risk Factors for Mortality in Patients with Cancer and COVID-19 in Hamadan, the West of Iran	http://dx.doi.org/10.1007/s12029-021-00677-z	Exclusion reason: Wrong outcomes;

Sagiraju 2021	The effectiveness of SARS-CoV-2 vaccination in preventing severe illness and death â€“ real-world data from a cohort of patients hospitalized with COVID-19	10.1101/2021.08.26.21262705	Exclusion reason: Insufficient Sample Size;
Salcher-Konrad 2021	Emerging Evidence on Effectiveness of COVID-19 Vaccines Among Residents of Long-Term Care Facilities	http://dx.doi.org/10.1016/j.jamda.2021.05.017	Exclusion reason: Wrong study design;
Saul 2021	Reanalysis of the Pfizer mRNA BNT162b2 SARS-CoV-2 vaccine data fails to find any increased efficacy following the boost: Implications for vaccination policy and our understanding of the mode of action	10.1101/2021.02.23.21252315	Exclusion reason: Duplicate;
Selarka 2021	Mucormycosis and COVID-19: An epidemic within a pandemic in India	http://dx.doi.org/10.1111/myc.13353	Exclusion reason: Wrong outcomes;
Sen-Crowe 2021	COVID-19 fatalities by zip codes and socioeconomic indicators across various U.S. regions	http://dx.doi.org/10.1016/j.amsu.2021.102471	Exclusion reason: Wrong study design;
Shamier 2021	Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in healthcare workers	10.1101/2021.08.20.21262158	Exclusion reason: Wrong outcomes;
Shapiro 2021	Efficacy Estimates for Various COVID-19 Vaccines: What we Know from the Literature and Reports	10.1101/2021.05.20.21257461	Exclusion reason: Wrong study design;
Sharma 2021	The Effect of Pandemic Prevalence on the Reported Efficacy of SARS-CoV-2 Vaccine Candidates: A Systematic Review and Meta-analysis	10.1101/2021.06.05.21258394	Exclusion reason: Wrong study design;
Shenai 2021	Equivalency of Protection from Natural Immunity in COVID-19 Recovered Versus Fully Vaccinated Persons: A Systematic Review and Pooled Analysis	10.1101/2021.09.12.21263461	Exclusion reason: Wrong study design;
Shenoy 2021	Hybrid immunity versus vaccine-induced immunity against SARS CoV2 in Patients with Autoimmune Rheumatic Diseases	10.1101/2021.08.26.21258418	Exclusion reason: Wrong outcomes;

Shepherd 2021	1557O Adaptive immunity to SARS-CoV-2 infection and vaccination in cancer patients: The CAPTURE study	http://dx.doi.org/10.1016/j.annonc.2021.08.1550	Exclusion reason: Wrong outcomes;
Shimabukuro 2021	Reports of Anaphylaxis after Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021	http://dx.doi.org/10.1001/jama.2021.1967	Exclusion reason: Wrong outcomes;
Shmueli 2021	Efficacy and safety of BNT162b2 vaccination inÂ patients with solid cancer receiving anticancer therapy - a single centre prospective study	10.1016/j.ejca.2021.08.007	Exclusion reason: Wrong outcomes;
Shrestha 2021	Effectiveness of mRNA COVID-19 Vaccines among Employees in an American Healthcare System	10.1101/2021.06.02.21258231	Exclusion reason: Wrong outcomes;
Shrotri 2021	Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study)	10.1101/2021.03.26.21254391	Exclusion reason: Wrong intervention;
Shrotri 2021	Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study	http://dx.doi.org/10.1016/S1473-3099%2821%2900289-9	Exclusion reason: Wrong intervention;
Silva 2021	The effectiveness of Vaxzevria and CoronaVac vaccines: A nationwide longitudinal retrospective study of 61 million Brazilians (VigiVac-COVID19)		Exclusion reason: Wrong comparator;
Silva 2021	Effectiveness of the BBIPB-CorV Vaccine in Preventing Infection and Death in Healthcare Workers in Peru 2021	10.2139/ssrn.3922632	Exclusion reason: Wrong intervention;
Simon 2021	Haemodialysis patients show a highly diminished antibody response after COVID-19 mRNA vaccination compared to healthy controls	http://dx.doi.org/10.1093/ndt/gfab179	Exclusion reason: Wrong outcomes;
Singer 2021	Effectiveness of BNT162b2 mRNA COVID-19 Vaccine Against SARS-CoV-2 Variant Beta (B.1.351) Among Persons Identified Through Contact Tracing in Israel	10.2139/ssrn.3904701	Exclusion reason: Time since vaccination unclear;
Singh 2021	Genomic analysis of symptomatic SARS-CoV-2 vaccine breakthrough infections from a tertiary care centre in India		Exclusion reason: Full Text Not Available;

Siwak 2021	Remote Monitoring Reduces Mortality and Hospitalizations Among COVID-19 Patients. Data from the Polish Nationwide Program	10.2139/ssrn.3927060	Exclusion reason: Wrong intervention;
Skowronski 2021	Single-dose mRNA vaccine effectiveness against SARS-CoV-2, including P.1 and B.1.1.7 variants: a test-negative design in adults 70 years and older in British Columbia, Canada	10.1101/2021.06.07.21258332	Exclusion reason: Wrong intervention;
Skowronski 2021	Comparative single-dose mRNA and ChAdOx1 vaccine effectiveness against SARS-CoV-2, including early variants of concern: a test-negative design, British Columbia, Canada	10.1101/2021.09.20.21263875	Exclusion reason: Wrong intervention;
Sofonea 2021	Quantifying the real-life impacts of vaccination on critical COVID-19		Exclusion reason: Wrong study design;
Soundararajan 2021	FDA-approved COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system	10.21203/rs.3.rs-237155/v1	Exclusion reason: Insufficient follow-up;
Starrfelt 2021	High vaccine effectiveness against COVID-19 infection and severe disease among residents and staff of long-term care facilities in Norway, November â€“ June 2021	10.1101/2021.08.08.21261357	Exclusion reason: Time since vaccination unclear;
Strengert 2021	Cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine in patients on haemodialysis	http://dx.doi.org/10.1016/j.ebiom.2021.103524	Exclusion reason: Wrong outcomes;
Stumpf 2021	Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine	10.1016/j.lanepe.2021.100178	Exclusion reason: Insufficient follow-up;
Subbaraman 2021	Pregnancy and COVID: what the data say	10.1038/d41586-021-00578-y	Exclusion reason: Opinion piece;

Tagliamento 2021	Mortality in adult patients with solid or hematological cancers and SARS-CoV-2 infection with a specific focus on lung and breast malignancies: A systematic review and meta-analysis	http://dx.doi.org/10.1200/JCO.2021.39.suppl.e18608	Exclusion reason: Wrong outcomes;
Tande 2021	Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening	http://dx.doi.org/10.1093/cid/ciab229	Exclusion reason: Insufficient follow-up;
Tang 2021	BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar	10.1101/2021.08.11.21261885	Exclusion reason: Insufficient follow-up;
Tarrant 2020	Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial	http://dx.doi.org/10.1016/S0140-6736%2820%29316 04-4	Exclusion reason: Insufficient follow-up;
Taubel 2021	Longitudinal analysis of COVID-19 infection rates and antibody levels pre-and post-vaccination	http://dx.doi.org/10.1007/s00228-021-03164-3	Exclusion reason: Wrong outcomes;
Teerawattananon 2021	A Systematic Review of Methodological Approaches for Evaluating Real-World Effectiveness of Covid-19 Vaccines: Advising Resource-Constrained Settings	10.2139/ssrn.3900521	Exclusion reason: Wrong study design;
Tene 2021	The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data	http://dx.doi.org/10.1093/cid/ciab438	Exclusion reason: Insufficient follow-up;
Tenforde 2021	Effectiveness of SARS-CoV-2 mRNA Vaccines for Preventing Covid-19 Hospitalizations in the United States	10.1093/cid/ciab687	Exclusion reason: Insufficient follow-up;
Tenforde 2021	Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged >=65 Years - United States, January-March 2021	http://dx.doi.org/10.15585/mmwr.mm7018e1	Exclusion reason: Insufficient Sample Size;

Tessier 2021	Monitoring the COVID-19 immunisation programme through a National Immunisation Management System â€“ Englandâ€™s experience	10.1101/2021.09.14.21263578	Exclusion reason: Wrong study design;
Theodoridou 2020	Paediatric infectious diseases in Greece: Insights from a tertiary reference unit and perspectives for the future	http://dx.doi.org/10.3892/etm.2020.9418	Exclusion reason: Wrong outcomes;
Thomas 2021	1558O COVID-19 vaccine in participants (ptcpts) with cancer: Subgroup analysis of efficacy/safety from a global phase III randomized trial of the BNT162b2 (tozinameran) mRNA vaccine	http://dx.doi.org/10.1016/j.annonc.2021.08.1551	Exclusion reason: Full Text Not Available;
Thompson 2021	Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Healthcare Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March	http://dx.doi.org/10.15585/mmwr.mm7013e3	Exclusion reason: Insufficient follow-up;
Tober-Lau 2021	Long-term immunogenicity of BNT162b2 vaccination in the elderly and in younger healthcare workers	10.1101/2021.08.26.21262468	Exclusion reason: Wrong outcomes;
Tomassetti 2021	Evaluation of S-RBD and high specificity ACE-2-binding antibodies on SARS-CoV-2 patients after six months from infection	10.1016/j.intimp.2021.108013	Exclusion reason: Wrong outcomes;
Toniasso 2021	Reduction in COVID-19 prevalence in healthcare workers in a university hospital in southern Brazil after the start of vaccination	http://dx.doi.org/10.1016/j.ijid.2021.07.025	Exclusion reason: Wrong intervention;
Topol 2021	Messenger RNA vaccines against SARS-CoV-2	10.1016/j.cell.2020.12.039	Exclusion reason: Wrong study design;
Torreggiani 2021	Neutralizing SARS-CoV-2 antibody response in dialysis patients after the first dose of the BNT162b2 mRNA COVID-19 vaccine: the war is far from being won	http://dx.doi.org/10.1016/j.kint.2021.04.010	Exclusion reason: Wrong outcomes;

Trougakos 2021	Comparative kinetics of SARS-CoV-2 anti-spike protein RBD IgGs and neutralizing antibodies in convalescent and naive recipients of the BNT162b2 mRNA vaccine versus COVID-19 patients	http://dx.doi.org/10.1186/s12916-021-02090-6	Exclusion reason: Wrong outcomes;
Truszkowska 2021	Predicting the effects of waning vaccine immunity against COVID-19 through high-resolution agent-based modeling		Exclusion reason: Wrong study design;
Twohig 2021	Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study	http://dx.doi.org/10.1016/S1473-3099%2821%29004 75-8	Exclusion reason: Wrong intervention;
TzurBitan 2021	COVID-19 hospitalisation, mortality, vaccination, and postvaccination trends among people with schizophrenia in Israel: a longitudinal cohort study	10.1016/S2215-0366(21)00256-X	Exclusion reason: Wrong outcomes;
Ukey 2021	Dichotomy between the humoral and cellular responses elicited by mRNA and adenoviral vector vaccines against SARS-CoV-2	10.1101/2021.09.17.21263528	Exclusion reason: Wrong outcomes;
Vahidy 2021	Real World Effectiveness of COVID-19 mRNA Vaccines against Hospitalizations and Deaths in the United States	10.1101/2021.04.21.21255873	Exclusion reason: Study Withdrawn;
Vaishya 2021	SARS-CoV-2 infection after COVID-19 immunization in healthcare workers: A retrospective, pilot study	10.4103/ijmr.ijmr_1485_21	Exclusion reason: Full Text Not Available;
Vaishya 2021	Lack of vaccination and associated comorbidities predispose to the need for intensive care in individuals infected with the delta variant - A case cohort study from a tertiary care hospital in New Delhi, India	10.1016/j.dsx.2021.102203	Exclusion reason: Wrong study design;
Varshney 2021	Sars-cov-2 vaccines: A systematic review		Exclusion reason: Wrong study design;
Vasileiou 2021	Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study	10.1016/S0140-6736(21)00677-2	Exclusion reason: Insufficient follow-up;

Vasileiou 2021	Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People	10.2139/ssrn.3789264	Exclusion reason: Wrong intervention;
Vazin 2021	A focused review on technologies, mechanisms, safety, and efficacy of available COVID-19 vaccines	http://dx.doi.org/10.1016/j.intimp.2021.108162	Exclusion reason: Wrong study design;
Villela 2021	Effectiveness of Mass Vaccination in Brazil against Severe COVID-19 Cases	10.1101/2021.09.10.21263084	Exclusion reason: Wrong comparator;
Visci 2021	One year of SARS-CoV-2 pandemic: comparison of infection between healthcare workers and general population before and after vaccination		Exclusion reason: Wrong outcomes;
Waissengrin 2021	Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors	http://dx.doi.org/10.1016/S1470-2045%2821%2900155-8	Exclusion reason: Wrong outcomes;
Waldman 2021	Real-world impact of vaccination on COVID-19 incidence in healthcare personnel at an academic medical center	http://dx.doi.org/10.1017/ice.2021.336	Exclusion reason: Insufficient follow-up;
Weber 2021	Immunogenicity of COVID-19 Tozinameran Vaccination in Patients on Chronic Dialysis	http://dx.doi.org/10.3389/fimmu.2021.690698	Exclusion reason: Insufficient Sample Size;
Whiteman 2021	Demographic and Social Factors Associated with COVID-19 Vaccination Initiation Among Adults Aged >=65 Years - United States, December 14, 2020-April 10, 2021	http://dx.doi.org/10.15585/mmwr.mm7019e4	Exclusion reason: Wrong outcomes;
Wijtvliet 2021	mRNA-1273 vaccine (Moderna): a better option than BNT162b2 (Pfizer) in kidney transplant recipients and dialysis patients?	10.1101/2021.09.15.21263320	Exclusion reason: Wrong outcomes;
Wilcox CR 2021	Correction: Association between influenza vaccination and hospitalisation or all-cause mortality in people with COVID-19: a retrospective cohort study	10.1136/bmjresp-2020-000857corr1	Exclusion reason: Wrong outcomes;

Williams 2021	Measuring vaccine efficacy against infection and disease in clinical trials: sources and magnitude of bias in COVID-19 vaccine efficacy estimates	10.1101/2021.07.30.21260912	Exclusion reason: Opinion piece;
Williamson 2021	Risks of covid-19 hospital admission and death for people with learning disability: Population based cohort study using the OpenSAFELY platform	http://dx.doi.org/10.1136/bmj.n1592	Exclusion reason: Wrong outcomes;
Wisnewski 2021	Human IgG and IgA responses to COVID-19 mRNA vaccines	http://dx.doi.org/10.1371/journal.pone.0249499	Exclusion reason: Wrong outcomes;
Wu 2021	1562MO Effectiveness of COVID-19 vaccination in cancer patients: A nationwide Veterans Affairs study	http://dx.doi.org/10.1016/j.annonc.2021.08.1555	Exclusion reason: Full Text Not Available;
Xiang 2021	Exploring Drugs and Vaccines Associated with Altered Risks and Severity of COVID-19: A UK Biobank Cohort Study of All ATC Level-4 Drug Categories Reveals Repositioning Opportunities	10.3390/pharmaceutics13091514	Exclusion reason: Wrong intervention;
Xiang 2021	Association of COVID-19 vaccination with risks of hospitalization and mortality due to cardiovascular and other diseases: A study of the UK Biobank	10.1101/2021.08.15.21262097	Exclusion reason: Wrong intervention;
Yalcin 2021	Immunogenicity after two doses of inactivated virus vaccine in healthcare workers with and without previous COVID-19 infection: Prospective observational study	http://dx.doi.org/10.1002/jmv.27316	Exclusion reason: Wrong outcomes;
Yang 2021	Persistent while declined neutralizing antibody responses in the convalescents of COVID-19 across clinical spectrum during the 16 months follow up	10.1101/2021.09.18.21263550	Exclusion reason: Wrong outcomes;
Yang 2021	Endogenously Produced SARS-CoV-2 Specific IgG Antibodies May Have a Limited Impact on Clearing Nasal Shedding of Virus during Primary Infection in Humans	10.3390/v13030516	Exclusion reason: Wrong outcomes;

Yang 2021	Efficacy of ancestral receptor-binding domain, S1 and trimeric spike protein vaccines against SARS-CoV-2 variants B.1.1.7, B.1.351, and B.1.617.1	10.1101/2021.06.02.446698	Exclusion reason: Wrong outcomes;
Yang 2021	Reactogenicity of SARS-CoV-2 vaccines in patients with autoimmune and inflammatory disease	http://dx.doi.org/10.1136/annrheumdis-2021-eular.3834	Exclusion reason: Insufficient Sample Size;
Yang 2021	Association of Age With SARS-CoV-2 Antibody Response	10.1001/jamanetworkopen.2021.4302	Exclusion reason: Wrong outcomes;
Yelin 2021	Associations of the BNT162b2 COVID-19 vaccine effectiveness with patient age and comorbidities	10.1101/2021.03.16.21253686	Exclusion reason: Wrong outcomes;
Ying 2021	Protective activity of mRNA vaccines against ancestral and variant SARS-CoV-2 strains	10.1101/2021.08.25.457693	Exclusion reason: Wrong study design;
Yorsaeng 2021	Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults	10.1101/2021.09.16.21263692	Exclusion reason: Wrong outcomes;
Young-Xu 2021	Coverage and Effectiveness of mRNA COVID-19 Vaccines among Veterans	10.1101/2021.06.14.21258906	Exclusion reason: Time since vaccination unclear;
Yu 2021	mRNA Vaccine-Induced Antibodies More Effective than Natural Immunity in Neutralizing SARS-CoV-2 and its High Affinity Variants	10.21203/rs.3.rs-659065/v1	Exclusion reason: Wrong outcomes;
Zdanowski 2021	Evaluation of sars-cov-2 spike protein antibody titers in cord blood after covid-19 vaccination during pregnancy in polish healthcare workers: Preliminary results	http://dx.doi.org/10.3390/vaccines9060675	Exclusion reason: Wrong outcomes;
Zeng 2021	Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis	10.1101/2021.09.23.21264048	Exclusion reason: Wrong study design;
Zhang 2021	Safety and immunogenicity of a recombinant interferon-armed RBD dimer vaccine (V-01) for COVID-19 in	http://dx.doi.org/10.1080/22221751.2021.1951126	Exclusion reason: Wrong outcomes;

	healthy adults: a randomized, double-blind, placebo-controlled, Phase I trial		

Table App.A7.2 (updated search 18 Oct 2021; n=27 excluded studies)

Study	Title	DOI	Reason for exclusion
Anonymous 2021	Erratum: Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: National prospective cohort study (BMJ (2021) 374 (n2244) DOI: 10.1136/bmj.n2244)	http://dx.doi.org/10.1136/bmj.n2300	Exclusion reason: Wrong outcomes;
Bachul 2021	The impact of covid-19 on kidney transplant recipients in pre-vaccination and delta strain era: A systematic review and meta-analysis	http://dx.doi.org/10.3390/jcm10194533	Exclusion reason: Wrong study design;
Bar-On 2021	Protection Across Age Groups of BNT162b2 Vaccine Booster against Covid-19	10.1101/2021.10.07.21264626	Exclusion reason: Wrong comparator;
Bjork 2021	High level of protection against COVID-19 after two doses of BNT162b2 vaccine in the working age population-first results from a cohort study in Southern Sweden	http://dx.doi.org/10.1080/23744235.2021.1982144	Exclusion reason: Time since vaccination unclear;
Braunisch 2021	Covid-19 vaccination acceptance and hesitancy among healthcare workers in Germany	http://dx.doi.org/10.3390/vaccines9070777	Exclusion reason: Wrong study design;
Chandan 2021	Postvaccination SARS-CoV-2 infection among healthcare workers â€" A Systematic Review and meta-analysis	10.1101/2021.10.04.21264542	Exclusion reason: Wrong study design;
Di Fusco 2021	Evaluation of COVID-19 vaccine breakthrough infections among immunocompromised patients fully vaccinated with BNT162b2	10.1101/2021.10.12.21264707	Exclusion reason: Wrong comparator;
Earnest 2021	Comparative transmissibility of SARS-CoV-2 variants Delta and Alpha in New England, USA	10.1101/2021.10.06.21264641	Exclusion reason: Wrong outcomes;
Emary 2021	Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil	http://dx.doi.org/10.1038/s41467-021-25982-w	Exclusion reason: Wrong outcomes;

Gimenez 2021	Evolution of SARS-CoV-2 immune responses in nursing home residents following full dose of the Comirnaty COVID-19 vaccine	10.1101/2021.10.06.21264616	Exclusion reason: Wrong outcomes;
Goel 2021	mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern	10.1126/science.abm0829	Exclusion reason: Insufficient Sample Size;
Grebe 2021	Estimating COVID-19 vaccine effectiveness using repeat blood donor data	http://dx.doi.org/10.1111/trf.16670	Exclusion reason: Wrong intervention;
Hulme 2021	Comparative effectiveness of ChAdOx1 versus BNT162b2 COVID-19 vaccines in Health and Social Care workers in England: a cohort study using OpenSAFELY	10.1101/2021.10.13.21264937	Exclusion reason: Wrong intervention;
Kostner 2021	Comparing SARS-CoV-2 case rates between pupils, teachers and the general population: results from Germany	10.1101/2021.03.04.21252877	Exclusion reason: Wrong outcomes;
Keegan 2021	Review 2:" Delta variant and mRNA Covid-19 vaccines effectiveness: higher odds of vaccine infection breakthroughs"		Exclusion reason: Wrong comparator;
Naranbhai 2021	Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2 and Ad26.COV2.S COVID-19 vaccines	10.1101/2021.07.18.21260732	Exclusion reason: Wrong outcomes;
Notarte 2021	Effects of Age, Sex, Serostatus and Underlying Comorbidities on Humoral Response Post-SARS-CoV-2 Pfizer-BioNTech Vaccination: " A Systematic Review	10.1101/2021.10.10.21264825	Exclusion reason: Wrong study design;
Pouwels 2021	Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK	10.1101/2021.08.18.21262237	Exclusion reason: Preprint - subsequently published;
Rajakaruna 2021	Dynamical Regulations On Mobility and Vaccinations To Control Covid19 Spread	10.21203/rs.3.rs-949900/v1	Exclusion reason: Wrong study design;

Ranzani 2021	Vaccine effectiveness of Ad26.COV2.S against symptomatic COVID-19 and clinical outcomes in Brazil: a test-negative study design	10.1101/2021.10.15.21265006	Exclusion reason: Wrong study design;
Rossi 2021	BNT162b2 mRNA Vaccination Leads to Long-Term Protection from COVID-19 Disease	10.3390/vaccines9101164	Exclusion reason: Wrong outcomes;
Saragoussi 2021	Test-negative designs applied to COVID-19 vaccine effectiveness assessment: Methodological challenges	http://dx.doi.org/10.1002/pds.5305	Exclusion reason: Wrong study design;
Semenzato 2021	Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: A cohort study of 66 million people	http://dx.doi.org/10.1002/pds.5305	Exclusion reason: Wrong intervention;
Siedner 2021	Duration of viral shedding and culture positivity with post-vaccination breakthrough delta variant infections	10.1101/2021.10.14.21264747	Exclusion reason: Insufficient Sample Size;
Taghioff 2021	The Impact of the Influenza Vaccine on Postoperative Outcomes in Covid-19 Positive Patients: An Analysis of 43,580 Patients Utilizing a Globally Federated Electronic Medical Record Network	http://dx.doi.org/10.1016/j.jamcollsurg.2021.07.156	Exclusion reason: Wrong intervention;
Vaishya 2021	Symptomatic post-vaccination SARS-CoV-2 infections in healthcare workers- A multicenter cohort study	http://dx.doi.org/10.1016/j.dsx.2021.102306	Exclusion reason: Wrong intervention;
Wang 2021	Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021	http://dx.doi.org/10.1002/wps.20921	Exclusion reason: Wrong comparator;

Table App.A8.3 (updated search 27 Oct 2021; n=36 excluded studies)

Study	Title	DOI	Reason for exclusion
Agrawal 2021	COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2.57 million people in Scotland (EAVE II): a prospective cohort study	10.1016/S2213-2600%2821%29003 80-5	Exclusion reason: Insufficient follow-up;
Ambosino 2021	Sars-cov-2 reinfection is a new challenge for the effectiveness of global vaccination campaign: A systematic review of cases reported in literature	10.3390/ijerph1820 11001	Exclusion reason: Wrong study design;
Andrejko 2021	Predictors of SARS-CoV-2 infection following high-risk exposure	10.1101/2021.10.20 .21265295	Exclusion reason: Wrong intervention;
Ben-Dov 2021	Response to Tozinameran (BNT162b2) booster in twice-vaccinated kidney transplant and maintenance dialysis patients	10.1101/2021.10.20 .21264403	Exclusion reason: Wrong outcomes;
Bergami 2021	Humoral and cell-mediated response against SARS-CoV-2 variants elicited by mRNA vaccine BNT162b2 in healthcare workers: a longitudinal observational study	http://dx.doi.org/10. 1016/j.cmi.2021.09. 016	Exclusion reason: Wrong outcomes;
Bianchi 2021	BNT162b2 mRNA COVID-19 vaccine effectiveness in the prevention of SARS-CoV-2 infection and symptomatic disease in five-month follow-up: A retrospective cohort study	10.3390/vaccines91 01143	Exclusion reason: Duplicate;
Bierle 2021	Monoclonal Antibody Treatment of Breakthrough COVID-19 in Fully Vaccinated Individuals with High-Risk Comorbidities	10.1101/2021.10.19 .21265222	Exclusion reason: Wrong comparator;
Brunelli 2021	Comparative Effectiveness of BNT162b2 versus Ad26.COV2.S for the Prevention of COVID-19 among Dialysis Patients	10.1101/2021.10.21 .21265339	Exclusion reason: Time since vaccination unclear;

De 2021	Effectiveness of partial COVID-19 vaccination on the outcome of hospitalized COVID-19 patients during the second pandemic In India	10.21203/rs.3.rs-964720/v1	Exclusion reason: Insufficient follow-up;
Evangelou 2021	Impact of mass vaccination on SARS-CoV-2 infections among the total multiple sclerosis population receiving immunomodulatory disease-modifying therapies in England	10.21203/rs.3.rs-1016584/v1	Exclusion reason: Time since vaccination unclear;
Gardner 2021	Third doses of COVID-19 vaccines reduce infection and transmission of SARS-CoV-2 and could prevent future surges in some populations	10.1101/2021.10.25.21265500	Exclusion reason: Wrong outcomes;
Gounant 2021		10.1016/S1877-1203%2821%2900121-X	Exclusion reason: Wrong outcomes;
Harder 2021	Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection with the Delta (B.1.617.2) variant: second interim results of a living systematic review and meta-analysis, 1 January to 25 August 2021	10.2807/1560-7917.ES.2021.26.41.2100920	Exclusion reason: Wrong study design;
Iftimie 2021	Differential features of the fifth wave of COVID-19 associated with vaccination and the Delta variant in a reference hospital in Catalonia, Spain	10.1101/2021.10.14.21264933	Exclusion reason: Wrong study design;
Ivanauskaite 2021	Successful COVID-19 vaccination for patients on dialysis in Vilnius County	10.1111/hdi.12972	Exclusion reason: Wrong outcomes;
Korves 2021	Coverage and Estimated Effectiveness of mRNA COVID-19 Vaccines among US Veterans	10.1001/jamanetworkopen.2021.28391	Exclusion reason: Time since vaccination unclear;
Kumar 2021	HERD IMMUNITY AND COVID-19 VACCINES-A BRIEF DISCUSSION		Exclusion reason: Wrong study design;
Laing 2021	Durability of antibody responses and frequency of clinical and subclinical SARS-CoV-2 infection six months	10.1101/2021.10.16.21265087	Exclusion reason: Wrong outcomes;

	after BNT162b2 COVID-19 vaccination in healthcare workers		
Marques 2021	SARS-CoV-2 variants associated with vaccine breakthrough in the Delaware Valley through summer 2021	10.1101/2021.10.18.21264623	Exclusion reason: Wrong outcomes;
Martinez-Baz 2021	Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021	10.2807/1560-7917.ES.2021.26.39.2100894	Exclusion reason: Insufficient follow-up;
Mason 2021	Effects of BNT162b2 mRNA vaccine on COVID-19 infection and hospitalisation amongst older people: matched case-control study for England	10.1186/s12916-021-02149-4	Exclusion reason: Insufficient follow-up;
Massarweh 2021	Immunogenicity of The BNT162b2 mRNA COVID-19 Vaccine in Patients With Primary Brain Tumors: A Prospective Cohort Study	10.21203/rs.3.rs-986572/v1	Exclusion reason: Wrong outcomes;
Peeters 2021	Reduced humoral immune response after BNT162b2 coronavirus disease 2019 messenger RNA vaccination in cancer patients under antineoplastic treatment	10.1016/j.esmoop.2021.100274	Exclusion reason: Wrong outcomes;
Pierobon 2021	Outbreak of SARS-CoV-2 B.1.617.2 (Delta) variant in a Nursing Home 28 weeks after two doses of mRNA anti-Covid-19 vaccines: evidence of a waning immunity	10.1101/2021.10.25.21265370	Exclusion reason: Insufficient Sample Size;
Reis 2021	Effectiveness of BNT162b2 Vaccine against Delta Variant in Adolescents	10.1056/NEJMc2114290	Exclusion reason: Insufficient follow-up;
Romero-Ibarguengoitia 2021	Effect of the third dose of BNT162b2 vaccine in quantitative SARS-CoV-2 spike 1-2 IgG antibody titers in healthcare workers	10.1101/2021.10.20.21265269	Exclusion reason: Wrong intervention;
Sapienza 2021	Evaluation of the effectiveness and safety of the bnt162b2 covid-19 vaccine in the vaccination campaign among the health workers of fondazione policlinico universitario agostino gemelli irccs	10.3390/ijerph182111098	Exclusion reason: Wrong intervention;

Sariol 2021	Limited impact of Delta variants mutations in the effectiveness of neutralization conferred by natural infection or COVID-19 vaccines in a Latino population	10.1101/2021.10.25.21265422	Exclusion reason: Wrong outcomes;
Schwartz 2021	Impact of mRNA vaccines in curtailing SARS-CoV-2 infection and disability leave utilisation among healthcare workers during the COVID-19 pandemic: Cross-sectional analysis from a tertiary healthcare system in the Greater Houston metropolitan area	10.1136/bmjopen-2021-054332	Exclusion reason: Wrong outcomes;
Shehab 2021	Immunogenicity of BNT162b2 Vaccine in Patients with Inflammatory Bowel Disease on Infliximab Combination Therapy: A Multicenter Prospective Study	10.1101/2021.10.20.21265239	Exclusion reason: Wrong outcomes;
Singh 2021	Effectiveness of COVID-19 Vaccine in Preventing Infection and Disease Severity: A Case-control Study from an Eastern State of India	http://dx.doi.org/10.1017/S0950268821002247	Exclusion reason: Wrong outcomes;
Slezak 2021	Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study	http://dx.doi.org/10.1016/S0140-6736%2821%2902183-8	Exclusion reason: Duplicate;
Strahm 2021	Symptoms compatible with long-COVID in healthcare workers with and without SARS-CoV-2 infection â€“ results of a prospective multicenter cohort	10.1101/2021.10.19.21265187	Exclusion reason: Wrong study design;
Thathai 2021	Study of COVID-19 Infection, its Severity and Outcome in COVID-19 Vaccinated People at Tertiary Healthcare Center, North West Rajasthan		Exclusion reason: Insufficient Sample Size;
Wack 2021	No SARS-CoV-2 reinfection among staff health-care workers: Prospective hospital-wide screening during the first and second waves in Paris	10.1016/j.jcv.2021.104999	Exclusion reason: Wrong outcomes;
Yamamoto 2021	COVID-19 breakthrough infections and pre-infection neutralizing antibody	10.1101/2021.10.20.21265301	Exclusion reason: Wrong comparator;

Appendix B Quality Appraisal of included observational studies

The quality appraisal of a cohort or a cross sectional study was assessed using tool: The National Institutes of Health (NIH) quality assessment tool for Cohort and Cross Sectional Studies, available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Table App.B1: Quality appraisal of cohort studies

Quality appraisal criteria	Chemaitelly (2021) [46]	Nordstrom (2021)	Liu (2021) [48]	Polinski (2021)[35]	Pouwels (2021)[53]	Saciuk (2021)[54]
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	✓	✓
3. Was the participation rate of eligible persons at least 50%?	✓	✓	✓	✓	CD	✓
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	✓	✓	X	✓	✓	✓
5. Was a sample size justification, power description, or variance and effect estimates provided?	✓	✓	✓	✓	✓	✓

Quality appraisal criteria	Chemaitelly (2021) [46]	Nordstrom (2021)	Liu (2021) [48]	Polinski (2021)[35]	Pouwels (2021)[53]	Saciuk (2021)[54]
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✓
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	✓	X	✓	X	✓	X
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	X	✓	✓
10. Was the exposure(s) assessed more than once over time?	✓	✓	✓	✓	✓	✓
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	CD	CD	✓	✓	✓	CD
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD

Quality appraisal criteria	Chemaitelly (2021) [46]	Nordstrom (2021)	Liu (2021) [48]	Polinski (2021)[35]	Pouwels (2021)[53]	Saciuk (2021)[54]
13. Was loss to follow-up after baseline 20% or less?	✓	✓	✓	✓	CD	✓
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	X	X	X	✓	✓	✓
Quality Rating†	**Fair**	Fair	Fair	Poor	Good	Fair
Comment	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level	Some concern regarding outcome ascertainment bias, and certain confounders not taken into consideration	Some concerns regarding how participants were recruited, and certain confounders not taken into consideration	Critical potential for bias by assuming that 40% are unvaccinated are actually vaccinated		Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level

The quality appraisal of a case-control study was assessed using tool: The National Institutes of Health (NIH) quality assessment tool for CASE-Control studies, available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Table App.B2: Quality appraisal of case-control studies

Quality appraisal criteria	Andrews (2021)[44]	Pilishvili (2021) [51]	McKeigue (2021) b [49]	Tenforde (2021) [55]	Thompson (2021) [83]
1. Was the research question or objective in this paper clearly stated and appropriate?	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	✓
3. Did the authors include a sample size justification?	X	✓	X	X	✓

Quality appraisal criteria	Andrews (2021)[44]	Pilishvili (2021) [51]	McKeigue (2021) b [49]	Tenforde (2021) [55]	Thompson (2021) [83]
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	✓	✓	✓	✓	✓
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	CD	✓
6. Were the cases clearly defined and differentiated from controls?	✓	✓	X	✓	✓
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	✓	N/A	N/A	CD	✓
8. Was there use of concurrent controls?	✓	✓	✓	CD	✓
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	✓	✓	✓	✓	✓
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	✓	✓	✓	✓	✓
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	CD	CD	CD	CD	CD
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	✓	✓	✓	✓	✓
Quality Rating†	Good	Good	Good	Fair	Good

Quality appraisal criteria	Andrews (2021)[44]	Pilishvili (2021) [51]	McKeigue (2021) b [49]	Tenforde (2021) [55]	Thompson (2021) [83]
Comment				Incomplete information on matching process. Most key confounding variables adjusted for no adjustment for socioeconomic status.	

†Quality can be rated as Good, Fair or Poor**.** ✓Yes. **x** No, CD = could not be determined, NA = not applicable, NR = none reported.

Appendix C Data Extraction (search conducted on 27 October 2021)

Randomised Control Trials

Janssen

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Sadoff (2021)[38] **Title:** Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19 **DOI:** 10.1056/NEJMoa2101544 FDA Emergency Use Authorisation Report (Janssen Biotech) **NCT**: NCT04505722 **Study Design***:* RCT **Country**: Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the USA **Setting***:* General Population **Time Period***:*	**Intervention**: Ad26.COV2.S (Janssen) **Comparator:** Placebo (saline) **Time since final vaccination dose:** Median 8.29 weeks	**Description:** Stage A enrolled patients 18+ in good health. Stage B was initiated later and included patients with comorbidities. Participants with evidence of previous infection (or seropositive status) were excluded from the primary analysis (per protocol) but were not excluded from the trial. **N:** Per protocol set (FDA report) Ad26.COV2.S : 19,630 Placebo : 19,691 **Age: Median** 53 years (Range 18 to 100) ≥60 years: 34.6% ≥75 years: 3.7% **Male** = 54.5% **Comorbidities**: ≥1 Coexisting condition 39.9% **Sspecial populations**: Asthma: 1.3% (FAS) 1.5% (PP) Cancer 0.5% 1.4% (PP)	**Severe Disease** ≥ 28 days post vaccination (per protocol, seronegative at baseline)* *Hospitalisations* VE 100% (95% CI 74.3 to 100) *Severe Critical ~:* VE 85.4 (95% CI 54.2 to 96.9) *Moderate to Severe Critical +~* VE 66.1 (95% CI 55.0 to 74.8) **Mortality:** 3 deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related). All of which were considered by the investigators to be unrelated to the trial intervention.	**RT-PCR or Antigen Confirmed SARS-CoV-2 infection** (≥ 28 days follow-up Per protocol and seronegative) *Asymptomatic:* VE 65.5%; (95% CI 39.9 to 81.1) # *Symptomatic of any severity* VE 66.5% (95% CI 55.5 to 75.1) *Mild+:* Not computable (Zero cases in the Ad26.COV2.S group and 2 cases in the placebo group. *Moderate^:* VE 62.0% (95% CI 48.7 to 72.2) **Adjustments:** N/A

21 September 2020 to 22 January 2021 (some endpoints reported up to a data cut of February 5th from FDA report) **Variants of Concern:** NR **Publication status**: Peer-reviewed		CF <0.1% CKD 0.5% COPD: 1% 0.9% (PP) ICP <0.3% Pulmonary fibrosis <0.1%	All-Cause mortality (FAS) – FDA 22 Jan Cut Off *≥ 14 days post vaccination* VE 80.0% (95% CI 29.4 to 96.3) *≥ 28 days post vaccination* VE 75% (95% -25.2 to 97.4) At the later data cut of 5 Feb, (FDA report) there were 7 COVID-19 related deaths – all in the placebo group. **Adjustments:** N/A **Subgroups:** *Moderate to Severe-Critical COVID 19 ≥ 28 days post second vaccination.* A lower point estimate of VE was observed among participants 60 years of age or older with coexisting conditions for moderate to severe-critical COVID-19 (64.9%; 95% CI 42.2-79.4%). But subgroup analysis by age or co-morbidity on moderate to severe-critical COVID-19 showed no evidence to support a differential treatment effect (interaction p=0.25). However, the analysis was not powered for this.	**Subgroups:** *Symptomatic Covid-19 (weighted by burden of disease) (EPAR)* Age 18 – 59 years: VE: 69.3% (95% CI 57.4 to 77.7) ≥60 years : VE 67.9% (95% CI 38.2 to 82.8) **Variants:** NR **Efficacy over Time:** NR

			Asthma: 0 cases in 34.1 years follow up in the Ad26.COV2.S and 4 cases in the placebo arm in 38.9 person-years follow-up. (VE not estimable) Cancer: 0 cases in either arm after 14.1 and 14.8 person years follow up in the Ad26.COV2.S and placebo arms respectively. (VE not estimable) Chronic Kidney Disease: 0 cases in 29.9 person years follow up in the intervention and control groups. (VE not estimable) COPD: 1 cases in 30.1 years follow up in the Ad26.COV2.S and 3 cases in the placebo arm in 27.9 person-years follow-up. (VE not estimable) <u>Serious heart conditions</u>: VE = 79.4%(-83.7 to 99.6) <u>HIV:</u> VE = 47.5% (95% CI -266 to 95.3%) <u>Hypertension</u> VE = 35.7%(-45.6 to 72.8) Immunocompromised from blood transplant: 1 case in the Ad26.COV2.S arm in 35 person years of follow-up and 0 cases in the placebo arm with 32	

			person years follow up. (VE not estimable) Liver disease: 1 case in 96 person-years follow-up in the intervention arm, 0 cases in 98 person years in the control arm. (VE not estimable) Neurologic conditions: 0 cases in 77 years follow-up in the intervention arm, 1 case in the 114 person-years in the control arm (VE not estimable) Obesity: VE = 65.9% (47.8 to 78.3) <u>Diabetes Mellitus, type 2</u> VE: 23.0% (-90.1 to 69.8) <u>With comorbidities[@]</u> VE = 58.6% (95% CI 40.6 to 71.6) <u>Without comorbidities[@]</u> *Moderate to Severe-Critical COVID-19* VE = 68.8% (CI 59.0 to 76.6) **Variants of Concern:** Despite the high prevalence of the Beta variant in South Africa (94.5% of sequenced cases); VE was 64.0% against moderate to severe–critical disease and 81.7% against severe–critical disease with onset at ≥28 days after administration	

			Efficacy over Time: The onset of efficacy was evident as of 14 days after administration for moderate to severe–critical disease and as of 7 days after administration for severe–critical disease. Efficacy continued to increase through approximately 8 weeks after administration, especially for severe–critical Covid-19. No evidence of waning efficacy was noted among the approximately 3000 participants who were followed for 11 weeks or among 1,000 participants who were followed for 15 weeks.	

*Includes non-centrally confirmed cases.

The analysis of vaccine efficacy against asymptomatic infection included all the participants with a newly positive N-immunoassay result at day 71 (i.e., those who had been seronegative or had no result available at day 29 and who were seropositive at day 71). Only 2650 participants had an N-immunoassay result available at day 71, and therefore only a preliminary analysis could be performed.

+Mild cases of Covid-19 were defined as a positive result on RT-PCR testing and the presence of at least one of the following symptoms: fever (body temperature, ≥38.0°C), sore throat, malaise, headache, myalgia, gastrointestinal symptoms.

^Moderate cases were defined as a positive RT-PCR test and either the presence of at least two of the following symptoms: fever (≥38.0°C), heart rate of at least 90 beats per minute, shaking chills or rigors, sore throat, cough, malaise, headache, myalgia, gastrointestinal symptoms, loss of taste or smell, or red or bruised-looking feet or toes; or the presence at least one of the following symptoms: respiratory rate of at least 20 breaths per minute, abnormal oxygen saturation (but >93% while the patient was breathing ambient air at sea-level), clinical or radiologic evidence of pneumonia, radiologic evidence of deep-vein thrombosis, or shortness of breath or difficulty breathing.

~Severe–critical cases were defined as a positive RT-PCR test and the presence of at least one of the following features: clinical signs at rest that were indicative of severe systemic illness (respiratory rate of ≥30 breaths per minute, heart rate of ≥125 beats per minute, oxygen saturation of ≤93% while the patient was breathing ambient air at sea level, or partial pressure of oxygen divided by the fraction of inspired oxygen, <300 mm Hg); respiratory failure (defined as the use of high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation);shock; clinically meaningful acute renal, hepatic, or neurologic dysfunction; intensive care unit admission; or death.

@ Comorbidities include: Asthma, Cancer, Chronic Kidney Disease, COPD, Serious heart conditions, HIV infection, Hypertension, Immuno-compromised from blood transplant, liver disease, neurologic conditions, obesity, Type 2 Diabetes Mellitus.

Key: CI – Confidence Interval; COPD – Chronic Obstructive Pulmonary Disorder; CF – Cystic Fibrosis, CKD – Chronic Kidney Disease; EPAR – European Public Assessment Report; FAS – Full Analysis Set; FDA – Food and Drug Administration; ICP – Immunocompromised State; N/A – Not applicable; NCT – National Clinical Trial; NR – Not Reported; PP – Per-protocol; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Moderna

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Baden (2021)[45] **Title:** Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine **DOI:** 10.1056/NEJMoa2035389 European Public Assessment Report **NCT:** NCT04470427 **Country**: USA **Setting***:* Ninety-nine Clinical Trial Sites **Time Period***:* 27 July 2020 to 21 November 2020. **Variants of Concern:** NR **Publication status**: Peer-reviewed	**Intervention:** mRNA-1273 (Moderna) **Control:** Placebo (Saline) **Time since final vaccination dose:** Median 9 weeks (Range 0 – 13.86)	**Description:** Adults aged 18 years of age or older with no known history of SARS-CoV-2 infection, in locations or circumstances that put them at an appreciable risk of SARS-CoV-2 infection, a high risk of severe covid-19 or both. Participants who were seropositive at baseline were excluded from the primary and secondary analyses (per protocol) but were not excluded from the trial. The FAS therefore includes individuals who were both seropositive and seronegative at baseline. **N:** 28,207 (PP) Intervention – 14,134 Control – 14,073 **Age:** Mean 51.6 years (Range: 18-95) **Male** = 52.6 % **Co-morbidities:** Chronic lung disease – 4.8% Healthcare Workers – 25.1% [+] Personal Care or In-home services – 3.1%[+] Nursing Home or Assisted Living Facility – 0.2%[+]	**Severe Disease:** **≥14 days after second dose** *Severe Disease~* VE – 100% (95% CI NE to 1.0) *Hospitalisations [#]* Intervention – 0 Control – 9 *ICU admissions [#]* Intervention – 0 Control - 2 **Adjustments:** NA **Mortality** [$] *COVID-19 related death* Intervention – 0 Control - 1 Three deaths occurred in the placebo group (two in the vaccine group)	**Confirmed RT-PCR ≥14 days after second/final dose** *Symptomatic[@]* (PP) VE = 94.1% (95% CI 89.3 to 96.8%) *Symptomatic[@]* (FAS) VE = 93.6% (95% CI 88.6 to 96.5) **Adjustments:** N/A **Variants of Concern:** NR **Subgroups:** *Symptomatic infection by age [@]* ≥18 to <65 yr. VE = 95.6 (95% CI 90.6 to 97.9) ≥65 years

			Based on the pharmacovigilance database which includes data from study start through 3 December 2020, there have been 13 deaths during the study. Six participants who died received mRNA-1273 and 7 received placebo. **Variants of Concern:** NR **Subgroups**: *Severe COVID-19 in those at risk of severe COVID-19** Intervention – 0 Control – 20 *Severe COVID-19 in those >65 years* Intervention – 0 Control – 10 **Efficacy/effectiveness over time: NR**	VE = 86.4 (95% CI 61.4 to 95.2) ≥65 to ≤75 VE = 82.4% (95% CI 46.9 to 93.9) 75 and older € VE = 100% (95% CI NE, 100%) *Symptomatic infection by risk for severe COVID-19 @* At risk * VE = 90.9% (95% CI 74.7 to 96.7) Not at risk * VE = 95.1% (95% CI 85.2 to 96.8) 18 and <65 and at risk* VE = 94.4% (95% CI 76.9 to 98.7) 18 to <65, not at risk VE = 95.9 (90.0–98.3) ≥65 and at risk* VE = 75.2% (NE, 94.7%) No risk factors * VE = 95.1 (95% CI 89.6 to 97.7) Only 1 risk factor *

				VE = 91.7 (95% CI 73 to 97.4) ≥ 2 risk factors *,% VE = 87.2 (95% CI -2.7 to 98.4) **Efficacy over time**.NR

Abbreviations – PPA = per-protocol analysis (includes those who are seronegative at baseline), FAS = Full Analysis Set (includes all participants regardless of baseline serostatus).

* Definition for at risk of severe COVID 19. includes Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma, Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension), Severe obesity (body mass index ≥ 40 kg/m2), Diabetes (Type 1, Type 2 or gestational), Liver disease, HIV infection

Results presented from the population with severe COVID-19 only.

$ Definition of mortality used: Vaccine efficacy of mRNA-1273 to prevent death due to a cause directly attributed to a complication of Covid-19, starting 14 days after the second IP dose.

~ Severe disease was defined as one of the following criteria: respiratory rate of 30 or more breaths per minute; heart rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; acute respiratory distress syndrome; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death

+ Results presented for the safety set (n=30,351) which includes all individuals regardless of baseline serostatus. This included (n=680) participants who were seropositive at baseline.

@ Definition of symptomatic COVID-19 - Covid-19 is defined as symptomatic disease based on the following criteria: The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND The participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR. Note, results for a secondary definition are also available.

^ Obtained from the European Public Assessment Report (Available at https://www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf). [Accessed on 08/09/21]

€ Given the few participants (n = 1318) above 75 and only 7 accrued cases in the placebo arm (none in the active arm) no reliable estimates in this group can be derived.

% Given the very low number of participants with more than one risk factor, this trend cannot be confirmed.

& Obtained from the EPAR report

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): El Sahly (2021) [47] **Title:** Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase **DOI:** 10.1056/NEJMoa2113017 **NCT:** NCT04470427 **Study Design***:* RCT **Country**: USA **Setting***:* Clinical Trial **Time Period***:* 27 July 2020 to 26 March 2021 **Variants of Concern:** Low circulation. **Publication status**: Peer-reviewed	**Intervention/Exposure**: mRNA-1273 **Comparator/Control:** Placebo (Saline) **Time since final vaccination dose:** Median – 21.08 weeks (Duration of follow up from 0 to 220 days for 113 participants).	**Description:** Adults at least 18 years old with no known history of SARS-CoV-2 infection and whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection or who were at high risk for severe disease. **N:** Efficacy population - 28,451 FAS – 30,346 **Age:** (FAS) Mean – 51.4 (Range 18-95) **Male** (FAS) = 52.6% **Co-morbidities** (FAS)**:** Chronic Lung Disease – 4.8% Significant Cardiac Disease – 5.0% Severe obesity – 7.0% Diabetes – 9.6% Liver disease – 0.7% HIV – 0.6% Healthcare Providers – 25.2% Emergency Response – 2.0% Personal Care and In-Home Services – 3.1% Nursing home or assisted living facility – 0.2%	**Severe Disease: ≥14 days after second/final dose** *Severe Disease* [%] VE = 98.2% (95% CI 92.8 to 99.6) *Hospitalisation*[*] Intervention – 1 Placebo – 27 *ICU admissions* Intervention – 0 Placebo - 4 **Adjustments:** N/A **Mortality** *COVID-19* VE = 100% (95% CI NE to 100) **Variants of Concern:** NR **Subgroups**: NA **Efficacy/effectiveness over time:** NR	**Confirmed RT-PCR infection (PP)** **≥14 days after second/final dose** [$] *Symptomatic* VE = 93.2 (95% CI 90.9 to 94.8) *Asymptomatic* VE = 63.0% (95% CI 56.6 to 68.5) *Any* VE 82.0% (95% CI 79.5 to 84.2) **Adjustments:** N/A **Variants of Concern:** NR **Subgroups** To Prevent Symptomatic Confirmed RT-PCR infection Covid-19[$](PP) by age *≥18 to <65 years* VE = 93.4% (95% CI 91.1 to 95.1)

				≥65 years VE = 91.5% (95% CI 83.2 to 95.7) ≥65 to <75 years VE = 89.7% (95% CI 79.6 to 94.9) ≥75 years VE = 100% (95% NE to 100) <u>To Prevent Symptomatic Confirmed RT-PCR infection Covid-19[$](PP) by comorbidity or risk group</u> *Healthcare Providers* VE = 94.4% (95% CI 90.3 to 96.8) *Emergency Response providers* VE = 93.0% (95% CI 70.6 to 98.4) *Personal care and in-home service providers* VE = 93.5% (95% to 72.8 to 98.5) **Co-existing Conditions** Chronic lung disease VE = 87.2% (63.8 to 95.5) Significant cardiac disease VE = 88.0% (65.9 to 95.8) Severe obesity (BMI >40) VE = 91.4% (81.4 to 96.0)

				Diabetes VE = 96.2% (87.9 to 98.8) Liver disease VE = 81.0% (−64.8 to 97.8) HIV VE = 100% (NE to 100) **Efficacy/effectiveness over time** To Prevent Symptomatic Confirmed RT-PCR infection Covid-19$(PP) over time *≥14 Days to <2 months* VE = 91.8 (95% CI 86.9 to 95.1) *2 months to <4 months* VE = 94.0 (95% CI 91.2 to 96.1) *≥ 4 months* VE = 92.4% (95% CI 84.3 to 96.8 There is no evidence of waning efficacy in the Kaplan Meier curve for the 23,395 patients at 17.1 weeks or 113 patients at 31.3 weeks.

* Due to SARS-CoV-2
% Severe Covid-19 was defined as confirmed Covid-19 plus one clinical sign of severe systemic illness

$ Per protocol. Covid-19 cases were defined by at least 2 systemic symptoms (temperature ≥38°C, chills, myalgia, headache, sore throat, or new olfactory or taste disorders), or at least one respiratory sign or symptom (cough, shortness of breath, or clinical or radiologic evidence of pneumonia), and were confirmed by positive SARS-CoV-2 reverse-transcriptase polymerase chain- reaction (RT-PCR) assay of nasopharyngeal swab, nasal, or saliva samples.

^ Asymptomatic infection was identified by absence of symptoms and infections as detected by RT-PCR or seroconversion.

Key: CI – Confidence Interval; ICU – Intensive Care Unit; FAS – Full Analysis Set; ICU – Intensive Care Unit; N/A – Not applicable; NCT – National Clinical Trial; NR – Not Reported; PP – Per-protocol; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Pfizer

(These two papers report separate analysis from the same trial at different time points.)

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Polack (2020)[52] **Title:** Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine **DOI:**10.1056/NEJMoa2034577 **NCT:** NCT04368728 **Study Design***:* RCT, multinational, placebo-controlled, observer-blinded, pivotal efficacy trial **Country:** International [number of sites]: US [n=130], Argentina [n=1], Brazil [n=2], South Africa [n=4], Germany [n=6], Turkey [n=9]	**Intervention/Exposure**: Vaccination with BNT162b2 (Pfizer/BioNtech) **Comparator/Control:** Placebo (saline) **Time since final vaccination dose:** Average follow up time per person from dose 2: 7.55 weeks (treatment) 7.54 weeks (placebo)	**Description: Adults aged ≥16 years who were healthy or had stable chronic medical conditions.** Analysis done for seronegative only and also for those with and without evidence of SARS-CoV-2 **N:** 43,548 Underwent randomization. 43,448 Were injected with vaccine or placebo 21,720 Were assigned to receive BNT162b2 21,728 Were assigned to receive placebo The modified intention-to-treat efficacy population includes all age groups 12 years of age or older (43,355 persons; 100 participants who were 12 to 15 years of age contributed to person-time years but included no cases Of those with median ≥ 2 months f/up, 18,556 Received dose 2 of BNT162b2 18,530 Received dose 2 of placebo **Age:** median = 52 years for those ≥16 years	**Severe Disease:** **≥7 days after second dose** *Severe Disease* Vaccine efficacy: 75% (95%CI -52 to 99.5) *Hospitalisation* NR *ICU admissions* NR **Adjustments:** surveillance time **Mortality** *All Cause* NR *COVID-19* NR **Variants of Concern**: NR **Subgroups**: NR **Efficacy/effectiveness over time.** NR	**Confirmed RT-PCR SARS-CoV-2 infection*** **≥7 days after second dose** *Symptomatic* a) (seronegative) VE 95.0% (95% CI 90.3 to 97.6) b) Regardless of evidence of prior infection 94.6% (95% CI 89.9 to 97.3) **Adjustments:** Surveillance time **Variants of Concern:** NR **Subgroups** In sub-group analysis, the vaccine efficacy ranged

<table>
<tr>
<td>Time Period: 27 July 2020 -14 November 2020 (enrolment period).

Variants of Concern: NR

Publication status: Peer-reviewed</td>
<td></td>
<td>(100 participants who were 12 - 15 years contributed to person-time years but included no cases)

Male = 50.6 %

Co-morbidities:
19 reported,
e.g. diabetes, malignancy, chronic pulmonary disease, cerebrovascular disease, combined for Charlson comorbidity index

Participants with any Charlson comorbidity: 20.5% (N = 37,706)</td>
<td></td>
<td>from 91.7% to ~100% for combinations of age (16-64 v. 65+) and at risk (yes/no)

At risk is defined as having at least one of the Charlson Comorbidity Index categories or obesity

<u>At risk £</u>

VE = 95.3 (87.7, 98.8)

<u>Not at risk £</u>

VE= 94.7 (85.9 to 98.6)

<u>Obese $</u>

VE = 95.4 (86.0 to 99.1)

<u>Non-Obese $</u>

VE = 94.8 (87.4 to 98.3)

<u>Hypertension</u>

VE = 94.6 (68.7 to 99.9)

Efficacy/effectiveness over time: NR</td>
</tr>
<tr>
<td colspan="4">Vaccine effectiveness by underlying comorbidities and age group
<table>
<tr><th>Risk£</th><th>VE(95% CI)</th><th></th><th>Obese$</th><th>VE(95% CI)</th></tr>
<tr><td>16 – 64 years and not at risk</td><td>94.2 (84.4, 98.5)</td><td></td><td>16–64 and not obese</td><td>95.2 (87.3, 98.7)</td></tr>
<tr><td>16 – 64 and at risk</td><td>95.9 (87.6, 99.2)</td><td></td><td>16–64 and obese</td><td>94.9 (84.4, 99.0)</td></tr>
<tr><td>≥65 and not at risk</td><td>100 (29.0, 100)</td><td></td><td>≥65 and not obese</td><td>91.8 (44.5, 99.8)</td></tr>
<tr><td>≥65 and at risk</td><td>91.7 (44.2, 99.8)</td><td></td><td>≥65 and obese</td><td>100 (27.1, 100)</td></tr>
</table>
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<td></td>
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<tr>
<td colspan="5">* The definition of confirmed COVID-19 included the presence of ≥1 symptom (i.e., fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea, vomiting) and being SARS-CoV- 2 NAAT-positive during, or within 4 days before or after, the symptomatic period (either at the central laboratory or at a local testing facility and using an acceptable test).</td>
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#Diagnosis of severe COVID-19 included confirmed COVID-19 and the presence of ≥1 of the following: (1) clinical signs at rest indicative of severe systemic illness (e.g., respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mmHg; (2) respiratory failure (i.e., needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); (3) evidence of shock (i.e., systemic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors); (4) significant acute renal, hepatic, or neurologic dysfunction; (5) intensive care unit(ICU) admission; or (6) death. Severe COVID-19, as defined by the US Centers for Disease Control and Prevention (CDC), includes: 1) hospitalization; 2) admission to the ICU; 3) intubation or mechanical ventilation; or 4) death (https://www.cdc.gov/coronavirus/2019-ncov/need-extraprecautions/people-with-medical-conditions

£ At risk is defined as having at least one of the Charlson Comorbidity Index categories or obesity (body mass index [BMI] ≥30 kg/m^2).

$ Obese is defined as BMI ≥30 kg/m^2.

Key: CI – Confidence Interval; ICU – Intensive Care Unit; F/UP – follow-up; NCT – National Clinical Trial; NR – Not Reported; PP – Per-protocol; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Thomas (2021)[56] **Title:** Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months **DOI:** 10.1056/NEJMoa2110345 **NCT:** NCT04368728 **Study Design***:* RCT (ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy study)	**Intervention** BNT162b2 (Pfizer/BioNtech) **Comparator/Control:** Placebo (saline injection) **Time since final vaccination:** Mean 16.7 weeks (intervention) 16.1 weeks (placebo) Up to 6 months follow-up post vaccination	**Description:** Vaccine efficacy was assessed in seronegative only and separately with previous positives included. **N:** Randomised: 44,165 Total: 44, 060 Intervention:22,030, placebo: 22,030 **for participants ≥16 years old,** total: 44,047 intervention:22026, placebo: 22,021 **Age:** median 51.0 (min = 16,max = 91) **Male** = 50.9%	**Severe Disease:** **≥7 days after second/final dose** *Severe Disease* # VE (≥12 yrs., those with and without prior evidence of infection): 95.7% (95%CI 73.9, 99.9) *Hospitalisation* NR *ICU admissions* NR **Adjustments:** For surveillance time **Mortality** There were 15 deaths in the BNT162b2 arm (1 due to COVID-	**Confirmed RT- SARS-CoV-2 infection*** *Symptomatic* *Seronegative only:* VE (≥12 yrs.) was 91.3% (95% CI 89.0–93.2) Irrespective of prior SARS-CoV-2 infection Vaccine efficacy (≥12 yrs.): 91.1% (95% CI 88.8 to 93.0). **Adjustments:** Surveillance time **Variants of Concern:** NR **Subgroups:**

Note: from Dec 2020, participants ≥16yrs had option for un-blinding. Un-blinded participants were followed in open-label study. Results here represent blinded period only. **Country**: international [number of sites]: US [n=130], Argentina [n=1], Brazil [n=2], South Africa [n=4], Germany [n=6], Turkey [n=9] **Time Period***:* Between 27 July and 29 Oct 2020, participants were enrolled. Efficacy analysis conducted on cases accrued to 13 Mar 2021. **Variants of Concern:** B.1.351 (beta) **Publication status**: Peer-reviewed		**Co-morbidities:** 34% BMI ≥30 g/m2, 21% had ≥1 underlying comorbidity	19) and 14 deaths in the placebo arm. (1 due to COVID-19) **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time**. NR	For beta variant (seronegative, South Africa site): Vaccine efficacy: 100% (95% CI 53.5 to 100) Although the study was not powered to definitively assess efficacy by subgroup, supplemental analyses indicated that VE post-dose 2 among subgroups defined by age, sex, race, ethnicity, presence of comorbid conditions, and country was generally consistent with that observed in the overall population. Subgroup analysis by age, obesity or co-morbidity on COVID-19 infection showed no evidence to support a differential treatment effect. At risk[†] VE = 91.6 (88.2 to 94.3) Not at risk VE = 91.0 (87.6 to 93.6) 16–64 and at risk[†] VE = 91.5 (87.5 to 94.4) ≥65 and at risk VE = 91.8 (81.4 to 97.1) Obese[‡]

				91.6 (87.6 to 94.6) Not Obese VE = 91.1 (88.1 to 93.5) 16-64 and obese VE = 91.3 (86.7 to 94.5) ≥65 and obese VE = 93.2 (78.9 to 98.7) **Efficacy/effectiveness over time.** Evaluated on those with or without evidence of prior infection Time after dose two: ≥7 days to <2 months: VE 96.2% (95% CI 93.3 to 98.1) ≥ 2 months to < 4 months VE 90.1% (95% CI 86.6 to 92.2) ≥ 4 months VE 83.7% (74.7% to 89.9%) It is stated that: Vaccine efficacy peaked at 96.2% (95% CI 93.3 to 98.1) during the interval from 7 days to <2 months post-dose 2, and declined gradually to 83.7% (95%

				CI 74.7-89.9) from 4 months to the data cut-off

*The definition of SARS-CoV-2-related cases was the presence of ≥1 of the following symptoms and SARS-CoV-2-NAAT positivity during or within 4 days before or after the symptomatic period: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea, and/or vomiting. The onset date of the case was the date that symptoms were first experienced by the participant. If new symptoms were reported ≤4 days after resolution of all previous symptoms, they were considered part of a single illness.

#Confirmed severe COVID-19 required confirmation of COVID-19 and the presence of ≥1 of the following: clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mmHg); respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors); significant acute renal, hepatic, or neurologic dysfunction; intensive care unit admission; and/or death.

†At risk includes participants who had ≥1 Charlson Comorbidity Index category or obesity (body mass index [BMI] ≥30 kg/m^2 [≥16 years old] or BMI ≥95th percentile [12–15 years old]).

‡Obesity defined as participants who had BMI ≥30 kg/m^2 (≥16 years old) or BMI ≥95th percentile (12–15 years old).

Key: BMI – Body Mass Index, CI – Confidence Interval; ICU – Intensive Care Unit; NCT – National Clinical Trial; NR – Not Reported; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Observational studies

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Andrews (2021) [44] **Title:** Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK **DOI:** **https://doi.org/10.1101/2021.09.15.21263583** **NCT: NA** **Study Design***:* test-negative case-control design **Country**: UK (England only) **Setting***:* general population **Time Period***:* Community testing data between 08 December 2020 and 03 September 2021 were included in the analysis **Variants of Concern:** alpha Delta Prior to May 2021, the Alpha variant was the main COVID-19 variant circulating	**Intervention/Exposure**: Comirnaty (Pfizer)(BNT162b2) Vaxzevria (AstraZeneca)(ChAdOx1-SARS-COV-2) Moderna (Spikevax)(mRNA-1273) **Comparator/Control:** unvaccinated **Time since final vaccination:** (See results by time)	**Description:** Individuals who had a PCR test in England in the study period (subject to exclusions below) were included. Data were restricted to persons who had reported symptoms and PCR-testing within 10 days of symptom onset. Individuals who had previously tested positive (PCR or antibody) prior to vaccination were excluded from the analysis. **N:** 4,774,735 individuals - Of these, AstraZeneca (ChAdOx1-SARS-COV-2): 38.7% Pfizer(BNT162b2): 31.7% Moderna (mRNA-1273): 2.4% 1,475,391 with positive SARS-CoV-2 test and 3,299,344 with negative test For the 5,233,372 tests in 4,774,735 individuals **Age:** 16-39: 56.2% 40-64: 37.1% 65-79: 5.4% 80+ : 1.3% **Male** =44 % **Co-morbidities:** clinically extremely vulnerable (CEV) Clinical at risk group Numbers/proportions NR	**Severe Disease: ≥14 days after second/final dose** Vaccine effectiveness was assessed for each vaccine separately and by intervals and at least 14 days post second dose. To assess potential waning, intervals of 1 week (7 to 13 days), 2 to 9 weeks, 10 to 14 weeks, 15 to 19 weeks and over 20 weeks were used. *Severe Disease/ Hospitalisation* Reported by vaccine (see below) *ICU admissions* NR **Adjustments:** age, sex, index of multiple deprivation, ethnic group, care home residence status (for analyses including adults aged ≥65 years),	**Confirmed RT-PCR SARS-CoV-2 infection** *Symptomatic* Reported by vaccine type below **Adjustments:** age, sex, index of multiple deprivation, ethnic group, care home residence status (for analyses including adults aged >=65 years), geographic region, period (calendar week), health and social care worker status (for analyses with adults aged <65 years), and clinical risk group (only available for <65 year-olds) or a clinically extremely vulnerable group (any age) **Variants of Concern:** Reported by vaccine type below **Subgroups:** NR **Efficacy/effectiveness over time.** Reported by vaccine type below

in the UK. Delta variant predominated after this. From this study Delta variant 894,965/1,475,391 (60.7%) Alpha from 04 January 2021 to 02 May 2021 and **Delta from 24 May 2021** as these variants were responsible for >80% of cases in all weeks during this period (>95% in most weeks)" **Publication status**: preprint			geographic region, period (calendar week), health and social care worker status (for analyses with adults aged <65 years), and clinical risk group (only available for <65 year-olds) or a clinically extremely vulnerable group (any age) **Mortality** Reported by vaccine type below **Variants of Concern** Reported by vaccine type below **Subgroups**: Age and co-morbidities. Reported by vaccine type below **Efficacy/effectiveness over time.**	

Primary outcome results	**Secondary Outcome results**
Pfizer (Comirnaty) (BNT162b2) *Severe Disease/ Hospitalisation* See * for VE over all time-period Wk 1 2-9wks 10- 14 wks 15-19 wks 20+ wks	Vaccine effectiveness against Delta symptomatic disease. See * for VE over all time-period

Age group	wk 1	2 to 9 weeks	10 to 14	15 to 19	20+ weeks

16+	99.7 (97.6 to 100.0)	98.4 (97.9 to 98.8)	96.5 (95.9 to 97.1)	94.4 (93.4 to 95.2)	92.7 (90.3 to 94.6)

ICU admissions
NR

Mortality

Delta deaths

Age group	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
16+	98.2 (95.9 to 99.2)	95.2 (93.0 to 96.7)	93.9 (91.1 to 95.8)	90.4 (85.1 to 93.8)
65+	97.0 (91.2 to 99.0)	95.2 (92.3 to 97.0)	94.3 (91.2 to 96.3)	91.0 (85.3 to 94.5)

Variants of Concern

Main analysis reports are for Delta (dates vary by subgroup and outcome)

Subgroups: (age and clinically extremely vulnerable (CEV)/ clinical risk)

Vaccine effectiveness against Delta hospitalisation

65+ years	Wk1	2-9wks	10- 14 wks	15-19 wks	20+ wks
All	100.0 (0 case, 908 con)	97.9 (95.9 to 99.0)	95.7 (94.3 to 96.8)	93 (90.9 to 94.6)	90.7 (86.0 to 93.8)
CEV	100.0 (0 case, 139 con)	94.6 (80.6 to 98.5)	91.7 (84.1 to 95.7)	83.4 (70.6 to 90.7)	71.4 (40.9 to 86.1)
Not CEV	100.0 (0 case, 769 con)	98.3 (96.2 to 99.3)	96.2 (94.7 to 97.3)	94.6 (92.7 to 96.1)	94.6 (90.5 to 97.0)

40-64 yrs	Wk 1	2-9wks	10- 14 wks	15-19 wks	20+ wks
All	100.0 (0 case, 2687 con)	98.5 (97.7 to 99.0)	97.5 (96.7 to 98.2)	96.2 (94.1 to 97.5)	95.7 (69.5 to 99.4)
Risk/CEV group	100.0 (0 case, 992 con)	98.1 (97 to 98.8)	96.8 (95.6 to 97.8)	95.4 (92.6 to 97.2)	
Not risk/CEV group	100.0 (0 case, 1695 con)	98.7 (97.1 to 99.4)	98.4 (96.4 to 99.3)	97.6 (92.6 to 99.2)	
16 to 39					
All	99.5 (96.7 to 99.9)	98.9 (97.5 to 99.5)			

			weeks	weeks	
16+	92.4 (92.1 to 92.7)	89.8 (89.6 to 90.0)	80.3 (79.9 to 80.6)	73.4 (72.9 to 73.9)	69.7 (68.7 to 70.5)

Variants of Concern:

Main analysis reports are for Delta (dates vary by subgroup and outcome)

Subgroups

Age group	wk 1	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
65+	65.4 (34.2 to 81.8)	80.1 (77.5 to 82.4)	69.1 (66.2 to 71.8)	62.1 (58.6 to 65.4)	55.3 (50.2 to 60.0)
40 to 64	87.9 (86.1 to 89.4)	84.9 (84.3 to 85.4)	78.2 (77.5 to 78.9)	74.2 (73.1 to 75.3)	75.7 (71.1 to 79.5)
16 to 39	92.5 (92.1 to 92.8)	91.0 (90.8 to 91.3)	77.1 (71.4 to 81.6)		

Efficacy/effectiveness over time.

See above

Efficacy/effectiveness over time. See above

Vaxzevria (AstraZeneca) (ChAdOx1-SARS-COV-2)

VE against Delta hospitalisation. See * for VE over all time-period

age	week 1	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
16+	93.9 (91.3 to 95.7)	95.2 (94.6 to 95.6)	91.4 (90.5 to 92.2)	86.8 (85.1 to 88.4)	77.0 (70.3 to 82.3)

ICU admissions NR

Mortality

Delta deaths

Age group	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
16+	94.1 (91.8 to 95.8)	92.4 (89.7 to 94.4)	89.1 (84.2 to 92.5)	78.7 (52.7 to 90.4)
65+	92.8 (87.4 to 95.9)	93.1 (89.6 to 95.4)	89.2 (83.3 to 93.0)	79.1 (51.6 to 91.0)

Variants of Concern

Delta hospitalisation and deaths reported in main analysis

Subgroups: Vaccine effectiveness against Delta hospitalisation

age	Sub group	week 1	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
65+	All	86.2 (40.5 to 96.8)	92.2 (89.4 to 94.3)	90.2 (87.8 to 92.2)	85.4 (81.6 to 88.5)	76.3 (65.3 to 83.8)
	CEV	N too small	79.3 (59.2 to 89.5)	78.6 (63.1 to 87.6)	75.1 (56.3 to 85.8)	59.4 (14.1 to 80.8)
	Not CEV	92.5 (43.4 to 99.0)	93.7 (91.0 to 95.6)	91.7 (89.3 to 93.6)	86.5 (82.5 to 89.7)	78.4 (65.7 to 86.4)
40 to 64	All	95.0 (92.4 to 96.7)	96.2 (95.7 to 96.7)	92.7 (91.5 to 93.6)	89.0 (85.9 to 91.3)	64.8 (30.1 to 82.2)
	Risk/CEV group	94.3 (86.1 to 97.7)	93.7 (92.3 to 94.8)	90.2 (88.2 to 91.9)	86.6 (82.2 to 89.9)	69.7 (29.7 to 86.9)
	Not risk/CEV group	95.3 (92.5 to 97.0)	97.4 (96.9 to 97.8)	94.5 (93.1 to 95.6)	93.0 (87.5 to 96.1)	

Vaccine effectiveness against Delta symptomatic disease. See * for VE over all time-period

Age group	week 1	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
16+	62.7 (61.7 to 63.8)	66.7 (66.3 to 67.0)	59.3 (58.8 to 59.9)	52.6 (51.7 to 53.5)	47.3 (45.0 to 49.6)

Variants of Concern:

Delta hospitalisation and deaths reported in main analysis

Subgroups

Vaccine effectiveness against Delta symptomatic disease

Age group	wk 1	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ weeks
65+	63.8 (48.2 to 74.8)	58.9 (54.8 to 62.6)	49.9 (45.4 to 54.0)	43.3 (38.1 to 48.0)	36.6 (28.7 to 43.7)
40 to 64	57.1 (55.5 to 58.6)	63.6 (62.9 to 64.3)	59.8 (58.8 to 60.7)	56.9 (55.3 to 58.4)	57.8 (50.9 to 63.7)
16 to 39	62.2 (52.5 to 70.0)	65.5 (60.9 to 69.5)			

Efficacy/effectiveness over time.

<table>
<tr><td>Efficacy/effectiveness over time. See above</td><td>See above</td></tr>
<tr><td>Moderna (Spikevax)(mRNA-1273)

VE against Delta hospitalisation, See * for VE over all time-period

<table>
<tr><td></td><td>Wk 1</td><td>2-9wks</td><td>10- 14 wks</td></tr>
<tr><td>16+</td><td>97.5 (82.3 to 99.7)</td><td>100.0 (0 cases, 6363 con)</td><td></td></tr>
</table>
</td><td>VE against Delta symptomatic disease. See * for VE over all time-period
<table>
<tr><td></td><td>Wk 1</td><td>2-9 wks</td><td>10-14 wks</td></tr>
<tr><td>16+</td><td>95.2 (94.4 to 95.9)</td><td>94.5 (94.1 to 95.0)</td><td>90.3 (67.2 to 97.1)</td></tr>
</table>
Subgroups

VE against Delta symptomatic disease

<table>
<tr><td></td><td>Wk 1</td><td>2-9 wks</td><td>10-14 wks</td></tr>
<tr><td>40 to 64</td><td>94.0 (92.1 to 95.5)</td><td>93.7 (92.9 to 94.4)</td><td>96.1 (70.1 to 99.5)</td></tr>
<tr><td>16 to 39</td><td>95.0 (94.1 to 95.8)</td><td>94.9 (94.2 to 95.5)</td><td></td></tr>
</table>
</td></tr>
</table>

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Chemaitelly (2021)[46] **Title:** SARS-CoV-2 vaccine effectiveness in immunosuppressed kidney transplant recipients **NCT**: N/A **DOI:** 10.1101/2021.08.07.21261578	**Exposure**: BNT162b2 (93%) mRNA-1273 (7%) **Comparator:** No vaccination **Time since final vaccination:** Mean 10.47 weeks	**Description:** Kidney transplant recipients with no prior PCR confirmed diagnosis of SARS-CoV-2 infection **N:** 782 Out of the 782 transplant recipients, 506 were fully vaccinated at the index date or crossed over during the study period. **Age :** Unvaccinated**:** Median 49 years (IQR 39-61)	**Severe Disease:** *Any severe critical or fatal disease*: * Days after the second dose: ≥14 days VE 72.3% (95% CI: 0.0 to 90.9%). ≥42 days VE 85.0% (95% CI: 35.7 to 96.5%)	**Confirmed RT-PCR or SARS-CoV-2 infection** *Any infection symptomatic or asymptomatic* Days after the second dose: ≥14 days

Country: Qatar **Setting***:* Public healthcare provider. **Time Period***:* February 1-July 21, 2021 **Study Design***:* Retrospective cohort study with cross over **Variants of Concern** Dominated by Alpha and Beta. Low incidence of Delta **Publication status**: Preprint		Vaccinated: Median 52 years (IQR 40-61) **Male**: Vaccinated : 63.1% Unvaccinated: 70.4% **Comorbidities:** NR **Special populations**: 100% Kidney transplant recipients.	≥56 days: VE 83.8% (95% CI: 31.3 to 96.2%) *Mortality*: No COVID-19 deaths occurred in either group. **Adjustments**: Age, sex, nationality group, competing risks. **Subgroups:** NR **Variants:** NR **Effectiveness over Time:** No other analysis	VE 46.6% (95% CI: 0.0 to 73.7%) ≥42 days follow-up VE 66.0% (95% CI: 21.3 to 85.3%) ≥56 days VE 73.9% (95% CI: 33.0 to 89.9%) **Adjustments** Age, sex, nationality group, competing risks **Variants:** NR **Effectiveness over Time**: "However, vaccine protection mounted slowly and did not reach a high level until several weeks after the second dose. Notably, the build-up of vaccine protection mirrored the slow development of antibodies in transplant recipients that has been previously reported."
*Definitions for severe, critical and Covid-19 death as per WHO classifications**.**				

Key: CI – Confidence Interval; Interquartile Range – IQR; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

<table>
<tr><th>Study characteristics</th><th>Intervention and Comparators</th><th>Population and Patient demographics</th><th>Primary outcome results</th></tr>
<tr>
<td>Author (Year): Liu (2021)[48]

Title: A Retrospective Analysis of COVID-19 mRNA Vaccine Breakthrough Infections – Risk Factors and Vaccine Effectiveness

NCT: NR

<u>DOI:</u>
<u>10.1101/2021.10.05.21264583</u>

Country: US

Setting: A quaternary care academic medical centre that includes an academic hospital, children’s hospital, and community-based hospital

Time Period:
Pre-vax cohort: 1 January 2020 – 10 December 2020
Vax/Un-vax cohorts: 18 January 2021 - 21 September 2021

Study Design:</td>
<td>Exposure: BNT162b2 (67.5%), mRNA-1273 (32.5%)

Comparator:
No vaccination

Time since final vaccination:
Mean: 14.4 weeks</td>
<td>Description: Adults ≥18 years residing in New York State who received routine clinical care from Columbia University Irving Medical Centre/New York-Presbyterian (CUIMC/NYP) were included. Individuals who received doses from more than 1 manufacturer or only received one vaccine dose were excluded.

6 cohorts were constructed:

1) “Vax positive” (N = 198):* Individuals with a positive PCR test after full vaccination and without evidence of SARS-CoV-2 infection before full vaccination.
2) “Vax negative” (N = 14,164):* Individuals with a negative PCR test after full vaccination and without evidence of SARS-CoV-2 infection at any time in their records
3) “Pre-Vax positive” (N = 6,462):* Individuals with a positive PCR test before the vaccination period.
4) “Pre-Vax negative” (N = 55,580):* Individuals with a negative PCR test and without any evidence of SARS-CoV-2 infection before the vaccination period.
5) “Un-Vax positive” (N = 3,902):* Individuals with a positive PCR test after entry date and before administration of a first vaccination dose (if ever administrated), while having no evidence of SARS-CoV-2 infection before entry date
6) “Un-Vax negative” (N = 33,850):* Individuals with a negative PCR test after entry date and before administration of a first vaccination dose (if ever administrated), while having no evidence of SARS-CoV-2 infection before entry date.

Average (SD), Age:*
1) “Vax positive” 58.5 years (20.34)
2) “Vax negative” 59.4 years (18.86)
3) “Pre-Vax positive” 58.9 years (19.46)</td>
<td>Severe Disease:

SARS-CoV-2 associated severe clinical events, including hospitalisation (includes emergency room visits), mechanical ventilation, tracheostomy, and death

Vaccine effectiveness against COVID-19 associated severe outcomes in breakthrough cohort compared to matched <u>historical</u> COVID-19 infection cohort.
<table>
<tr><th></th><th>Event (Pre-Vax/Vax) [1]</th><th>Event rate / 1000 person-days (Pre-Vax/Vax)</th><th>Hazard Ratio (95% CI)</th><th>Adjusted Hazard Ratio (95% CI)</th></tr>
<tr><td>Hospitalisation</td><td>1071/120</td><td>47.58/59.2</td><td>1.19 (0.982-1.43)</td><td>1.17 (0.969-1.41)</td></tr>
<tr><td>Mechanical Ventilation</td><td>155/9</td><td>3.57/1.85</td><td>0.539 (0.275-1.06)</td><td>0.518 (0.265-1.02)</td></tr>
<tr><td>Tracheostomy</td><td>19/0</td><td>0.42/0</td><td>3.52e-08 (0-Inf)</td><td>3.32e-08 (0-Inf)</td></tr>
<tr><td>Death</td><td>195/5</td><td>4.3/1.01</td><td>0.235 (0.0966-0.57)</td><td>0.2 (0.0824-0.487)</td></tr>
</table>
Vaccine effectiveness against COVID-19 associated severe outcomes in the breakthrough cohort compared to a matched <u>unvaccinated</u> COVID-19 infection cohort.
<table>
<tr><th></th><th>Event (Un-Vax/Vax) [1]</th><th>Event rate / 1000 person-days (Un-Vax/Vax)</th><th>Hazard Ratio (95% CI)</th><th>Adjusted Hazard Ratio (95% CI)[3]</th></tr>
<tr><td>Hospitalisation</td><td>1445/120</td><td>93.52/59.2</td><td>0.726 (0.603-0.875)</td><td>0.723 (0.6-0.872)</td></tr>
</table>
</td>
</tr>
</table>

Retrospective cohort study (with matching for some analyses) **with crossover**

Variants of Concern

NR

Publication status: Preprint

4) "Pre-Vax negative" 52.2 years (19.79)
5) "Un-Vax positive" 54.2 years (20.06)
6) "Un-Vax negative" 50.9 years (19.73)

Male:*

1) "Vax positive" 44.4%
2) "Vax negative" 36.4%
3) "Pre-Vax positive" 49%
4) "Pre-Vax negative" 37.8%
5) "Un-Vax positive" 43.6%
6) "Un-Vax negative" 37.7%

Comorbidities:*

	Vax+	Vax-	Un-vax+	Un-vax-	Pre-vax+	Pre-vax-
Solid tumor	46 (23.2%)	2354 (16.6%)	274 (7%)	2826 (8.3%)	629 (9.7%)	6702 (12.1%)
Chronic Kidney Disease	28 (14.1%)	1486 (10.5%)	364 (9.3%)	2124 (6.3%)	910 (14.1%)	4098 (7.4%)
HIV	9 (4.5%)	478 (3.4%)	114 (2.9%)	982 (2.9%)	190 (2.9%)	1603 (2.9%)
On immunosuppressive therapy	13 (6.6%)	362 (2.6%)	74 (1.9%)	616 (1.8%)	156 (2.4%)	1248 (2.2%)
immunodeficiency disorders	49 (24.7%)	2545 (18%)	370 (9.5%)	3124 (9.2%)	759 (11.7%)	6660 (12%)
Organ transplant	10 (5.1%)	366 (2.6%)	108 (2.8%)	610 (1.8%)	244 (3.8%)	1288 (2.3%)
Not immucompromised	108 (54.5%)	9031 (63.8%)	3072 (78.7%)	26835 (79.3%)	4641 (71.8%)	41150 (74%)
Mechanical Ventilation	122/9	2.36/1.85	0.747 (0.38-1.47)	0.716 (0.363 -1.41)		
Tracheostomy	8/0	0.15/0	3.63e-08 (0-Inf)	3.74e-08 (0-Inf)		
Death	115/5	2.19/1.01	0.457 (0.187 -1.12)	0.409 (0.167 -1)		

[1]The N of the Pre-Vax/Un-vax cohort will be 10 times N of the Vax because of 1:10 matching.

Adjustments:

Unadjusted Hazard ratio for the effect of vaccination on severe outcome was obtained by fitting a Cox regression with one independent variable (vaccinated v. unvaccinated.

Adjusted Hazard ratios were obtained by fitting a Cox regression adjusted for previous number of visits, observational days, age at PCR test and underlying immune conditions (binary). Individuals were censored at their last encounter or 28 days after their PCR results, whichever comes first

Subgroups: NR

Variants: NR

Effectiveness over Time:

No other analysis

*** some individuals are in multiple cohorts at different times**

Secondary outcomes

Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥14 days after second/final dose

Vaccine effectiveness against SARS-CoV-2 infection comparing "Vax" cohort to a matched "Pre-Vax" cohort before 11 Dec 2020.

	N[1] (Pre-Vax/Vax)	Prevalence - (Pre-Vax/Vax)	Odds Ratio (95% CI)[2]	Adjusted Odds Ratio (95% CI)[3]	% VE (95% CI)[4]
Overall	14,362/14,362	1,556/198	0.115 (0.099-0.134)	0.116 (0.0998-0.135)	88.4% (86.5 to 90)

1 Both cohorts contained 14,362 individuals in total because of 1:1 matching; Matching was based on previous visit counts, observational days, demographics, underlying immune conditions and New York City 7 days rolling average of COVID-19 cases at the PCR test date.

Adjustments:

2. Odds ratio obtained by fitting a univariate logistic regression between "Vax" cohort and a matched "Pre-Vax" cohort.

3. Odds ratio obtained by fitting a logistic regression adjusted for previous number of visits and observational days.

Variants of Concern: NR

Subgroups:

	N[1] (Pre-Vax/Vax)	Prevalence - (Pre-Vax/Vax)	Odds Ratio (95% CI)[2]	Adjusted Odds Ratio (95% CI)[3]	% VE (95% CI)[4]
Age					
<= 65	8,335/8,191	734/111	0.142 (0.116-0.174)	0.145 (0.118-0.177)	85.5% (82.3 to 88.2)
> 65	6,027/6,171	822/87	0.0905 (0.0724-0.113)	0.0909 (0.0727-0.114)	90.9% (88.6 to 92.7)
Sex					
Male	5,142/5,241	702/88	0.108 (0.0862-0.135)	0.108 (0.0865-0.136)	89.2% (86.4 to 91.4)
Female	9,220/9,120	854/110	0.12 (0.0978-0.146)	0.121 (0.0989-0.148)	87.9% (85.2 to 90.1)
Is immune compromised					
True	5,287/5,223	642/90	0.127 (0.101-0.159)	0.129 (0.103-0.162)	87.1% (83.8 to 89.7)
False	9,075/9,139	914/108	0.107 (0.0873-0.131)	0.106 (0.0864-0.129)	89.4% (87.1 to 91.4)

1 Both cohorts contained 14,362 individuals in total because of 1:1 matching; Matching was based on previous visit counts, observational days, demographics, underlying immune conditions and New York City 7 days rolling average of COVID-19 cases at the PCR test date.

Adjustments:
2. Odds ratio obtained by fitting a univariate logistic regression between "Vax" cohort and a matched "Pre-Vax" cohort.

3. Odds ratio obtained by fitting a logistics regression adjusted for previous number of visits and observational days.

4. VE estimated by calculating (1 –aOR)*100

Vaccine effectiveness against SARS-CoV-2 infection comparing "Vax" cohort to a matched "Un-Vax" cohort after 18 Jan 2021

	N# (Un-Vax/Vax)	**Incident rate / 1000 person-days (Un-Vax/Vax)**	**Incident Rate Ratio (95% CI)##**	**Adjusted Incident Rate Ratio (95% CI)###**
Overall	14,362/1,4362	0.37/0.16	0.422 (0.362-0.493)	0.411 (0.352-0.48)

Both cohorts contained 10,283 individuals in total because of 1:1 matching; Matching was based on by previous visit counts, observational days, demographics, underlying immune conditions and NYC 7 days rolling average of COVID-19 cases at the PCR test date

Adjustments:
Incident rate ratio obtained by fitting a univariate Poisson regression between vaccinated cohort and a matched "Un-Vax" cohort

Incident rate ratio obtained by fitting a Poisson regression adjusted for previous number of visits and observational days

Variants of Concern: NR

Subgroups:

	N# (Un-Vax/Vax)	**Incident rate / 1000 person-days (Un-Vax/Vax)**	**Incident Rate Ratio (95% CI)##**	**Adjusted Incident Rate Ratio (95% CI)###**
Age				
<= 65	9,453/8,191	0.35/0.16	0.47 (0.383-0.576)	0.471 (0.384-0.579)
> 65	4,909/6,171	0.43/0.15	0.354 (0.279-0.449)	0.325 (0.255-0.413)
Sex				
Male	5,272/5,241	0.4/0.19	0.489 (0.386-0.619)	0.483 (0.381-0.612)

Female	9,089/9,120	0.36/0.14	0.381 (0.31-0.469)	0.368 (0.299-0.452)
Is immune com promised				
True	4,079/5,223	0.41/0.19	0.466 (0.366-0.593)	0.432 (0.338-0.553)
False	10,283/9,139	0.36/0.14	0.382 (0.311-0.469)	0.375 (0.305-0.461)

Both cohorts contained 10,283 individuals in total because of 1:1 matching; Matching was based on by previous visit counts, observational days, demographics, underlying immune conditions and NYC 7 days rolling average of COVID-19 cases at the PCR test date

Adjustments:
Incident rate ratio obtained by fitting a univariate Poisson regression between vaccinated cohort and a matched "Un-Vax" cohort

Incident rate ratio obtained by fitting a Poisson regression adjusted for previous number of visits and observational days

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Risk factors associated with breakthrough case rate

Risk Factors	**IR (95% CI) per 1000 person-days**	**IRR (95% CI)†**	**p-value**	**Adjusted IRR (95% CI) ‡**	**p-value adj**
Not immunocompromised	0.14 (0.11-0.17)	Ref	Ref	Ref	Ref
Is immunocompromised	0.19 (0.15-0.24)	1.49 (1.1-2)	0.009	1.48 (1.09-2)	0.011
Active tumour	0.22 (0.16-0.29)	1.57 (1.11-2.21)	0.010	1.56 (1.1-2.2)	0.012
CKD	0.2 (0.13-0.29)	1.35 (0.887-2.07)	0.160	1.33 (0.864-2.06)	0.194
HIV	0.21 (0.1-0.4)	1.24 (0.628-2.44)	0.538	1.25 (0.634-2.47)	0.518
On immunosuppressed therapy	0.21 (0.16-0.28)	1.46 (1.03-2.05)	0.031	1.45 (1.03-2.04)	0.033
Primary immunodeficiency	0.4 (0.21-0.68)	2.55 (1.41-4.6)	0.002	2.53 (1.4-4.58)	0.002
Organ transplant	0.31 (0.15-0.57)	1.9 (0.976-3.71)	0.059	1.9 (0.977-3.71)	0.058

Adjustments:

† Adjusted for number of visits, days of previous observation, calendar month of the PCR test result

‡ Adjusted for number of visits, days of previous observation, calendar month of the PCR test result and age at last vaccine dose

Top 10 (ranked by p-value) condition and drugs associated with breakthrough cases in "Vax" cohort

Condition name*	**IRR (95% CI)¥**	**p-value**
Chronic pulmonary heart disease	4.07 (2.07-7.99)	<0.001
Asteatosis cutis	2.6 (1.56-4.33)	<0.001
Immunodeficiency disorder	3.62 (1.81-7.22)	<0.001
Post-inflammatory pulmonary fibrosis	3.34 (1.69-6.59)	<0.001
Tubulointerstitial nephritis	3.84 (1.78-8.28)	0.001
Alzheimer's disease	3.5 (1.68-7.28)	0.001
Bacterial pneumonia	2.97 (1.5-5.87)	0.002
Epidermoid cyst	2.45 (1.39-4.32)	0.002
Peripheral circulatory disorder due to type 2 diabetes mellitus	2.78 (1.45-5.36)	0.002
Acute deep venous thrombosis of femoral vein	3.62 (1.58-8.27)	0.002
Drug name*	**IRR (95% CI)¥**	**p-value**
valganciclovir	4.33 (1.92-9.76)	<0.001
donepezil	2.91 (1.5-5.65)	0.002
pegfilgrastim	3.62 (1.54-8.49)	0.003

vitamin A	3.27 (1.42-7.53)	0.005
telmisartan	3.18 (1.4-7.24)	0.006
albuterol (salbutamol)	1.56 (1.13-2.15)	0.007
linagliptin	3.01 (1.32-6.86)	0.009
enalapril	2.21 (1.21-4.02)	0.010
cetirizine	1.93 (1.17-3.17)	0.010
mycophenolate mofetil	2.77 (1.27-6.04)	0.010

* Only conditions/drugs that occurred in more than 100 individuals were included in this analysis.

Adjustments:

¥ Poisson regression was fitted for each variable with adjustment for age, number of visits, and observational days

Efficacy/effectiveness over time:

Change of Incidence rate from time to fully vaccination.

	Pfizer/BNT162b2			**Moderna/mRNA-1273**		
Time since fully vaccinated	**Total person-days at risk£**	**Incidence**	**Incident rate / 1000 person-days**	**Total person-days at risk£**	**Incidence**	**Incident rate / 1000 person-days**
210-240 days	3,074	6	1.952	443	1	2.257
180-210 days	16,811	24	1.428	5,543	5	0.902
150-180 days	34,847	16	0.459	16,525	6	0.363
120-150 days	66,486	27	0.406	32,243	7	0.217
90-120 days	105,697	15	0.142	52,162	5	0.096

60-90 days	150,864	16	0.106	74,806	5	0.067
30-60 days	203,392	26	0.128	100,706	5	0.050
0-30 days	259,596	26	0.100	126,977	8	0.063

£ Incidence rate / 1000 person-days were calculated for each time interval relative to the fully vaccinated date

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): McKeigue (2021)[49] **Title:** Efficacy of two doses of COVID-19 vaccine against severe COVID-19 in those with risk conditions and residual risk to the clinically extremely vulnerable: the REACT-SCOT case-control study **DOI:** doi.org/10.1101/2021.09.13.21262360; **NCT:** N/A **Study Design***:* Case-control **Country**: Scotland **Setting***:* Community	**Exposure**: • COVID-19 cases were those with a positive nucleic acid test, or a hospital admission or death with COVID-19 ICD-10 codes. • Vaccination with AstraZeneca or mRNA vaccine (Pfizer or Moderna). • Defined by risk group: ○ No risk condition ○ Moderate risk condition ○ Eligible for shielding^ **Control:** For every incident case of COVID-19 in the Scottish population	**Description:** Cases of COVID-19 among community population in Scotland and then matched to controls from general population. Not reported if serostatus assessed prior to inclusion for controls. **N:* 223, 742** **(53,264 fully vaccinated)** **Age:** NR **Male/Female:** NR **Co-morbidities##:** Moderate risk condition: 65,020 Solid organ transplant:447 Specific cancers: 2,106	**Severe Disease:** **≥14 days after second dose** *Severe Disease*** No risk condition RR# 0.06 (95% CI 0.04 to 0.07) VE 94% (95 % CI 93% to 96%) Moderate risk condition RR 0.11 (95% CI 0.09 to 0.14) VE= 89% (95% CI 86% to 91%) Condition eligible for shielding RR 0.27 (95% CI 0.21 to 0.36) VE = 73% (95% CI 64% to 79%) *Hospitalisation or mortality**** No risk condition RR# 0.14 (95% CI 0.12 to 0.15) VE = 86% (85 to 88) Moderate risk condition RR 0.17 (95% CI 0.15 to 0.18) VE = 83% (82 to 85)	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose** NR **Variants of Concern:** NR **Subgroups** NR **Efficacy/effectiveness over time.** NR

Time Period*:* 1 December 2020 to 8 September 2021 **Variants of Concern:** Delta. **Publication status**: Preprint	10 controls matched for one-year age, sex and primary care practice and alive on the day of presentation of the case that they were matched to were selected using the Community Health Index database in Scotland. Not reported if serostatus assessed prior to inclusion for controls. **Time since final vaccination dose:** There is at least a median of 9.57 weeks. [IQR = 6 – 12.71 weeks. Max 26 weeks], with an additional 2.3 weeks follow up in the updated report. (From McKeigue: Efficacy of vaccination against severe COVID-19 in relation to Delta variant and time since second dose: the REACT-SCOT case-control study.)	Severe respiratory: 7,168 Rare diseases: 732 On immunosuppressants: 1,792 Additional conditions: 3,764	Condition eligible for shielding RR 0.32 (95% CI 0.29 to 0.37) VE = 68% (95 percent CI 63% to 71%) **Adjustments:** care home residence, number of adults in household, number of non-cardiovascular drug classes dispensed and recent hospital stay. **Mortality** NR separately (see above). **Variants of Concern:** NR. **Subgroups**: See below **Efficacy/effectiveness over time:** Reported for risk conditions (see below)	
	Risk conditions	**RR for severe disease:**	**RR for hospitalisation/mortality**	**Rate per 1000 per month**
	Solid organ transplant:	31.4 (13.8 to 71.2) 0.6 (95% CI 0.24 to 1.51) +	9.2 (95% CI 6.2 to 13.7) 0.6 (95% CI: 0.38to 0.95) ~	1.48
	Specific cancers:	12.7 (95% CI:7.3 to 22.0) 0.34 (95% CI: 0.2 to 0.59) +	3.86 (3.04 to 4.90) 0.31 (95% CI: 0.23 to 0.41~	0.35
	Severe respiratory:	4.75 (95% CI:3.17 to 7.11) 0.18 (95% CI: 0.13 to 0.26) +	2.87 (2.45 to 3.37) 0.28 (95% CI: 0.24 to 0.33) ~	0.26

	Rare diseases:	3.24 (95% CI:1.21 to 8.66) 0.1 (95% CI: 0.03 to 0.28) +	2.87 (95% CI 2.45 to 3.37) 0.31 (95% CI:0.19 to 0.50) ~	0.28 (combined with additional conditions)
	On immunosuppressants:	13.3 (95% CI:7.3 to 24.3) 0.53 (95% CI: 0.29 to 0.97) +	3.74 (95% CI 2.87 to 4.86) 0.4 (95% CI:0.29 to 0.54) ~	0.25
	Additional conditions:	6.3 (95% CI:3.9 to 10.0) 0.24 (95% CI: 0.15 to 0.39) +	3.67 (95% CI 3.02 to 4.46) 0.32 (95% CI:0.26to 0.39) ~	0.28
	Astra Zeneca		**RR for severe disease** No risk condition RR# 0.07 (0.05, 0.09) Moderate risk condition RR 0.13 (0.10, 0.17) Condition eligible for shielding RR 0.28 (0.21, 0.37) VE = (72% (95 percent CI 63% to 79%)) **RR for hospitalisation or mortality with unvaccinated as reference category:** No risk condition RR# 0.19 (0.17 to 0.2)) Moderate risk condition RR 0.22 (0.2 to 0.25) Condition eligible for shielding RR 0.38 (0.33, 0.43)	
	Pfizer/Moderna	**mRNA**	**RR for severe disease:** No risk condition RR# 0.04 (0.03, 0.06) Moderate risk condition RR 0.07 (0.05, 0.09) Condition eligible for shielding RR 0.27 (0.17, 0.371) VE= 73% (95% CI 59% to 83%)). **RR for hospitalisation or mortality :** No risk condition RR# 0.08 (0.07, 0.09) Moderate risk condition RR 0.09 (0.08, 0.11)	

			Condition eligible for shielding RR 0.23 (0.19, 0.29)	

* Calculated from Table 1 and Table S1 (reported by vaccination status).

** Severe COVID-19: diagnosed cases with entry to critical care within 28 days of presentation or fatal outcome (death within 28 days of a positive test or any death for which COVID-19 was coded as underlying cause).

*** Hospitalised and fatal disease reported together.

Rate ratio

Calculated from Table 1 and Table S1.

~Compared to unvaccinated control

^ the CEV category was subdivided is subdivided into 6 categories categories: solid organ transplant, specific cancers, severe respiratory conditions, other rare conditions, on immunosuppressants, and additional conditions

+ RR associated with vaccine dose within extremely vulnerable subgroups

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Nordstrom (2021)[50] **Title:** Effectiveness of Covid-19 vaccination against risk of symptomatic infection, hospitalization, and death up to 9 months: a Swedish total-population cohort study **DOI:** doi.org/10.2139/ssrn.3949410 **NCT:** N/A **Study Design***:* Retrospective Cohort Study **Country**: Sweden **Setting***:* Nationwide Registries **Time Period***:*	**Intervention/Exposure**: ChAdOx1 (AstraZeneca) mRNA-1273 (Moderna) BNT162b2 (Pfizer/BioNTech) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Symptomatic Infection Mean = 16.52 weeks (Range: 2.14 to 39.88 weeks) Hospitalisations and mortality Mean = 16.1 weeks Range: (2.14 to 39.03)	**Description:** Fully vaccinated (2 doses) individuals were matched 1:1 to one randomly sampled unvaccinated individuals. Matched unvaccinated individuals were excluded if they received a first dose of vaccine or died within 14 days of baseline, and a new individual was searched from the remaining total cohort. **N:** Vaccinated – 842,974 Unvaccinated – 842,974 ChAdOx1 – 76,597 Mrna-1273 – 76,880 BNT162b2 – 637,107 BNT162b2/mRNA – 51,766 **Age: (Mean)** Vaccinated - 53.0 (SD 19.0) Unvaccinated - 53.0 (SD 19.0) **Male**%: Vaccinated – 40.7% Unvaccinated – 40.7% **Co-morbidities/Special Populations: N (%)**	**Severe Disease: >14 days after second/final dose** [$] Covid-19 hospitalization or death *277 cases in vaccinated group vs 825 cases in unvaccinated group* *Day 15 to 30VE = 89% (VE = 83 to 93, P<0·001)* *Day 121 to 180* *VE = 74% (47 to 87, P<0·001)* *Day 180+* *VE = 42%; (-35-75, P=0·21).* **Adjustments:** Age, baseline date, sex, home maker service, place of birth, education and comorbidities.	**Confirmed RT-PCR infection** **≥14 days after second/final dose**[*] *Symptomatic* [#] See below Table 2 and Table 3 **Adjustments:** Age, baseline date, sex, home maker service, place of birth, education and comorbidities. See below supplemental Table 4 **Variants of Concern:** Apply mainly to Delta

12 January, 2021 – 4 October, 2021 **Variants of Concern:** A timely component of the study is that the results apply primarily to the Delta variant of the virus, according to sequencing analyses presented by the Public Health Agency of Sweden **Publication status**: Preprint **Supplementary Appendix:** No		*Myocardial infarction* Vaccinated - 21,885 (2.6) Unvaccinated – 18,350 (2.2) *Stroke* Vaccinated – 29,493 (3.5) Unvaccinated – 16,808 (2.0) *Diabetes* Vaccinated – 91,203 (10.6) Unvaccinated – 62,198 (7.4) *Hypertension* Vaccinated – 262,659 (31.2) Unvaccinated - 207,862 (24.7) *Kidney failure* Vaccinated – 20,027 (2.4) Unvaccinated – 10,317 (1.2) *COPD* Vaccinated – 17,257 (2.0) Unvaccinated – 13,353 (1.6) *Athsma* Vaccinated – 50,341 (6.0) Unvaccinated – 36,671 (4.4) *Cancer* Vaccinated – 48,512(5.8) Unvaccinated – 37,092 (4.4) **N: (Secondary cohort)** ~ Vaccinated – 1,983,315 Unvaccinated - 1,983,315	See below supplemental Table 5 **Variants of Concern** Apply mainly to Delta	

		Age: Vaccinated – 59.4 (SD – 17.2) Unvaccinated – 56.2 (SD – 20.2) Male: Vaccinated – 43.5% Unvaccinated – 48.4% **Outcome measurement:** First outcome – symptomatic infection Confirmed using polymerase chain reaction and in 4.8% by sequencing, according to the SmiNet registry Second outcome - a composite endpoint of severe disease until 28 Sept 2021 latest Inpatient hospitalization with Covid-19 as the main diagnosis, or all-cause mortality within 30 days after confirmed infection.		

Table 2. Vaccine effectiveness against symptomatic infection up to 9 months after full vaccination (Fully adjusted) – VE (95% CI)

Time	**Vaccine**				
	Any 2 doses	**BNT162b2/BNT162b2**	**mRNA-1273/mRNA-1273**	**ChAdOx1/ChAdOx1**	**ChAdOX1/mRNA vaccine**
Total	84 (83-84)	85 (84-85)	89 (88-90)	44 (36-52)	65 (59-70)
15-30 days	92 (91-93)	92 (92-93)	96 (94-97)	68 (52-79)	89 (79-94)
31-60 days	89 (88-89)	89 (88-90)	93 (90-94)	49 (28-64)	72 (59-82)

61 -120 days	82 (81-83)	85 (84-85)	85 (82-88)	41 (29-51)	55 (45-64)
121-180 days /(* = 120 days +)	48 (41-54)	47 (39-55)	71 (56-81)	-19 (-97-28) *	66 (41-80) *
181 – 210 days / (* = 180 days+)	32 (19-44)	29 (15-42)	59 (18-79) *	NR	NR
>210 days	23 (-2-41)	23 (-2-41)	NR	NR	NR

Table 3. Vaccine effectiveness against symptomatic infection up to 9 months after full vaccination (>14 days after the second dose) according to sex, age and for individuals with homemaker service and with any comorbidity at baseline

	Time since vaccination				
Category	**15-30 days**	**31-60 days**	**61-120 days**	**121-180 days**	**>180 days**
<50 years	95 (94-95)	91 (90-92)	84 (83-84)	51 (43-58)	37 (24-48)
50 – 64 years	88 (86-91)	85 (83-87)	81 (79-83)	27 (-8-50)	8 (-36-38)
65-79 years	82 (75-88)	71 (64-76)	65 (56-72)	30 (-16-58)	11 (-32-40)
≥80 years	74 (63-82)	73 (65-79)	50 (30-64)	44 (15-66)	5 (-53-41)
Any diagnosis at baseline [£]	86 (84-89)	85 (83-86)	79 (77-80)	55 (42-65)	15 (-17-38)

Supplemental Table 4. Vaccine effectiveness against symptomatic infection up to 9 months after full vaccination (>14 days after the second dose) in the second matched cohort (N=3,966,630) according to age and for individuals with homemaker service and

with any comorbidity at baseline (Fully adjusted)

	Time since vaccination					
Category	**15-30 days**	**31-60 days**	**61-120 days**	**121-180 days**	**180-210 days**	**>210 days**
<50 years	94 (93-95)	90 (90-91)	83 (82-83)	50 (43-57)	41 (27-51)	34 (8-52)
50 – 64 years	87 (85-89)	82 (80-84)	76 (74-78)	45 (38-57)	18 (-49-43)	-77 (-390-19)
65-79 years	85 (81-88)	73 (68-77)	63 (59-67)	52 (39-62)	-5 (-213-48)	-32 (-376-54)
≥80 years	79 (74-82)	75 (71-79)	55 (45-63)	65 (57-71)	55 (39-66)	-66 (-296-7)
Any diagnosis at baseline £	86 (84-87)	80 (80-83)	74 (72-75)	60 (54-66) 56	41 (24-55)	1 (-147-33)

Supplemental Table 5. Vaccine effectiveness in the second matched cohort (N=3,966,630) against Covid-19 hospitalization or death up to 9 months after full vaccination (>14 days after the second dose)

	Time since vaccination				
Category	**15-30 days**	**31-60 days**	**61-120 days**	**121-180 days**	**>180 days**
Overall	92 (89-94)	90 (88-91)	89 (87-91)	83 (75-88)	75 (43-78)
<80 years	92 (87-95)	92 (89-94)	92 (92-94))	87 (75-93)	83 (72-93)
≥80 years	92 (88-95)	88 (84-91)	84 (79-89)	78 (65-86)	51 (2-74)

Any diagnosis at baseline£	86 (84-87)	87 (85-90)	86 (83-89)	85 (77-90)	58 (26-77)	

~ - This cohort was formed using less strict matching criteria to increase the size of the cohort. In this dataset, each vaccinated individual was matched to the rest of the cohort on age only, with an allowance of a 5-year difference in age within each pair. This process was repeated 10 times and one unvaccinated individual could be paired with several vaccinated individuals.

$ - Severe disease was measured until 28 September 2021 latest, defined as inpatient hospitalization with Covid-19 as main diagnosis, or all-cause mortality within 30 days after confirmed infection.

- The term "symptomatic" was defined on the basis that in Sweden, health authorities have urged citizens to take a test if they experience any symptoms of Covid-19, measured until 4 October 2021.

£ Any diagnosis defined as – Myocardial infarction, Stroke, Diabetes, Hypertension, Kidney Failure, COPD, Athsma, Cancer

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Pilishvili (2021) [51] **Title:** Effectiveness of mRNA Covid-19 Vaccine among U.S. Healthcare Personnel **DOI:** 10.1056/NEJMoa2106599	**Intervention/Exposure**: • BNT162b2 (Pfizer/BioNTech) (Cases: 78%, Controls 79%) • mRNA-1273 (Moderna) (Cases: 21%, Controls 20%) **Comparator/Control:** Unvaccinated individuals.^	**Description:** Healthcare personnel who had been tested for SARS-CoV-2 and had the potential for direct exposure to patients or the potential for indirect exposure to infectious materials at the workplace. Participants who had been tested within 0 to 2 days after the second dose were excluded. **N:**	**Severe Disease:** **≥7 days after second/final dose** *Hospitalisation in cases by vaccination status* & Completely vaccinated – 4 (2%) Partially vaccinated 1 (1%)	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection**$, + *Symptomatic* **≥7 days after second dose** Any COVID vaccine VE: 90.4% (95%CI 87.0% to 92.9%) BNT162b2

NCT: N/A **Study Design***:* Test negative case-control. **Country**: US **Setting***:* 33 sites across 25 states. Acute care hospitals (68%) (with or without affiliated outpatient and urgent care clinics), and long-term care facilities (32%). **Time Period***:* 28 December 2020 to 19 May 2021 **Variants of Concern:** NR **Publication status**: Peer-reviewed.	**Time since final vaccination dose:** Median – 5.98 weeks (range 1 to 23.5 weeks	Cases – 1,482 Controls – 3,449 **Age:** *Cases †* Median (range) yrs: 37 (18 to 69) *Controls†* Median (range) yrs: 37 (18 to 78) **Male**: *Cases* N=250 (17%) *Control* N=574 (17%) **Co-morbidities:** *Cases* Asthma –14% Immunocompromising condition [%] – 4% COPD – 0.3%	Unvaccinated 21 (3%) *ICU admissions* Among hospitalised cases, 3 cases were admitted to intensive care unit. Among hospitalised controls HCP was admitted to intensive care unit. **Adjustments:** NR **Mortality:** NR **Variants of Concern:** NR **Subgroups**:NR **Efficacy/effectiveness over time:** NR	VE: 88.8% (95%CI 84.6% to 91.8%) <u>mRNA-1273</u> VE: 96.3% (95%CI 91.2% to 98.4%) **Adjustments:** Age, race and ethnic group, underlying conditions, and exposures to persons with Covid-19. **Variants of Concern:** NR **Subgroups** <u>≥1 Underlying condition or risk factor[#]</u> VE: 90.3% (95%CI 86.4% to 93.0%) <u>≥2 Underlying conditions or risk factors[#]</u> VE: 88.5% (95%CI 83.2% to 92.2%) <u>≥3 Underlying conditions or risk factors[#]</u> VE: 89.4% (95%CI 83.1% to 93.4%) <u>No underlying risk factor[#]</u>

		Controls Asthma – 18% Immunocompromising condition [%] – 4% COPD – 1%		VE: 91.1% (95%CI 85.5% to 94.6%) <u>Asthma</u> VE: 90.5% (95%CI 81.9% to 95.0%) <u>Obesity</u> VE: 92.1% (95%CI 87.6% to 95.0%) <u>Obesity or overweight</u> VE: 91.0% (95%CI 87.0% to 93.7%) <u>Hypertension</u> VE: 91.8% (95%CI 83.9% to 95.8%) <u>Diabetes</u> VE: 80.2% (95%CI 45.8% to 92.7%) <u>Pregnancy (assessed for partial and complete vaccination)[€]</u> VE: 77.1% (95%CI 32.2% to 92.2%) <u>Any immunocompromising condition, (assessed for partial and complete vaccination)[€]</u>

				VE: 39.1% (95%CI −45.0% to 74.4%) <u><50 years</u> VE: 90.3% (95%CI 86.5% to 93.0%) <u>≥50 years</u> VE: 90.7% (95%CI 84.2% to 94.6%) **Efficacy/effectiveness over time.** The point estimate of vaccine effectiveness, assessed in 2-week intervals, was highest during weeks 3 and 4 after receipt of the second dose (VE: 96.3%; 95%CI, 92.5% to 98.2%). Estimates of vaccine effectiveness were lower during weeks 9 through 14 but confidence intervals overlapped.

Estimated Adjusted Effectiveness of mRNA Vaccines against Symptomatic Covid-19 among Healthcare Personnel According to Follow-up Time after Receipt of the Second Dose.[£]

Time	**1-2 weeks**	**3-4 weeks**	**5-6 weeks**	**7-8 weeks**	**9-10 weeks**	**11-12 weeks**	**13-14 weeks**

VE (95%CI)	92.73% (89.1 to 95.03)	96.55% (92.73 to 98.47)	91.77% (83.56 to 95.98)	88.71% (79.92 to 94.07)	83.74% (68.26 to 91.59)	82.79% (68.45 to 90.44)	80.88% (60.99 to 90.44)

^ Participants were considered to be unvaccinated if they had not received any dose of Covid-19 vaccine as of the test date.

*. The illness was defined as symptomatic if the participant had at least one of the following symptoms present within 14 days before or after the index test date: fever (a body temperature documented at ≥38°C or subjective fever), chills, cough (dry or productive), shortness of breath, chest pain or tightness, fatigue or malaise, sore throat, headache, runny nose, congestion, muscle aches, nausea or vomiting, diarrhea, abdominal pain, altered sense of smell or taste, loss of appetite, or red or bruised toes or feet.

% **Immunocompromising conditions include immunosuppressive medication (e.g., corticosteroids, chemotherapy, or other immunosuppressive medications), solid organ transplant, hematopoietic stem cell transplant, HIV, or active cancer (current cancer or in treatment or diagnosed in last 12 months).

$ At least one Covid-19–like symptom and a positive result for SARS-CoV-2 on polymerase- chain-reaction (PCR) testing, other nucleic acid amplification testing, or antigen-based testing

† Case participants were defined as healthcare person nel who had at least one Covid-19–like symptom and a positive result for SARS-CoV-2 on polymerase- chain-reaction (PCR) testing, other nucleic acid amplification testing, or antigen-based testing 14 Persons who tested negative on PCR or other laboratory-based nucleic acid amplification testing, regardless of symptoms, were eligible for inclusion as controls.

+ excluded participants who had been tested within 0 to 2 days after receipt of the second dose

& HCP who sought care for the current episode of illness were seen in an outpatient setting, emergency department, urgent care, or hospital. Among hospitalized cases, 5 cases required supplemental oxygen, 3 cases were admitted to intensive care unit, and 2 were intubated. Among hospitalized controls, 1 HCP was admitted to intensive care unit and required supplemental oxygen.

conditions as being associated with a definite or potential increased risk of severe Covid-19 according to the definitions of the Centers for Disease Control and Prevention (https://www .cdcgov/coronavirus/2019ncov/needextraprecautions/peoplewithmedica-conditions.html).

£ Extracted using WebPlotDigitizer software

€ Vaccine effectiveness was assessed in the interval from at least 14 days after receipt of the first dose through the receipt of the second dose or later given low sample size

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results

Author (Year): Polinski 2021 [35] **Title:** Effectiveness of the Single-Dose Ad26.COV2.S COVID **DOI:** 10.1101/2021.09.10.21263385 **NCT:** N/A **Study Design***:* Matched cohort study with crossover **Country**: USA **Setting:** US health insurance claims data (data aggregated by HealthVerity) **Time Period**: 1 March 2021 –17 July 2021 **Variants of Concern:** Delta **Publication status**: Preprint	**Intervention/Exposure**: Ad26.COV2.S (Janssen) **Comparator/Control:** Individuals in database with no evidence of vaccination **Time since final vaccination dose:** Mean 15.4 weeks Maximum 21.7 weeks	**Description:** Study participants entered cohort on day of vaccination. They were matched (1:10 risk-set sampling by time, location, age, sex, and comorbidity score, with further matching of the risk set sampled population by propensity score) with up to 10 unvaccinated individuals. Those with observed COVID-19 or receipt of any COVID-19 vaccine during the 365 days before cohort entry were excluded. At least one medical and pharmacy claim was required during 365 days before cohort entry to ensure each individual's activity in the system. **N:** 390,517 vaccinated 1,524,153 matched with no record of vaccination **Age:** Vaccinated: Mean age, yrs (SD) 55.05 (17.31) Unvaccinated: Mean age, yrs (SD) 54.94 (17.42) **Male** Vaccinated, male 43.7% Unvaccinated, male 43.7% **Co-morbidities:** Vaccinated COPD: 10.3% Organ transplant: 0.4% Malignancies: 4.5% Pulmonary fibrosis: 0.5% HIV: 0.3% Unvaccinated COPD: 10.4% Organ transplant: 0.4% Malignancies: 4.5%	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* VE 73% (95% CI 69%, 76%) **Adjustments:** Matched by time, location, age, sex, and comorbidity score, also propensity scores **Mortality:** NR **Variants of Concern** High delta states** *COVID-19 related Hositalisation* VE: 74% (61 to 83) *COVID-19 related Hositalisation* (June-July only***) VE: 77% (59 to 87) **Subgroups**: <50 years VE = 79% (95% CI 70 to, 85) ≥50 years VE = 71% (95% CI 66 to 74%) <60 years	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection (see definition of observed Covid-19§)** **≥14 days after second/final dose** ***Any*** VE: 69% (95% CI 67%, 71%) **Adjustments:** Matched by time, location, age, sex, and comorbidity score, also propensity scores **Variants of Concern:** High delta states** Observed COVID-19 VE 69% (95% CI 63% to 74%) Observed COVID-19 (as observed for period June and July only***) VE: 67% (95% CI 60 to 73) **Subgroups:** <50 years VE = 75% (95% CI 72 to 77%) ≥50 years VE = 65% (95% CI 63 to, 68%)

		Pulmonary fibrosis: 0.5% HIV: 0.4%	VE = 79% (74 to 84) <u>≥60 years</u> VE = 68% (63 to 73) <u>Immunocompromised</u> VE = 54% (95% CI 35 to 67) **Efficacy effectiveness over time.** It is stated that sustained and stable VE was observed, starting 14 days after vaccination to a maximum of 152 days after vaccination. Monthly VE estimates for COVID-19-related hospitalization were stable	<u><60 years</u> VE = 72% (69 to 74) <u>≥60 years</u> VE = 65% (61 to 68) <u>Immunocompromised</u> VE = 52% (95% CI 42% to 60%) **Efficacy/effectiveness over time.** The VE for observed COVID-19 rose slightly until May to 81% (79% to 83%) and remained at a high level until the end of the follow-up period in July (77%; 74% to 79%) (see fig 3a)

§observed COVID-19 was defined by either recording of an in- or outpatient ICD-10-CM diagnosis code of U07.1 (85% of cases) in any position, and/or a recorded positive SARS-CoV-2 diagnostic PCR or nucleic acid amplification test result (15%).
*All VE estimates extracted here do not incorporate the adjustment applied by the authors in the primary analysis as it was not considered robust. See the statement below.
"Given the expedited national vaccination effort, a sizable proportion of COVID-19 vaccinations were administered by employers, mass vaccination sites, pharmacies, and other settings where often no health insurance claims were submitted. The CDC reported that 57% of US residents 12 years and older were vaccinated as of July 22, 2021, while only 34% were recorded among the same people in our claims data, which confirms substantial under-recording (Suppl. S4). As a result, it is highly likely that a substantial proportion of the unvaccinated group in claims data was in fact vaccinated and thus observed VE estimates will appear lower than indeed true. To compensate, we conservatively assumed 40% under-recording of vaccinations and applied a correction factor to all VE estimates using standard methods for correcting exposure misclassification."
**High Delta States were Arkansas, Florida, Louisiana, and Missouri.
*** For June and July 2021 results within four states (Arkansas, Florida, Louisiana, and Missouri) with high prevalence of the Delta variant of concern, incident rate ratios (IRR) after PS matching are reported instead of hazard ratios and VE is estimated using (1-IRR)x100 for patients contributing follow-up time from June 1, 2021 through July 31, 2021

<table>
<tr><th>Study characteristics</th><th>Exposure and Controls</th><th>Population and Patient demographics</th><th>Primary outcome results</th><th>Secondary outcome results</th></tr>
<tr>
<td>Author (Year):
Pouwels (2021) [53]

Title: Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK

DOI: 10.1038/s41591-021-01548-7

NCT: N/A

Study Design: Prospective cohort study (with cross-over).

Country: UK

Setting: National longitudinal survey from UK National statistics agency.

Time Period:
1 December 2020 to 01 August 2021</td>
<td>Exposure*
• BNT162b2
• ChAdOx1

Control:
No vaccination no prior positive, >21 days before vaccination no prior positive.

Time since final vaccination dose:
Median (IQR)

• BNT162b2: 8.4 weeks(4.98 to 12.25 weeks)
• ChAdOx1: 5.84 weeks (3.84 to 8.12 weeks)</td>
<td>Description:
• UK Office for National Statistics Covid-19 Infection survey.
• Random selection of households.
• People aged over 18 years included in this analysis.~
• Swabs monthly from consenting participants regardless of patient history.
• participant was classified into one of 13 different exposure groups based on current vaccination status, study antibody and PCR tests
• Patients with no prior (study or national testing program swab) positive and > 21 days before vaccination formed the not vaccinated reference group. But these patients are included in the vaccinated cohort.
<table>
<tr><td></td><td colspan="4">Dominant Phase</td></tr>
<tr><td></td><td>Alpha</td><td colspan="3">Delta</td></tr>
<tr><td>Individuals</td><td>384,543</td><td></td><td>358,983</td><td></td></tr>
<tr><td>Households</td><td>221,909</td><td></td><td>213,825</td><td></td></tr>
<tr><td>Visits</td><td>2,580,021</td><td></td><td>811,624</td><td></td></tr>
<tr><td>Visits per person - Median (IQR)</td><td>7 (6-8)</td><td></td><td>2 (2-3)</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Characteristics of visits included in the analyses (All ≥18 years)#</td></tr>
<tr><td>Not vaccinated, no prior positive, >21 days before vaccination</td><td>1,561,154</td><td></td><td>27,135</td><td></td></tr>
</table>
</td>
<td>Severe Disease:
NR

Adjustments:
NA

Mortality: NR

Variants of Concern: NA

Subgroups: NA

Effectiveness over time: NR</td>
<td>See below</td>
</tr>
</table>

≥ 14 days after second dose, BNT162b2	70,058		199,411		
≥ 14 days after second dose ChAdOx1	30,178		303,511		
	≥18 years old	*≥18 years old*	*18-34 years*	*35-64 years*	
Male:	46.40%	45.80%	45.40%	44.200 %	
Age - median (IQR) years	56 (41-68)	57 (42-69)	28 (23-32)	52 (44,58)	
Ever reported to have a long-term health condition	28.0%	28.5%	17.5%	24.2%	
Ever reported to be a care home worker	1.2%	1.1%	1.5%	1.6%	
Ever reported to be a person-facing healthcare worker	2.6%	2.6%	3.6%	3.6%	

Variants of Concern:
Delta 61% of sequenced positives from the symptomatic testing program in the week commencing 17 May and 99% from 27 June onwards
Alpha Dominant: 1 December 2020 – 17 May 2021
Delta dominant:17 May 2021 to 01 August 2021

Publication status: Peer-reviewed

Secondary Outcome Results

Adjustments

Geographic area, age in years, sex, ethnicity (white versus non-white as small numbers), index of multiple deprivation (percentile, calculated separately for each country in the UK), working in a care-home, having a patient-facing role in health or social care, presence of long-term health conditions, household size, multigenerational household, rural-urban classification45-47, direct or indirect contact with a hospital or care-home, smoking status, and visit frequency

Any Infection

(≥14 days following second vaccination)

		BNT162b2 (Pfizer) VE (95% CI)			*ChAdOx1 (Astra Zeneca) VE (95% CI)*			*Heterogeneity p for BNT162b2 v ChAdOx1*	
		Alpha	Delta	Heterogeneity p Alpha vs delta period	Alpha	Delta	Heterogeneity p Alpha vs delta period	Alpha	Delta

18 + years	*All PCR positive*	78% (68-84%)	80% (77-83%)	0.50	79% (56-90%)	67% (62-71%)	0.23	0.85	<0.0001
	Ct <30	94% (91-96%)	84% (82-86%)	<0.0001	86% (71-93%)	70% (65-73%)	0.04	0.03	<0.0001
	PCR positive with Self-reported symptoms	97% (96-98%)	84% (82-86%)	<0.0001	97% (93-98%)	71% (66-74%)	<0.0001	0.52	<0.0001
18 to 64 years (65+ years is not reported)	*All infections*	NR	82% (79% -85%)	NA	NR	67% (62% - 71%)	NA	NA	<0.0001
	Ct <30	NR	86% (84% -88%)	NA	NR	69% (65% - 73%)	NA	NA	<0.0001
	Self-reported symptoms	NR	86% (83% -88%)	NA	NR	70% (66% - 74%)	NA	NA	<0.0001
	Ct >30	NR	71% (65% -75%)	NA	NR	59% (53% - 64%)	NA	NA	<0.0001
	No self-reported symptoms	NR	74% (69% -78%)	NA	NR	57% (51% - 63%)	NA	NA	<0.0001

Subgroups

18 to 64 years (Delta dominant phase)		*BNT162b2 (Pfizer) VE (95% CI)*			*ChAdOx1 (Astra Zeneca) VE (95% CI)*		
		Age					
		18-34	35-64	Heterogeneity p value	18-34	35-64	Heterogeneity p value
	VE Any infections	90% (85-93%)	77% (65-85%)	0.001	73% (65-80%)	54% (40-65%)	0.002
	VE infections with Ct < 30	95% (91-97%)	88% (79-93%)	0.002	74% (64-81%)	57% (41-69%	0.02
	VE against infection with self-reported symptoms	96% (93-98%)	88% (78-94%)	p<0.0001	76% (67-83%)	57% (39-70%)	0.007
		By self-reported long-term health conditions					
		No Long term health condition	Long term health condition	Heterogeneity p value	No Long term health condition	Long term health condition	Heterogeneity p value
	VE Any infections	86% (80-90%)	81% (69-89%)	0.23	69% (62-74%)	58% (39-71%)	0.10

18 to 64 years (Delta dominant phase)	VE infections with Ct < 30	92% (87-95%)	92% (85-96%)	0.96	70% (62-76%)	65% (46-77%)	0.48
	VE against infection with self-reported symptoms	94% (89-96%)	92% (84-96%)	0.38	73% (65-79%)	64% (44-77%)	0.23
		By evidence of prior infection					
		No evidence	Evidence	Heterogeneity p	No evidence	Evidence	Heterogeneity p
18 to 64 years (Delta dominant phase)	VE Any infections	85% (79-90%)	93% (87-96%)	0.006	68% (61-73%)	88% (83-92%)	<0.0001
	VE infections with Ct < 30	92% (87-95%)	98% (94-99%)	0.004	69% (61-75%)	92% (87-95%)	<0.0001
	VE against infection with self-reported symptoms	93% (89-97%)	99% (96-100%)	0.002	72% (64-78%)	94% (89-97%)	<0.0001

	Effectiveness over Time				
		Days since second dose	*BNT162b2 (Pfizer)*	*ChAdOx1 (Astra Zeneca)*	*Heterogeneity p* (Test for difference in relative rate of change between the two vaccines)
VE 18 – 64 year	*Any infection*	14	85% (79–90%)	68% (61–73%)	0.14
		30	83% (78–88%)	66% (61–71%)	
		60	80% (76–83%)	64% (58–69%)	
		90	75% (70–80%)	61% (53–68%)	
		Relative reduction in effectiveness per month from second dose	22% decline[a] (6% decline to 41% decline)	7% decline (18% decline to 2% increase)	
		Test for evidence of change over	0.007	0.15	

		time from second dose			
	Ct<30	14	92% (87–95%)	69% (61–75%)	0.003 " Extrapolating declines beyond the observed follow-up, both vaccines would be equally effective against PCR-positives with Ct<30 139 days (4.6 months) after the second dose and 116 days (3.8 months) against PCR-positives with symptoms"
		30	90% (86–93%)	67% (61–73%)	
		60	85% (81–89%)	65% (58–70%)	
		90	78% (72–82%)	61% (52–69%)	
		Relative reduction in effectiveness per month from second dose	52% decline[a] (26% decline to 84% decline)	9% decline (22% decline to 3% increase)	
		Test for evidence of change over time from second dose	< 0.0001	0.14	
	symptomatic infection	14	93% (89–96%)	72% (64–78%)	0.003
		30	92% (87–95%)	70% (64–76%)	
		60	86% (82–90%)	67% (60–72%)	
		90	78% (72–82%)	63% (53–71%)	
		Relative reduction in effectiveness per month from second dose	63% decline[a] (30% decline to 103% decline)	11% decline (26% decline to 2% increase)	
		Test for evidence of change over time from second dose	< 0.0001	0.10	
	[a]When initial effectiveness is very high, modest relative declines per month have less effect on absolute effectiveness.				
			Low Ct versus High Ct Population		

	Independently of this effect of calendar time (reflecting B.1.1.7 versus B.1.617.2 dominance), new PCR-positive cases were less likely to be in the low Ct subpopulation 14 d after two BNT162b2 vaccinations than two ChAdOx1 vaccinations (adjusted odds ratio (aOR) = 0.33 (95% CI, 0.16–0.67), *P* = 0.002), but this likelihood increased significantly over time from second vaccination (aOR per month = 1.43 (95% CI, 1.07–1.91), *P* = 0.01; unadjusted in Fig. 3d; Supplementary Table 7 and Extended Data Fig. 8). In contrast, there was no evidence of changing likelihood over time for ChAdOx1 (aOR per month = 0.97 (95% CI, 0.79–1.19), *P* = 0.78; heterogeneity *P* = 0.02). Overall, therefore, by around 3 months after second vaccination, the probability of being in the low-Ct subpopulation was similar for both BNT162b2 and ChAdOx1. Vaccine type and time from second vaccination had similar effects on the mean Ct within the low-Ct subpopulation, with higher Ct values in new PCR-positive cases 14 d after second BNT162b2 vaccination (P = 0.003), which then dropped significantly faster with time from second vaccination than for ChAdOx1 (interaction P = 0.01), leading to similar Ct values with both vaccines by around 3 months (Extended Data Fig. 8b). Individuals who were previously PCR/antibody positive were less likely to belong to the low-Ct subpopulation compared to individuals without evidence of previous infection (P < 0.0001), while **individuals who reported having long-term health conditions** were also associated with a lower probability of belonging to the low-Ct subpopulation (P = 0.006), potentially reflecting protection in the former and longer duration of PCR positivity in the latter, leading to late infections being more likely to be identified through the fixed testing schedule.
	Effectiveness over time by subgroup
18 – 64 years Delta dominant period	Graphs (Fig 2, ext data fig 4 and ext data fig 5) showing the VE for three outcomes (any infection, Ct<30 , and reported symptoms) by time (up to 75 days since 14 days after 2nd dose) are presented for the following subgroups • age (16-34, 35-64) • self-reported long term health condition • prior infection status • dosing interval. Numerical results are not provided for the sub-groups. Confidence intervals are wide and formal statistical tests are not reported. **NB.** For these reasons, descriptions of the graphs for the subgroups by the evidence synthesis team below should be interpreted as a description with caution as the direction of **point estimates only**. They should not be interpreted as evidence of an effect. Interpretations are provided below for the "All PCR positive" outcome only <u>Long term health condition (lthc)</u>: It is difficult to ascertain from the graph whether there is an interaction between the rate of treatment waning and evidence of a long term health condition. The estimated VE for Pfizer is 86% (80-90%) for those without lthc at day 14, while estimated VE was 81% (69-89%) for those with lthc at day 14 (interception points). No numerical estimates are given for any later days. The estimated VE for AstraZeneca is 69% (62-74%) for those without long term health conditions at day 14, while estimated VE was 58% (39-71%) for those with lthc at day 14 (interception points). No numerical estimates are given for any later days. In ext data fig 4 (measuring VE against cases with with Ct<30), there does not appear to be an interaction between the rate of treatment waning and evidence of a long term health condition for either Pfizer or Astra-Zeneca

	In ext data fig 5 (measuring VE against cases with reported symptoms), it appears that there may be faster treatment waning for those with lthc compared with those without lthc in the Pfizer treatment group. There does not appear to be an interaction between the rate of treatment waning and evidence of a lthc in the Astra-Zeneca treatment group.

*Some participants received mRNA mRNA-1273 (Moderna). These participants are included in the population and patient demographics but the authors report that there was insufficient data to present effectiveness results.

Note: analysis is based on visits rather than participants and restricted to those either being unvaccinated or vaccinated with ChAdOx1, BNT162b2 or mRNA-1273: factors above and vaccination exposure

~The methods section states that enrollees aged 16 + are included but all the results refer to patients aged ≥18 years.

Key: AZ – AstraZeneca; CI – Confidence Interval; IQR – Interquartile Range ; NCT – National Clinical Trial; N/A – Not applicable; NR – Not Reported; OR – Odds Ratio; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Saciuk (2021)[54] **Title:** Pfizer-BioNTech vaccine effectiveness against Sars-Cov-2 infection: findings from a large observational study in Israel **DOI:** http://dx.doi.org/10.2139/ssrn.3868853 **NCT:** N/A	**Exposure**: BNT162b2 vaccine (Pfizer/BioNtech) **Comparator:** No vaccination **Time since final vaccination dose:**	**Description:** HMO members aged 16 or over. Those who previously tested positive for SARS-CoV-2 were excluded. ^ **N:** 1,650,855 only vaccinated: 34·9% became vaccinated (during study period) 46·8% only unvaccinated 18·3% **Age:** | | only vaccinated | became vaccinated | only unvaccinated | |---|---|---|---| | 16-44 | 18% | 71% | 64% |	**Severe Disease:** **≥7 days after final dose** *Hospitalisation* N=1,047 VE 93.4% (95% CI 91.9 to 94.7) (adj) *ICU admissions:* NR **Adjustments:** Adjusted for gender, age, hypertension, diabetes and obesity and conditioned on geographical statistical area (proxy for population group and	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥7 days after second/final dose** *Any* VE: 93% (95% CI 92.6 to 93.4) **Adjustments:** As for primary outcomes. **Variants of Concern:** NR

Study Design: retrospective cohort study (crossover*)

Country: Israel

Setting*:* National insurance organisation (health maintenance organisation)

Time Period*:* 18 January 2021 – 25 April 2021

Variants of Concern: Alpha (B.1.1.7)

Publication status: Preprint

Follow up period: 98 days (maximum). Median: 10.14 weeks

Median follow up for unvaccinated: 5.7 weeks

45-59	33%	23%	20%
60-74	36%	5%	10%
75+	13%	1%	5%

Male = 48%

Co-morbidities/Special populations:

Co-morbidity	Vaccinated	Unvaccinated
Hypertension	34·99%	12·54%
Diabetes	16·06%	5·47%
Obese	23·55%	15·08%

geographical risk exposure)and calendar week (proxy for differential risk over time)

Mortality

N=164

COVID-19 related

Vaccine effectiveness 91.1% (95%CI 86.5 to 94.1) (adj)

Variants of Concern: NR

Subgroups:

For both hospitalization and mortality, the variation in vaccine effectiveness by age group was not significant, but this may be attributed to the small number of cases.

VE point estimates for hospitalization and mortality among those with hypertension, diabetes or obesity were not appreciably different from total population VE

VE against Hospitalisations

Underlying condition	*VE (CI) unadjusted*	*VE (CI) adjusted*
Hypertension	*95.3 (93.5, 96.7)*	*NR*

Subgroups:

VE when age by vaccine status interaction term included:#

16-44 : 94.7%

45-59: 93.8%

60-74: 91.5%

75+: 84.1%

comorbidities

Lower VE for infection was estimated for individuals with hypertension, diabetes and obesity compared to the total population.

VE against any COVID-19 Infection

Underlying condition	*VE (CI) unadjusted*	*VE (CI) adjusted*
Hypertension	*94 (93.2, 947.)*	*89.7 (88.6,91.7)*
Diabetes	*94.5 (93.9, 95)*	*88.9 (87.3-90.2)*
Obesity	*96.5 (96.2, 96.9)*	*89.7 (88.6-90.7)*

				Efficacy/effectiveness over time: NR

Diabetes	*95.1 (93.7, 96.2)*	*NR*
Obesity	*97.6 (96.2, 98.4)*	*NR*

VE against Mortality

Underlying condition	*VE (CI) unadjusted*	*VE (CI) adjusted*
Hypertension	*91.7 (85.9, 95.1)*	*NR*
Diabetes	*91.7 (87.1, 94.6)*	*NR*
Obesity	*83.3 (14.1, 96.8)*	*NR*

Efficacy/effectiveness over time: NR

* The groups were dynamic, such that people who were initially unvaccinated exited the 'unvaccinated group' on receipt of their first dose and entered the 'vaccinated group' eight days after receiving their second dose, provided that they had not been infected or died in the intervening period.
^Prior infection was defined for each group as follows: a positive PCR or IgG serology result prior to day eight after second dose of vaccination for the 'vaccinated group' and prior to 18.1.2021 for the 'unvaccinated group'.
Exponent of co-efficient

16-44 : 0.053
45-59: 0.053*1.163
60-74: 0.053*1.6
75+: 0.053 *2.996

Key: CI – Confidence Interval; ICU – Intensive Care Unit; HMO – Health Maintenance Organisation; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction; VE – Vaccine Efficacy.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Tenforde 2021[55] **Title:** Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults — United States, March–July 2021 **DOI:** http://dx.doi.org/10.15585/mmwr.mm7034e2 **NCT:** N/A **Study Design***:* Case-control **Country**: USA **Setting***:* 21 hospitals across 18 US states. **Time Period***:* 11 March to 14 July 2021	**Exposure**: mRNA vaccine Pfizer-BioNTech: 59% Moderna: 41% **Comparator/Control:** No Vaccination **Time since final vaccination dose:** Median 9.29 weeks (IQR 5.84 to 13.25 weeks)	**Description:** Adults aged ≥18 years admitted to 21 hospitals in 18 US states. Previous SARS-COV-2 or seronegative status: NR *Case*: COVID-19–like illness† and had received a positive SARS-CoV-2 RT-PCR or antigen test result. *Control* Negative SARS-COV-2 by all tests including one RT-PCR and Group 1: COVID-19–like illness† Group 2: No COVID-19 like illness† (Analysis conducted versus a combination of both groups) **N:** Cases: 1,194 (11.8% fully vaccinated[#]) Controls: 1,895 (52.1% fully vaccinated) **Age:** Median 59 (IQR 46–69) **Male** = 51.3%	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* VE 86% (95% CI 82% to 88%) **Adjustments:** Admission date, region, age, sex, race/ethnicity. **Mortality :** NR **Variants of Concern** *Alpha dominant period* March – May VE 87% (95% CI 83% to 90%) *Delta dominant period* [$] June to July VE 84% (95% CI 79%–89%). **Subgroups**: VE was numerically lower for those with an immunocompromising condition (63%; 95% CI 44% to	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection:** NR

<table>
<tr>
<td>Variants of Concern: Of sequenced cases: 53.3% Alpha, 16.3% Delta. Delta became dominant in Mid-June.

Publication status: Peer-reviewed.</td>
<td></td>
<td>Co-morbidities and Special Populations
≥1 chronic condition: 82.1%
Pulmonary Disease: 26%
Immunocompromising condition: 21.1%*
LTC Resident: 4.7%</td>
<td>76%) compared to those without (90%; 95% CI 87%–92%). No formal interaction tests are reported.

Effectiveness over time.

Hospitalization

Weeks 2-12: VE 86% (95% CI 82% to 90%)

Weeks 13-24: VE 84% (95% CI = 77% to 90%)

No statistically significant change in vaccine effectiveness observed between the two time periods (p for interaction = 0.854).

Sensitivity analysis using linear and natural cubic spline models showed similar results.

Subgroups

No statistically significant change in VE over a 24-week period was observed within subgroups (immunocompromised, aged ≥65 years and multiple morbidities). Numerical results for subgroups were not presented. Estimates below derived from digitising graph.

<table>
<tr><td>Group</td><td>2-12 weeks
VE (95% CI)</td><td>13-24 weeks
VE (95% CI)</td></tr>
</table>
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</table>

			Aged >65 years	86.73 (81.69 to 91.08)	80.09 (70.02 to 88.1)	
			Immuno compromised *	64.3 (48.51 to 79.63)	53.55 (12.81 to 77.8	
			With multiple morbidities &	72.31 (62.24 to 82.15)	70.02 (52.4 to 81.92)	

† COVID-19–like illness was defined as having one or more of the following: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia.

*Immunocompromising conditions included having one or more of the following: active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in the past 6 months), active hematologic cancer (such as leukaemia, lymphoma, or myeloma), HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, immunosuppressive medication, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease, including Crohn's disease or ulcerative colitis.

A patient was considered to be fully vaccinated if both doses of an authorized mRNA COVID-19 vaccine were administered, with the second dose received ≥14 days before illness onset.

$ Because of limited sequenced virus, Delta-specific VE was not assessed. VE was similar during June–July when circulation of Delta increased in the United States compared with VE during March–May when Alpha variants predominated, although further surveillance is needed.

& Multiple morbidities were defined as having chronic conditions within three or more of the following condition categories: cardiovascular disease, neurologic disease, pulmonary disease, gastrointestinal disease, endocrine disease, renal disease, hematologic disease, malignancy, immunosuppression not captured in other categories, autoimmune condition, or other condition (sarcoidosis, amyloidosis, or unintentional weight loss ≥10 pounds in the last 90 days).

£ Values extracted using WebPlotDigitiser® software

Key: CI – Confidence Interval; IQR – Interquartile Range; LTC – Long Term Care; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Thompson (2021) [41] **Title:** Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings **DOI:** 10.1056/NEJMoa2110362 **NCT:** N/A **Study Design***:* Test negative (case-control) **Country**: USA **Setting***:* Hospital, emergency departments and urgent care clinics **Time Period***:* 01 January 2021 to 22 June 2021 **Variants of Concern:** NR **Publication status**: Peer-reviewed	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.Cov2.S (Janssen) **Comparator/Control:** *Unvaccinated* **Time in days since final vaccination dose to index date*:** Hospitalisation – Median – 7.55 weeks IQR (4.7 to 10.68 weeks) ICU admission – Median – 7.4 weeks (IQR 4.84 to 10.39 weeks) ED/UC – Median 7.12 weeks (IQR 4.42 to 10.4 weeks)	**Description:** conducted a study involving adults (≥50 years of age) with Covid-19–like illness who underwent molecular testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) **N:** **Hospitalisations:** ***BNT162b2 (Pfizer/BioNtech)*** ***8,500*** ***mRNA-1273 (Moderna)*** ***6,374*** ***Ad26.COV2.S (Janssen)*** **707** ***Unvaccinated*** ***20,406*** **ED or urgent care visit:** *BNT162b2(**Pfizer/BioNtech)*** *3,589* *mRNA-1273 **(Moderna)*** *2,476* Ad26.COV2.S***(Janssen)*** 456 *Unvaccinated* *11,812*	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation % (95% CI):* *BNT162b2 vaccine 87 (85–90)* *mRNA1273 vaccine 91 (89–93)* *Ad26.COV2.S vaccine 68 (50–79)* *ICU admissions:* *BNT162b2 or mRNA1273 vaccine 90 (86–93)* Emergency department or urgent care visit: *BNT162b2 vaccine 89 (85–91)* *mRNA1273 vaccine 92 (89–94)* *Ad26.COV2.S vaccine 73 (59–82)* **Adjustments:** Vaccine effectiveness was adjusted with weights based on propensity-for vaccination scores and according to age, geographic region, calendar time (days from 1 January 2021, to the index date for each medical visit), and local virus circulation. **Mortality**	**Confirmed RT-PCR SARS-CoV-2 infection** N/R **Adjustments:** N/A **Variants of Concern:** NR **Subgroups**: N/R **Efficacy/effectiveness over time:** N/R

Age:
among hospitalized patients
median age was 74 years (interquartile range, 66 to 82)

among those who visited an emergency department or urgent care clinic.

70 years (interquartile range, 61 to 78)

Age of participants in study

	Un-vaccinated	*Full, 2 Doses of mRNA Vaccine*	*Full, Ad26.COV2.S Vaccine*
50–64 yr	5,532	1898	282
65–74 yr	6,681	4,481	187
75–84 yr	*5,233*	*5,189*	*153*
≥85 yr	*2,960*	*3,306*	*85*

Male = 47%

Co-morbidities: NR

All Cause/COVID-19: NR

Variants of Concern

NR

Subgroups:

Effectiveness against hospitalization [$] *:*

≥50 yr of age	89% (95% CI: 87 to 91)
≥85 yr of age	83% (95% CI: 77 to 87)
≥50 yr of age with no chronic condition	92% (95% CI 86 to 96)
≥50 yr of age with ≥1 chronic respiratory condition	90% (95% CI: 88 to 92)
≥50 yr of age with ≥1 chronic nonrespiratory condition	88% (95% CI: 86 to 90)

Effectiveness against ICU admission

≥50 yr of age	90% (95% CI: 86–93)

Effectiveness against SARS-CoV-2 Infection Leading to an Emergency Department or Urgent Care Clinic Visit

≥50 yr of age	*91% (95% CI:89 to 93)*
≥85 yr of age	84% (95% CI:73 to 91)
≥50 yr of age with ≥1 chronic respiratory condition	90% (95% CI:86 to 93)
≥50 yr of age with ≥1 chronic nonrespiratory condition	90% (95% CI: 87 to 92)

Efficacy/effectiveness over time:

Effectiveness against hospitalization ≥50 yr of age

42–55 Days after dose 2	90% (95% CI: 87 to 93)
56–69 Days after dose 2	86% (95% CI: 82 to 90)
70–83 Days after dose 2	93% (95% CI: 89 to 95)
84–97 Days after dose 2	86% (95% CI: 79 to 91)

98–111 Days after dose 2	82% (95% CI: 72 to 89)
≥ 112 Days after dose 2	86% (95% CI: 74 to 93)

Effectiveness against emergency department or urgent care visit ≥50 yr of age

42–55 Days after dose 2	95% (95% CI: 91 to 97)
56–69 Days after dose 2	88% (95% CI: 81 to 92)
70–83 Days after dose 2	86% (95% CI: 78 to 91)
84–97 Days after dose 2	92% (95% CI: 87 to 96)
98–111 Days after dose 2	86% (95% CI: 77 to 92)
≥ 112 Days after dose 2	86% (95% CI: 74 to 93)

messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated hospitalization by days past most recent dose

	14-27 days post dose 2	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**98 to 111 days post dose 2**	**(≥112 days post dose-2**
Pfizer-BioNTech	87% (80 to 91)	95% (91 to 97)	86% (79 to 91)_	83 (75 to 89)	90% (82 to 94)	87% (76 to 93)	75% (57 to 85)	83% (64 to 92)
	14-27 days post dose 2	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**≥ 56 days post dose 2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**(≥112 days post dose-2)**
Moderna	90% (81 to 94)	89% (83 to 93)	93% (87 to 97)	(91% (85% to 94)	96%(92 to 98)	86% (75 to 92)	93%(82 to 97)	95% (79 to 99)

	14-27 days post dose	**28 to 41 days post dose**	**42-55 days post dose**	**≥56 days post dose**				
Janssen	72% (38 to 88)	69% (34 to 86)	68%(18 – 87)	79% (48 to 91)			-	
messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated emergency department and urgent care (ED/UC) medical events								
Pfizer-BioNTech	**14-27 days post dose 2**	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**98 to 111 days post dose 2**	**(≥112 days post dose-2**
	93% (87 to 96)	94% (90 to 97)	93% (81 to 87)	82% (68 to 90)	80% (66 to 88)	91% (82 to 96)	78% (61 to 87)	83% (64 to 92)
	14-27 days post dose 2	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**≥ 56 days post dose 2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**(≥112 days post dose-2)**
Moderna	90% (81 to 95)	96% (92 to 98)	93% (85-96)	90% (79-95)	91%(79 – 96)	91% (79 – 97)	not recorded due to no breakthrough cases	90% (52 to 98)
	14-27 days post dose	**28 to 41 days post dose**	**42-55 days post dose**	≥ 56 days post dose				
Janssen	67% (30 to 84)	80% (52 to 92)	58% (5 to 81)	87% (71 to 94)				
* Index date defined as The index date for each medical visit was defined as either the date of collection of a respiratory specimen associated with the most recent positive or negative SARS-CoV-2 test result before the medical visit or the date of the medical visit (if testing occurred only after the admission or visit date).								

Appendix D Updated evidence tables for one-dose Ad26.COV2.S (Janssen) vaccination (search conducted on 8 November 2021)

Data Extraction

Randomised Control Trials

Janssen (ENSEMBLE/COV3001 trial)

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Sadoff (2021) **Title:** Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19 **DOI:** 10.1056/NEJMoa2101544 FDA Emergency Use Authorisation Report (Janssen Biotech) Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation Meeting	**Intervention**: Ad26.COV2.S (Janssen) **Comparator:** Placebo (saline) **Time since final vaccination dose:** Median 8.29 weeks	**Description:** Multicenter study across US, South Africa, and 6 countries in Latin America Age cohorts: 18-59 years, ≥60 years with and without comorbidities. Stage A enrolled patients 18+ in good health. Stage B was initiated later and included patients with comorbidities. Participants with evidence of previous infection (or seropositive status) were excluded from the primary analysis (per protocol) but were not excluded from the trial. **N:** Per protocol set (FDA report) Ad26.COV2.S : 19,630 Placebo : 19,691	**Severe Disease** **≥ 14 days post vaccination (per protocol, seronegative at baseline)*** *Moderate/*Severe *Disease* VE = 66.9% (95% CI 59.0 to 73.0) *Severe/Critical Disease* VE = 76.7% (95% CI 54.6 to 89.1) *COVID-19 requiring medical intervention* VE = 75.0% (95% CI -25.3 to 97.4) **≥ 28 days post vaccination**	**RT-PCR or Antigen Confirmed SARS-CoV-2 infection** (≥ 28 days follow-up Per protocol and seronegative) *Asymptomatic:* VE 65.5%; (95% CI 39.9 to 81.1) # *Symptomatic of any severity* VE 66.5% (95% CI 55.5 to 75.1) *Mild+:* Not computable (Zero cases in the Ad26.COV2.S group and 2 cases in the placebo group. *Moderate^:* VE 62.0% (95% CI 48.7 to 72.2)

NCT: NCT04505722 **Study Design***:* RCT **Country**: Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the USA **Setting***:* General Population **Time Period***:* 21 September 2020 to 22 January 2021 for published Sadoff et al. study (some endpoints reported up to a data cut of February 5th from FDA report) **Variants of Concern:** NR **Publication status**: Peer-reviewed		**Age: Median** 53 years (Range 18 to 100) ≥60 years: 34.6% ≥75 years: 3.7% **Male** = 54.5% **Comorbidities**: ≥1 Coexisting condition 39.9% **Special populations**: Asthma: 1.3% (FAS) 1.5% (PP) Cancer 0.5% 1.4% (PP) CF <0.1% CKD 0.5% COPD: 1% 0.9% (PP) ICP <0.3% Pulmonary fibrosis <0.1%	**(per protocol, seronegative at <u>baseline)*</u>** *Hospitalisations* VE 100% (95% CI 74.3 to 100) *Severe Critical~:* VE 85.4 (95% CI 54.2 to 96.9) *Moderate to Severe Critical* +~ VE 66.1 (95% CI 55.0 to 74.8) **Mortality:** 3 deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related). All of which were considered by the investigators to be unrelated to the trial intervention. All-Cause mortality (FAS) – FDA 22 Jan Cut Off *≥ 14 days post vaccination* VE 80.0% (95% CI 29.4 to 96.3)	**Adjustments:** N/A **Subgroups:** *Symptomatic Covid-19 (weighted by burden of disease) (EPAR)* Age <u>18 – 59 years</u>: VE: 69.3% (95% CI 57.4 to 77.7) <u>≥60 years</u> : VE 67.9% (95% CI 38.2 to 82.8) **Variants:** NR **Efficacy over Time:** NR

			≥ 28 days post vaccination VE 75% (95% -25.2 to 97.4) At the later data cut of 5 Feb, (FDA report) there were 7 COVID-19 related deaths – all in the placebo group. **Adjustments:** N/A **Subgroups:** ***Moderate to Severe-Critical COVID 19 ≥ 14 days post second vaccination.*** <u>Age 18-59 years</u> VE = 63.7% (95% CI 53.9 to 71.6) <u>Age ≥60 years</u> VE = 76.3% (95% CI 61.6 to 86.0) ***Moderate to Severe-Critical COVID 19 ≥ 28 days post second vaccination.*** A lower point estimate of VE was observed among participants 60 years of age or older with coexisting	

			conditions for moderate to severe-critical COVID-19 (64.9%; 95% CI 42.2-79.4%). But subgroup analysis by age or co-morbidity on moderate to severe-critical COVID-19 showed no evidence to support a differential treatment effect (interaction p=0.25). However, the analysis was not powered for this. Asthma: 0 cases in 34.1 years follow up in the Ad26.COV2.S and 4 cases in the placebo arm in 38.9 person-years follow-up. (VE not estimable) Cancer: 0 cases in either arm after 14.1 and 14.8 person years follow up in the Ad26.COV2.S and placebo arms respectively. (VE not estimable) Chronic Kidney Disease: 0 cases in 29.9 person years follow up in the intervention and control groups. (VE not estimable) COPD: 1 cases in 30.1 years follow up in the	

			Ad26.COV2.S and 3 cases in the placebo arm in 27.9 person-years follow-up. (VE not estimable) Serious heart conditions: VE = 79.4%(-83.7 to 99.6) HIV: VE = 47.5% (95% CI -266 to 95.3%) Hypertension VE = 35.7%(-45.6 to 72.8) Immunocompromised from blood transplant: 1 case in the Ad26.COV2.S arm in 35 person years of follow-up and 0 cases in the placebo arm with 32 person years follow up. (VE not estimable) Liver disease: 1 case in 96 person-years follow-up in the intervention arm, 0 cases in 98 person years in the control arm. (VE not estimable) Neurologic conditions: 0 cases in 77 years follow-up in the intervention arm, 1 case in the 114 person-years in the control arm (VE not estimable)	

			Obesity: VE = 65.9% (95% CI 47.8 to 78.3) Diabetes Mellitus, type 2 VE: 23.0% (95% CI -90.1 to 69.8) With comorbidities@ VE = 58.6% (95% CI 40.6 to 71.6) Without comorbidities@ *Moderate to Severe-Critical COVID-19* VE = 68.8% (95% CI 59.0 to 76.6) **Variants of Concern:** Despite the high prevalence of the Beta variant in South Africa (94.5% of sequenced cases); VE was 64.0% against moderate to severe–critical disease and 81.7% against severe–critical disease with onset at ≥28 days after administration. **Efficacy over Time:** The onset of efficacy was evident as of 14 days after administration for moderate to severe–critical disease and as of 7 days after	

			administration for severe–critical disease. Efficacy continued to increase through approximately 8 weeks after administration, especially for severe–critical Covid-19. No evidence of waning efficacy was noted among the approximately 3000 participants who were followed for 11 weeks or among 1,000 participants who were followed for 15 weeks.	
Extended follow-up **Time Period***:* 21 September 2020 to 9 July 2021[£] (some endpoints reported up to a data cut of February 5th from FDA report) Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation Meeting Booster Dose of Janssen COVID-19 Vaccine (Ad26.COV2.S) Following Primary Vaccination.	**Intervention:** Ad26.COV2.S (Janssen) **Comparator:** Placebo (saline) **Time since final vaccination dose:** Median 17.68 weeks 23% of participants had follow up of ≥ 6 months	**Description:** As above.	**Severe Disease:** **≥14 days after second/final dose*** *Moderate and severe/critical COVID-19*[^,~] VE = 56.3% (95% CI 51.3 to 60.8) *Severe/critical COVID-19*[~] VE = 73.3% (95% CI 63.9 to 80.5) *COVID-19 requiring medical intervention* VE = 76.1% (95% CI 56.9 to 87.7) **Mortality** *COVID-19 related deaths*	**RT-PCR or Antigen Confirmed SARS-CoV-2 infection** (≥ 28 days follow-up Per protocol and seronegative) VE = 53% (95% CIs not provided)

Advisory Committee on Immunization Practices (ACIP) October 21, 2021 **Variants of Concern:** Variants of concern: alpha (UK, B.1.1.7), beta (SA, B.1.351), gamma (Brazil, P.1), and delta (India, B.1.617.2), Variants of interest: including lambda (Peru, C.37), epsilon (California, B.1.427/429), zeta (Brazil, P.2) and B.1.621 (Colombia) **Publication status**: Regulatory/pharmaceutical company documents (not peer reviewed)			VE = 84.5% (95% CI 47.3 to 97.1) **Subgroup** Age group *Moderate and severe/critical^,~COVID-19* 18-59 years VE = 56.6% (95% CI 51.0 to 61.7) ≥60 years VE = 55.0% (95% CI 2.9 to 64.7) **Variants of Concern:** centrally confirmed moderate and severe/critical COVID-19 *Alpha* VE = 70.1% (95% CI 35.1 to 87.6) *Beta* VE = 38.1% (95% CI 4.2 to 60.4) *Gamma* VE = 36.4% (13.9, 53.2) *Delta* VE = -6.0% (95% CI -178.3 to 59.2)	

Effectiveness over time

Moderate and severe/critical COVID-19 at least 14 days after vaccination

Day	VE (95% CI)
15-28	72.3% (62.1 to 80.1)
29-56	61.7% (52.5 to 69.2)
57-112	50.8% (40.2 to 59.7)
113 to end of double blind phase	45.2% (33.0 to 55.3)

Severe/critical COVID-19 at least 14 days after vaccination

Day	VE (95% CI)
15-28	65.5% (27.3 to 85.0)
29-56	85.7% (71.0 to 93.7)
57-112	67.8% (44.2 to 82.2)
113 to end of double blind phase	71.7% (51.4 to 84.3)

£ Janssen analyses of July 9, 2021 data cut-off not verified by FDA

*Includes non-centrally confirmed cases.

The analysis of vaccine efficacy against asymptomatic infection included all the participants with a newly positive N-immunoassay result at day 71 (i.e., those who had been seronegative or had no result available at day 29 and who were seropositive at day 71). Only 2650 participants had an N-immunoassay result available at day 71, and therefore only a preliminary analysis could be performed.

+Mild cases of Covid-19 were defined as a positive result on RT-PCR testing and the presence of at least one of the following symptoms: fever (body temperature, ≥38.0°C), sore throat, malaise, headache, myalgia, gastrointestinal symptoms.

^Moderate cases were defined as a positive RT-PCR test and either the presence of at least two of the following symptoms: fever (≥38.0°C), heart rate of at least 90 beats per minute, shaking chills or rigors, sore throat, cough, malaise, headache, myalgia, gastrointestinal symptoms, loss of taste or smell, or red or bruised-looking feet or toes; or the presence at least one of the following symptoms: respiratory rate of at least 20 breaths per minute, abnormal oxygen saturation (but >93% while the patient was breathing ambient air at sea-level), clinical or radiologic evidence of pneumonia, radiologic evidence of deep-vein thrombosis, or shortness of breath or difficulty breathing.

~Severe–critical cases were defined as a positive RT-PCR test and the presence of at least one of the following features: clinical signs at rest that were indicative of severe systemic illness (respiratory rate of ≥30 breaths per minute, heart rate of ≥125 beats per minute, oxygen saturation of ≤93% while the patient was breathing ambient air at sea level, or partial pressure of oxygen divided by the fraction of inspired oxygen, <300 mm Hg); respiratory failure (defined as the use of high-flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation);shock; clinically meaningful acute renal, hepatic, or neurologic dysfunction; intensive care unit admission; or death.

@ Comorbidities include: Asthma, Cancer, Chronic Kidney Disease, COPD, Serious heart conditions, HIV infection, Hypertension, Immuno-compromised from blood transplant, liver disease, neurologic conditions, obesity, Type 2 Diabetes Mellitus.

Key: CI – Confidence Interval; COPD – Chronic Obstructive Pulmonary Disorder; CF – Cystic Fibrosis, CKD – Chronic Kidney Disease; EPAR – European Public Assessment Report; FAS – Full Analysis Set; FDA – Food and Drug Administration; ICP – Immunocompromised State; N/A – Not applicable; NCT – National Clinical Trial; NR – Not Reported; PP – Per-protocol; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Observational studies

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Arregocés Castillo (2021) **Title:** Effectiveness of COVID-19 vaccines in preventing hospitalizations and deaths in Colombia: A pair-matched, national-wide cohort study in older adults **DOI:** doi.org/10.2139/ssrn.3944059 **NCT:** N/A **Study Design***:* Population-based match-paired cohort study **Country**: Colombia **Setting***:* National linked databases **Time Period***:*	**Intervention/Exposure**: • Ad26.COV2.S (Janssen) • BNT162b2 (Pfizer) • ChAdOx1 (Astra Zeneca) • CoronaVac (Sinovac) ^ **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** BNT162b2 Median: 10.82 weeks NR for other vaccines	**Description:** The full cohort consists of every person eligible to receive a Covid-19 vaccine in Colombia 60 years old and above. Individuals diagnosed with COVID-19 prior to vaccination, those with heterologous vaccination schedules, those diagnosed with COVID-19 diagnosis, hospitalisation, or death from COVID-19 on the 14 days following the last dose in the schedule, and those with incomplete records were excluded from the Analysis. **N:** 3,346,826 Unvaccinated: 1,673,413 Vaccinated: 1,673,413 • Ad26.COV2.S – 44,127 • BNT162b2 – 591,431 • ChAdOx1 – 109,020 • CoronaVac – 928,835^ Ad26.COV2.S **Age:** Median – 65 (IQR 62 to 69) **Male** = 50.6%	**Severe Disease: ≥14 days after second/final dose*** Hospitalisation without death Ad26.COV2.S VE = 80.0% (95% CI 19.9 to 95.0) BNT162b2 VE = 90.3% (95% CI 87.1 to 92.7) ChAdOx1 VE = 75.4% (95% CI 48.2 to 88.3) Post-hospitalisation death Ad26.COV2.S NR BNT162b2 VE = 98.5% (97.8 to 98.9) ChAdOx1	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** NR

11 March to 11 August 2021 **Variants of Concern:** During this period Mu was the most prevalent variant in the country **Publication status**: Preprint **Supplementary Appendix:** No		**Co-morbidities/Special Populations:** Underlying condition - At least one comorbidity – 22.6 Cancer – 0.7^ Diabetes – 6.0 Chronic Kidney Disease – 2.5 Arterial hypertension – 20.8 HIV – AIDS – 0.1 <u>BNT162b2</u> **Age:** Median – 66 (IQR 63 to 69) **Male** = 43.3% **Co-morbidities/Special Populations:** Underlying condition - At least one comorbidity – 32.3 Cancer – 1.6^ Diabetes – 9.2 Chronic Kidney Disease – 4.5 Arterial hypertension – 29.3 HIV – AIDS – 0.1 <u>ChAdOx1</u> **Age:** Median – 70 (IQR 66 to 73) **Male** = 45.7% **Co-morbidities/Special Populations:** Underlying condition - At least one comorbidity – 37.9 Cancer – 1.8^ Diabetes – 11.1 Chronic Kidney Disease – 6.4	VE = 96.3% (88.4 to 98.8) **Adjustments:** Age group, sex, cancer, diabetes, chronic kidney disease, hypertension, HIV diagnosis, health system affiliation, vaccine, number of COVID-19 tests, municipality of residence. **Mortality** Death without <u>hospitalisation</u> Ad26.COV2.S VE 75.0 (95% CI 0.0 to 93.8) BNT162b2 VE 89.2 (95% CI 85.6 to 91.90) ChAdOx1 VE 88.7 (95% CI 64.8 to 96.4) **Variants of Concern** NR	

		Arterial hypertension – 34.8 HIV – AIDS – 0.1	**Subgroups**: See below **Efficacy/effectiveness over time.** The hazard for hospitalization or death due to COVID-19 was higher in the unvaccinated cohort, as shown in the survival curves. The median follow-up time was 64 days for BNT162b2. The authors report that was no loss of effectiveness during the observation period.	

S1: Vaccine effectiveness against hospitalisation without death

Age	**Ad26.COV2.S** VE (95% CI)	**BNT162b2** VE (95% CI)	**ChAdOx1** VE (95% CI)
60 – 69	71.3% (0 – 92.9)	92.3% (88.4 – 94.9)	46.6% (0 – 86.8)
70 – 79	NR	83.7% (75.9 – 88.9)	82.2% (56.8 – 92.7)
80+	NR	72.6% (33.9 – 88.7)	NR

S2: Vaccine effectiveness against post-hospitalisation death

Age	**Ad26.COV2.S** VE (95% CI)	**BNT162b2** VE (95% CI)	**ChAdOx1** VE (95% CI)

60 – 69	NR	97.4 (96.1 – 98.3)	NR
70 – 79	NR	96.7 (94.7 – 97.9)	96.4 (88.9 – 98.9)
80+	NR	86.6 (71.7 – 93.6)	NR

S3: Vaccine effectiveness against death without hospitalisation

Age	**Ad26.COV2.S** VE (95% CI)	**BNT162b2** VE (95% CI)	**ChAdOx1** VE (95% CI)
60 – 69	81.0 (0 – 97.3)	90.1 (84.9 – 93.5)	NR
70 – 79	59.2 (0 – 94.3)	87.4 (80 – 92)	86.5 (57.7 – 95.7)
80+	NR	67.0 (36.3 – 82.9)	NR

^ Results are not presented for CoronaVac (or where outcomes from CoronaVac are combined with other vaccines) as it falls outside the scope of the inclusion/ exclusion criteria given that this vaccine is currently not authorised for use by the European Medicines Agency

* Note that pooled vaccine effectiveness estimates are available, however these estimates are inclusive of vaccines that are not licensed in Ireland (CoronaVac).

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Cohn (2021) **Title:** SARS-Cov2-2 vaccine protection and deaths among US veterans during 2021 **DOI:** 10.1126/science.abm0620 **NCT:** N/A **Study Design***:* Retrospective cohort study with crossover **Country**: US **Setting***:* Veterans Health Administration **Time Period***:* February to October 2021	**Intervention/Exposure**: ▪ BNT162b2 (Pfizer–BioNTech) ▪ mRNA-1273 (Moderna) ▪ Ad26.COV2.S (Janssen) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Median: NR Estimated max follow-up 34.66 weeks ^	**Description:** U.S. Veterans age ≥18 years and receiving care in the Veterans Health Administration (VHA), covering 2.7% of the U.S. population. **N:** Total analysis: 780,225 (including vaccinated and unvaccinated individuals) Deaths: 775,536 mRNA-1273 (Moderna) - 230,762 (46.5%) BNT162b2 (Pfizer–BioNTech) - 231,724 (46.5%) Ad26.COV2.S (Janssen) – 35,662 (7.2%) **Age:** <50 – 185,437 (23.77%) 50-64 – 222,986 (28.58%) ≥65 – 371,802 (47.65%) **Male** = 668,266 (85.65%)	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* NR **Adjustments:** Age, sex, race, ethnicity, and comorbidity (Charlson Comorbidity score, overweight, type II diabetes, chronic obstructive pulmonary disease, bronchitis, acute respiratory failure, and chronic lung disease) **Mortality** All Cause* <65 years Any vaccine VE = 81.7% (75.7% to 86.2%) Ad26.COV2.S VE = 73.0% (52.0% to 84.8%)	**Confirmed RT-PCR infection** **≥14 days after second/final dose** *Any* See below **Adjustments:** Age, sex, race, ethnicity, and comorbidity (Charlson Comorbidity score, overweight, type II diabetes, chronic obstructive pulmonary disease, bronchitis, acute respiratory failure, and chronic lung disease) **Variants of Concern:** NR **Subgroups** The risk of infection accelerated in both unvaccinated and fully

Variants of Concern: By July 2021, the U.S. experienced a surge in cases of COVID-19, dominated by the B.1.617.2 (Delta) variant **Publication status**: Peer-reviewed **Supplementary Appendix**: Yes		**Co-morbidities/Special Populations:** Charlson Comorbidity Index Scores 0 – 314,159 (40.3%) 1-2 – 259,637 (33.3%) 3-4 – 119,360 (15.3%) ≥5 – 87,069 (11.1%) **Outcome measurement:** The reason for RT-PCR assay is not provided in the database. Veterans may have received a RT-PCR assay for many reasons.	mRNA-1273: VE 81.5% (70.7% to 88.4%) BNT162b2 VE 84.3% (76.3% to 89.7%) ≥65 years, Any vaccine VE 71.6% (95% CI: 68.6% to 74.2%) Ad26.COV2.S VE 52.2% (37.2% to 63.6%) mRNA-1273 VE 75.5% (71.8% to 78.7%) BNT162b2 VE 70.1% (66.1% to 73.6%). **Variants of Concern** NR **Subgroups**: NR **Efficacy/effectiveness over time.**	vaccinated Veterans beginning in July 2021 and through September 2021, consistent with the time dependence observed in the Cox proportional hazards models. This pattern was similar across age groups (all ages, > 50 years, 50-64 years, ≥ 65 years), and risk of infection was highest for unvaccinated Veterans. Veterans who were fully vaccinated with the Moderna vaccine had the lowest risk of infection, followed closely by those who received the Pfizer-BioNTech vaccine, then those who received the Janssen vaccine. **Efficacy/effectiveness over time.** Not reported.

			NR	

Vaccine effectiveness against SARS-CoV-2 infection* by month after vaccination (Vaccinated vs unvaccinated)[*, £]

Month of outcome measurement	Janssen VE (95% CI)	Moderna VE (95% CI)	Pfizer/BioNTech VE (95% CI)
March	86.4 (85.2-87.6)	89.2 (88.8-89.6)	86.9 (86.5-87.3)
April	81 (80 - 83)	86 (86-87)	83 (83-84)
May	75 (73-76)	83 (83-83)	79 (78-79)
June	66 (64-67)	79 (78-79)	73 (72-73)
July	53 (51-55)	73 (73-74)	65 (65-66)
August	36 (34-38)	67 (66-67)	56 (56-55)
September	13.1 (9.2-16.8)	58 (56.9-59.1)	43.3 (41.9 – 44.6)

^ For vaccinated Veterans, RT-PCR assessed 15 days after last dose that established full vaccination status;
for unvaccinated Veterans, RT-PCR assessed beginning in February 1, 2021, coincident with broadscale vaccine eligibility in the VA
* Vaccine effectiveness estimates were calculated based on the following formula: (1-HR)*100, using the adjusted hazard ratio, unless VE estimates were provided in the text.
£ For vaccinated Veterans, infection is assessed 15 days after the last vaccine that established full vaccination status. For unvaccinated Veterans, infection is assessed beginning in February 1, 2021, coincident with broadscale vaccine eligibility in the VA.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results

Author (Year): Corchado-Garcia (2021) **Title:** Analysis of the Effectiveness of the Ad26.COV2.S Adenoviral Vector Vaccine for Preventing COVID-19 **DOI:** 10.1001/jamanetworkopen.2021.32540 **NCT: N/A** **Study Design***:* Retrospective matched cohort **Country**: US **Setting***:* US (Mayo clinic and hospitals) **Time Period***:* February 27 to July 22, 2021 **Variants of Concern:** Alpha and Delta **Publication status**: peer-reviewed	**Exposure**: Ad26.COV2.S (Janssen) cohort **Control:** Unvaccinated cohort **Time since final vaccination dose:** Median:15.9 weeks (IQR 14.6, 18.7)	**Description:** Adults underwent testing at MAYO clinical and affiliated hospitals. Participants included: (1) underwent at least 1 SARS-CoV-2 PCR test at the Mayo Clinic between February 27 and July 22, 2021; (2) aged at least 18 years; (3) resides in a local area (based on zip code) in which at least 10 patients have received the Ad26.COV2.S vaccine. Exclusion criteria were as follows: (1) individuals with a positive SARS-CoV-2 PCR test result before the date of vaccine administration or the beginning of the study period (February 27, 2021); (2) individuals with no follow-up days after vaccination (ie, those who received the vaccine dose on the last date of data collection); (3) individuals who received the mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BioNTech) vaccines; and (4) individuals with no research authorization on file. **N:** of 8889 vaccinated patients 88 898 propensity-matched unvaccinated patients **Age:** Mean (SD) Vaccinated: 52.4 [16.9] years Unvaccinated: 51.7 [16.7] years	**Severe Disease:** **≥14 days after second/final dose** ***See table below*** **Adjustments:** Patients were propensity matched on the following: asthma, cancer, cardiomyopathy, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, heart failure, hypertension, obesity, pregnancy, severe obesity, sickle cell disease, solid organ transplant, stroke or cerebrovascular disease, and type 2 diabetes **Mortality : "**because only 60 individuals tested positive for SARS-CoV-2 after receiving the Ad26.COV2.S vaccine, our study was underpowered for definitive assessment of mortality" See also table below. **Variants of Concern:** NR **Subgroups**: NR **Effectiveness over time**. NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection:** >14 days after dose: VE: 74.2% (95%CI, 64.9% to 81.6%) **Effectiveness over time:** NR

		Male : Vaccinated: 4491 men (50.5%) Unvaccinated: 44 748 men (50.3%) **Co-morbidities and Special Populations** NR		

From supplementary material (etable 1)

	Vaccinated		unvaccinated		Odds Ratio (95% CI)		p-value
Hospitalization or ICU or admission or mortality	9/8880	0.10%	271/88627	0.31%	0.33	(0.19, 0.65)	0.00016
Hospitalization Rate	8/8881	0.09%	248/88650	0.28%	0.32	(0.18, 0.66)	2.833 x 10-4
ICU Admission Rate	0/8889	0.00%	54/88844	0.06%	0	(0.00, 1.43)	0.014
Mortality Rate	1/8888	0.01%	12/88886	0.01%	0.83	(0.26, 5.20)	1

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): de Gier (2021) [59] **Title:** COVID-19 vaccine effectiveness against hospitalizations and ICU admissions in the	**Exposure**: • All hospitalised COVID-19 patients. • Vaccinated with BNT162b2 (BioNTech/Pfizer),	**Description:** All hospitalised cases from June 2020 onwards included. **N:** Total, 15,571 Fully vaccinated, 887, Partially vaccinated, 1,111	**Severe Disease:** **≥14 days after second/final dose*** *Hospitalisation** VE in Alpha period: 94% (95%CI 93-95%).	**Confirmed RT-PCR SARS-CoV-2 infection** **≥14 days after second/final dose*** NR

Netherlands, April- August 2021 **DOI:** [10.1101/2021.09.15.21263613] **NCT:** N/A **Study Design***:* Cohort **Country**: The Netherlands **Setting***:* Hospital **Time Period***:* 4 April – 29 August 2021 **Variants of Concern:** Alpha period is 4 April 2021– 29 May 2021. Delta period is 4 July 2021 -29 August 2021. **Publication status**: Preprint	mRNA-1273 (Moderna), ChAdOx1-S (AstraZeneca), or Ad26.COV2-S (Janssen). **Control:** Hospitalised COVID-19 patients who were unvaccinated. Numbers of vaccinated people in the community taken from vaccination registries. **Time since final vaccination dose:** Over 20 weeks.	Unvaccinated, 13,574 **Age:** mean/median age NR **Male/Female:** NR **Co-morbidities:** NR	VE in Delta period: 95% (95%CI 94-95%). *adjusted for calendar date and age group. *ICU admissions** VE in Alpha period: 93% (95%CI 87-96%). VE in Delta period: 97% (95%CI 97-98%). *Adjusted for calendar date and age group. **Mortality:** NR **Variants of Concern** See above and table below. **Subgroups**: See table below for analysis by VOC and by vaccine. **Efficacy/effectiveness overtime:** See table below. Authors report no indication of VE waning observed up to 20 weeks after full vaccination.	**Adjustments:** NA **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time:** NR
	Primary outcomes results			
	Alpha	**Hospitalised (VE) – fully vaccinated**** Age 15-49: 93% (95% CI: 81-97) Age 50-69: 90% (95% CI: 85-93) Age 70+: 95% (95% CI: 94-96) Overall: 95% (95%CI 93-95)	**ICU admission (VE) – fully vaccinated**** Age 15-49: 88% (95% CI: 16-98)	

			Age 50-69: 96% (95% CI: 85-99) Age 70+: 92% (95% CI: 85-96) Overall: 93% (95%CI 87-96)	
		Hospitalised (VE) – partially vaccinated** Age 15-49: 61% (95% CI:41-74) Age 50-69: 80% (95% CI:76-82) Age 70+: 80% (95% CI:77-82) Overall: 79% (95% CI:77-80)	**ICU admission (VE) – partially vaccinated**** Age 15-49: 45% (95% CI:-33-77) Age 50-69: 81% (95% CI:73-86) Age 70+: 87% (95% CI:82-90) Overall: 83% (95% CI:79-86)	
	Delta	**Hospitalised (VE) – fully vaccinated**** Age 15-49: 96% (95% CI: 95-97) Age 50-69: 97% (95% CI: 96-97) Age 70+: 91% (95% CI: 89-92) Overall: 95% (95%CI 94-95)	**ICU admission (VE) – fully vaccinated**** Age 15-49: 99% (95% CI: 97-100) Age 50-69: 98% (95% CI: 97-99) Age 70+: 96% (95% CI: 93-97) Overall: 97% (95%CI 97-98)	
		Hospitalised (95% CI:VE) – partially vaccinated** Age 15-49: 95% (95% CI:94-96) Age 50-69: 92% (95% CI:90-94) Age 70+: 72% (95% CI:62-79) Overall: 91% (95% CI:90-93)	**ICU admission (95% CI:VE) – partially vaccinated**** Age 15-49: 97% (95% CI:93-98) Age 50-69: 93% (95% CI:89-95) Age 70+: 89% (95% CI:70-96)	

			Overall: 94% (95% CI:92-96)	
	Pfizer/BioNTech (BNT162b2)	**Hospitalised (VE) – fully vaccinated***** Age 15-49: 99% (95% CI: 98-100) Age 50-69: 99% (95% CI: 98-99) Age 70+: 92% (95% CI: 90-93) Overall: 96% (95% CI: 95-96)	**ICU admission (VE) - fully vaccinated***** Age 15-49: 100% (95% CI: --) Age 50-69: 100% (95% CI: 99-100) Age 70+: 97% (95% CI: 95-98) Overall: 99% (95% CI: 98-99)	
	Moderna (mRNA-1273)	**Hospitalised (VE) – fully vaccinated***** Age 15-49: 88% (95% CI: 82-92) Age 50-69: 89% (95% CI: 85-92) Age 70+: 64% (95% CI: 47-76) Overall: 84% (95% CI: 80-87)	**ICU admission (VE) – fully vaccinated***** Age 15-49: 98% (95% CI: 85-100) Age 50-69: 89% (95% CI: 80-93) Age 70+: 34% (95% CI: -29-66) Overall: 86% (95% CI: 79-90)	
	Astra Zeneca (ChAdOx1-S)	**Hospitalised (VE) – fully vaccinated***** Age 15-49: 95% (95% CI: 87-98) Age 50-69: 96% (95% CI: 95-97) Age 70+: 78% (95% CI: 63-86) Overall: 94% (95% CI: 92-95)	**ICU admission (VE) – fully vaccinated***** Age 15-49: 95% (95% CI: 64-99) Age 50-69: 96% (95% CI: 94-98) Age 70+: 100% (95% CI: --) Overall: 96% (95% CI: 94-98)	
	Janssen® (Ad26.COV2-S)	**Hospitalised (VE) – fully vaccinated***** Age 15-49: 93% (95% CI: 86-96)	**ICU admission (VE) – fully vaccinated***	

		Age 50-69: 92% (95% CI: 89-95) Overall: 91% (95% CI: 88-94)	Age 15-49: 96% (95% CI: 73-99) Age 50-69: 94% (95% CI: 86-98) Overall: 94% (95% CI: 88-98)	
	Time since final vaccination			
	0-4 weeks	**Hospitalised (VE) ***** Age 15-49: 99% (95% CI: 97-99) Age 50-69: 98% (95% CI: 97-98) Age 70+: 90% (95% CI: 85-93)	**ICU admission (VE) ***** Age 15-49: 100% (95% CI: --) Age 50-69: 99% (95% CI: 98-99) Age 70+: 99% (95% CI: 93-100)	
	5-9 weeks	**Hospitalised (VE) ***** Age 15-49: 93% (95% CI: 88-96) Age 50-69: 97% (95% CI: 96-98) Age 70+: 92% (95% CI: 90-93)	**ICU admission (VE) ***** Age 15-49: 98% (95% CI: 85-100) Age 50-69: 98% (95% CI: 97-99) Age 70+: 95% (95% CI: 92-97)	
	10-14 weeks	**Hospitalised (VE) ***** Age 15-49: 75% (95% CI: 56-86) Age 50-69: 90% (95% CI: 85-93) Age 70+: 90% (95% CI: 88-92)	**ICU admission (VE) ***** Age 15-49: 82% (95% CI: 29-96) Age 50-69: 93% (95% CI: 85-96) Age 70+: 96% (95% CI: 93-98)	
	15-19 weeks	**Hospitalised (VE) ***** Age 15-49: 97% (95% CI: 76-100) Age 50-69: 92% (95% CI: 84-96) Age 70+: 91% (95% CI: 88-92)	**ICU admission (VE) ***** Age 15-49: 100% (95% CI: --) Age 50-69: 89% (95% CI: 70-96) Age 70+: 97% (95% CI: 89-99)	

	20 or more weeks	**Hospitalised (VE) ***** Age 15-49: 97% (95% CI: 87-99) Age 50-69: 98% (95% CI: 94-99) Age 70+: 91% (95% CI: 87-94)	**ICU admission (VE) ***** Age 15-49: 100% (95% CI: --) Age 50-69: 100% (95% CI: --) Age 70+: 90% (95% CI: 57-98)	
* Fully vaccinated 28 days after the Janssen 1-dose schedule or 14 days after a second dose of other vaccines. **Adjusted for calendar date. ***Adjusted for calendar date and five year age group.				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Grannis (2021) **Title:** Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19–Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance — Nine States, June–August 2021 **DOI:** dx.doi.org/10.15585/mmwr.mm7037e2external icon. **NCT:** N/A **Study Design***:* Test-negative case-control[@] **Country**: US **Setting***:* 187 hospitals and 221 emergency departments	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2 (Janssen) **Comparator/Control:** Unvaccinated [*] **Time since final vaccination dose:** To hospital admission or Emergency department /Urgent care (EC/UC) *Pfizer-BioNTech* – Hospitalisation – Median: 17.66 weeks ED/UC – Median: 15.25 weeks *Moderna* – Hospitalisation – Median: 17.09 weeks ED/UC – Median: 15.68 weeks	**Description:** Adults aged ≥18 years who had received SARS-CoV-2 molecular testing (primarily reverse transcription–polymerase chain reaction assay within 14 days before or 72 hours after the admission or encounter) and a COVID-19–like illness discharge diagnosis. Patients who had received 1 mRNA dose only or had received the second dose <14 days before testing or encounter date were excluded. Full vaccination was defined as receipt of the second dose of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) mRNA vaccines, or a single dose of Ad26.COV2 (Janssen [Johnson & Johnson]) vaccine ≥14-days before the testing or encounter date. **N:** Hospitalised with COVID-19-like illness – 14,636 *Cases – 1,551* Vaccinated - 235 Unvaccinated – 1,316 *Controls – 13,085* Vaccinated – 7,441 Unvaccinated – 5,644 **Age:**	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* VE = 86% (95% CI 82 to 89) *ED / UC* VE = 82% (95% CI 81 to 84) **Adjustments:** VE was estimated using a test-negative design, adjusted for age, geographic region, calendar time (cubic spline with quartile knots), and virus circulation (percentage of SARS-CoV-2–positive results from testing within the counties surrounding the facility on the date of the event) and weighted for inverse propensity to be vaccinated or unvaccinated (calculated separately for each of the 10 VE models) using facility characteristics, sociodemographics, and underlying medical conditions **Mortality:** NR **Variants of Concern** In this multistate interim analysis of 32,867 medical encounter among	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose:** NR

(EDs) and urgent care (UC) clinics **Time Period***:* June to August 2021 **Variants of Concern:** From June 2021 the Delta variant accounted for >50% of sequenced isolates in each medical facility's state. **Publication status**: Peer-reviewed.	*Janssen* – Hospitalisation – Median: 15.39 weeks EC/UC – Median: 15.39 weeks	Median = 65 years (IQR: 48-77 years). *Admitted to ED/UC with COVID-19 <u>like illness –</u>* 18,231 *Cases[@] – 3,657* Vaccinated - 512 Unvaccinated – 3,145 *Controls – 14,574* Vaccinated – 6,847 Unvaccinated – 7,727 Age: 43 years (IQR = 29-62 years) **Male** = NR **Co-morbidities:** NR	adults of all ages during June–August 2021, whe the Delta variant was predominant in the United States, VE of all three authorized COVID-19 vaccines combined remained high against hospitalization (86%) and ED/UC encounters (82%). These overall VE estimates were similar to those during the months before Delta became predominant **Subgroups**: *Hospitalisation* <u>18-74 years</u> VE = 89% (95% CI 85 to 92) <u>≥75 years</u> VE = 76% (95% CI 64 TO 84) <u>Vaccine type</u> **Vaccine** / **VE (95% CI)** Pfizer-BioNTech / 80% (73 to 85) Moderna / 95% (92 to 97) Janssen / 60% (31 to 77)	

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<td>ED/UC encounter
<u>Vaccine type</u>
<table>
<tr><th>Vaccine</th><th>VE (95% CI)</th></tr>
<tr><td>Pfizer-BioNTech</td><td>77% (74 to 80)</td></tr>
<tr><td>Moderna</td><td>92% (89 to 93)</td></tr>
<tr><td>Janssen</td><td>65 (56 to 72)</td></tr>
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Efficacy/effectiveness over time.
NR</td>
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<td colspan="5">@ - Adults aged ≥18 years who had received SARS-CoV-2 molecular testing (primarily reverse transcription–polymerase chain reaction assay within 14 days before or 72 hours after the admission or encounter) and a COVID-19–like illness discharge diagnosis.
Abbreviations: ED/UC- Emergency depart Urgent Care Encounter.</td>
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Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Lin (2021) **Title:** Effectiveness of Covid-19 Vaccines in the United States Over 9 Months: Surveillance Data from the State of North Carolina **DOI:** doi.org/10.1101/2021.10.25.21265304 **NCT:** N/A **Study Design:** Retrospective, matched Cohort Study **Country**: US **Setting:** North Carolina COVID-19 Surveillance System and	**Exposure**: ▪ BNT162b2 (Pfizer–BioNTech) ▪ mRNA-1273 (Moderna) ▪ Ad26.COV2.S (Janssen) **Comparator/Control:** ▪ Unvaccinated **Time since final vaccination dose:** BNT162b2 and mRNA-1273 Max: 35.19 weeks ^ Ad26.COV2.S Max: 26.21 weeks *	**Description:** Surveillance data from the entire state of North Carolina, which has a population of ~10.6 million people. The 2020 Bridged-Race population estimates produced by the US Census Bureau in collaboration with the National Center for Health Statistics (NCHS) were used for demographic populations. The Esri 2020 NC Zip Code population was used to determine the total number of residents with each combination of demographic variables (age, sex, race/ethnicity, geographic region, county-level vaccination rate). **N:** 10,600,823 ▪ BNT162b2 (Pfizer–BioNTech) – 3,332,258 (33%) ▪ mRNA-1273 (Moderna) – 2,329,361 (22%) ▪ Ad26.COV2.S (Janssen) – 345,848 (3%) **Age:** ▪ <18 – 21.76% ▪ 18-34 – 22.94% ▪ 35-49 – 18.78% ▪ 50-64 – 19.4% ▪ 65+ - 17.12% **Male** 48.6%	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* BNT162b2 Vaccine effectiveness (VE) reached to peak level at 2 months VE = 96.4% (95% CI, 94.7 to 97.5) VE after 7 months VE = 87.7% (95% CI, 84.3 to 90.4) mRNA-1273 VE reached to peak level at 2 months VE = 97.5% (95% CI, 96.3 to 98.3) VE after 7 months VE = 92.3% (95% CI, 89.7 to 94.3) Ad26.COV2.S VE reached to peak level at 2 months	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection:** *Symptomatic (no definition provided)* BNT162b2 VE reached to peak level at 2 months VE = 94.9% (94.5 to 95.2) VE after 7 months VE = 70.1% (68.9 to 71.2) mRNA-1273 VE reached to peak level at 2 months VE = 96.0% (95.6 to 96.4) VE after 7 months

COVID-19 Vaccine Management System **Time Period***:* December 13, 2020 through September 8, 2021 **Variants of Concern:** the Delta variant accounts for the majority of Covid-19 cases in the state of North Carolina since July, 2021 **Publication status**: Pre-print		**Co-morbidities and Special Populations** NR	VE = 89.8% (95% CI, 78.8 to 95.1) VE after 5 months $ VE = stays above 80% through 5 months. **Adjustments:** Age, sex, race/ethnicity, geographicalregion, and county-level vaccination rate **Mortality@ :** VE reached to peak level at 2 months VE = 95.9% (95% CI, 92.9 to 97.6) VE after 7 months VE = 88.4% (95% CI, 83.0 to 92.1) mRNA-1273 VE reached to peak level at 3 months VE = 96.0% (95% CI, 91.9 to 98.0) VE after 7 months VE = 93.7% (95% CI, 90.2 to 95.9) Ad26.COV2.S VE reached to peak level at 3 months	VE = 81.9% (81.0 to 82.7) <u>Ad26.COV2.S</u> VE reached to peak level at 1 month VE = 79.0% (77.1 to 80.7) VE after 5 months$ VE = 64.3% (62.3 to 66.1) **Subgroups**: VE in reducing the risk of COVID-19 disease over time is presented using separate cumulative incidence curves for the following age groups; 18-34, 35-49, 50-64, 65+. For all three vaccines, effectiveness is lower in the 65+ age group than other age groups

			VE = 89.4% (95% CI, 52.3 to 97.6) VE after 5 months $ VE = stays above 80% through 5 months. **Variants of Concern:** NR **Subgroups**: Vaccine effectiveness in reducing the risk of hospitalisation over time is presented using separate cumulative incidence curves for the following age groups; 18-34, 35-49, 50-64, 65+. Effectiveness is lower in the 65+ age group than the 18-64 age group Vaccine effectiveness in reducing risk of death over time is presented using separate cumulative incidence curves for those aged; 18-64 and 65+. Effectiveness is lower in the 65+ age group than the 18-64 age group **Effectiveness over time.** The effectiveness of the Janssen vaccine against hospitalisation and death reaches a peak level similar to that of the two mRNA vaccines one month	**Effectiveness over time.** See below.

			after vaccination and then starts to decline afterward.	

Supplementary Table 1 - Effectiveness of the BNT162b2 (Pfizer-BioNTech) two-dose vaccine, mRNA-1273 (Moderna) two-dose vaccine, and Ad26.COV2.S (Janssen) one-dose vaccine in reducing the incidence of COVID-19 over successive time periods by vaccination cohort (by month of vaccination)

	Months since vaccination								
	0-1	**1-2**	**2-3**	**3-4**	**4-5**	**5-6**	**6-7**	**7-8**	**8-9**
Time period of full vaccination									
Pfizer/BioNTech									
All dates	67.2	92.4	91.0	84.3	83.1	77.6	68.0	66.8	63.2
Dec 15 – Jan 31	45.4	90.3	91.7	89.9	86.7	78.2	60.2	62.7	60.5
Feb 1 – Feb 28	57.9	91.0	93.0	88.2	82.4	73.1	74.8	81.1	
Mar 1 – Mar 31	56.7	93.1	92.3	85.0	76.8	76.7	79.1		
Apr 1 – Apr 30	62.7	92.7	88.5	81.8	81.3	85.3			
May 1 – May 31	68.0	91.5	88.6	88.0	90.0				
June 1 – June 30	75.0	94.0	91.1	87.1					
July 1 – July 31	84.3	94.3	90.6						
Aug 1 – Sept 8	93.5	96.3							
mRNA-1273									
All dates	69.4	91.6	93.5	92.3	89.2	85.8	82.6	80.8	85.1
Dec 15 – Jan 31	38.4	82.7	92.3	91.6	88.5	86.0	81.3	80.4	84.0
Feb 1 – Feb 28	62.6	90.6	90.0	94.8	90.9	83.8	82.4	78.9	
Mar 1 – Mar 31	71.3	94.0	95.5	91.7	87.2	85.0	85.9		
Apr 1 – Apr 30	71.6	92.9	94.5	90.7	89.1	90.5			
May 1 – May 31	68.8	94.2	93.2	92.3	91.6				
June 1 – June 30	78.1	94.2	94.9	93.6					

July 1 – July 31	86.3	96.0	95.8						
Aug 1 – Sept 8	92.0	95.0							
Janssen									
All dates	58.1	73.4	70.3	55.2	60.8	59.8	73.5		
Feb1 – Mar 15	64.7	81.5	78.5	79.5	58.8	60.8	73.5		
Mar 16 – Apr 15	55.0	79.9	67.4	57.8	51.7	59.0			
Apr 16 – Sept 8	58.0	70.3	69.6	45.7	73.6				

@ the hospitalization and death status were known for only approximately 40% and 60% of Covid-19 cases, respectively
$ Because the Janssen vaccine was not deployed until March 2021, the information about its effectiveness beyond 5 months is limited.
^ Maximum follow up estimated from the 4th of January,2021 until data cut-off.
* Maximum follow up estimated from the 7th of March,2021 until data cut-off

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results*	Secondary outcome results*
Author (Year): Polinski 2021 **Title:** Effectiveness of the Single-Dose Ad26.COV2.S COVID **DOI:** 10.1101/2021.09.10.21263385 **NCT:** N/A	**Intervention/Exposure**: Ad26.COV2.S (Janssen) **Comparator/Control:** Individuals in database with no evidence of vaccination **Time since final vaccination dose:** Mean 15.4 weeks Maximum 152 days = 21.7 weeks	**Description:** Study participants entered cohort on day of vaccination. They were matched (1:10 risk-set sampling by time, location, age, sex, and comorbidity score, with further matching of the risk set sampled population by propensity score) with up to 10 unvaccinated individuals. Those with observed COVID-19 or receipt of any COVID-19 vaccine during the 365 days before cohort entry were excluded. At least one medical and pharmacy claim was required during 365 days before cohort entry to ensure each individual's activity in the system.	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* VE 73% (95% CI 69%, 76%) **Adjustments:** Matched by time, location, age, sex, and comorbidity score, also propensity scores **Mortality:** NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection (see definition of observed Covid-19§)** **≥14 days after second/final dose** *Any* VE: 69% (95% CI 67%, 71%)

Study Design*:* Matched cohort study with crossover **Country**: USA **Setting:** US health insurance claims data (data aggregated by HealthVerity) **Time Period**: 1 March 2021 –17 July 2021 **Variants of Concern:** Delta **Publication status**: Preprint		**N:** 390,517 vaccinated 1,524,153 matched with no record of vaccination **Age:** Vaccinated: Mean age, yrs (SD) 55.05 (17.31) Unvaccinated: Mean age, yrs (SD) 54.94 (17.42) **Male** Vaccinated, male 43.7% Unvaccinated, male 43.7% **Co-morbidities:** Vaccinated COPD: 10.3% Organ transplant: 0.4% Malignancies: 4.5% Pulmonary fibrosis: 0.5% HIV: 0.3% Unvaccinated COPD: 10.4% Organ transplant: 0.4% Malignancies: 4.5% Pulmonary fibrosis: 0.5% HIV: 0.4%	**Variants of Concern** High delta states** *COVID-19 related Hospitalisation* VE: 74% (95% CI 61 to 83) *COVID-19 related Hospitalisation* (June-July only***) VE: 77% (95% CI 59 to 87) **Subgroups**: <50 years VE = 79% (95% CI 70 to 85) ≥50 years VE = 71% (95% CI 66 to 74%) <60 years VE = 79% (74 to 84) ≥60 years VE = 68% (63 to 73) Immunocompromised VE = 54% (95% CI 35 to 67) **Efficacy effectiveness over time.**	**Adjustments:** Matched by time, location, age, sex, and comorbidity score, also propensity scores **Variants of Concern:** High delta states** Observed COVID-19 VE 69% (95% CI 63% to 74%) Observed COVID-19 (as observed for period June and July only***) VE: 67% (95% CI 60 to 73) **Subgroups:** <50 years VE = 75% (95% CI 72 to 77%) ≥50 years VE = 65% (95% CI 63 to, 68%) <60 years VE = 72% (69 to 74) ≥60 years VE = 65% (61 to 68) Immunocompromised

			It is stated that sustained and stable VE was observed, starting 14 days after vaccination to a maximum of 152 days after vaccination. Monthly VE estimates for COVID-19-related hospitalization were stable	VE = 52% (95% CI 42% to 60%) **Efficacy/effectiveness over time.** The VE for observed COVID-19 rose slightly until May to 81% (79% to 83%) and remained at a high level until the end of the follow-up period in July (77%; 74% to 79%)
§observed COVID-19 was defined by either recording of an in- or outpatient ICD-10-CM diagnosis code of U07.1 (85% of cases) in any position, and/or a recorded positive SARS-CoV-2 diagnostic PCR or nucleic acid amplification test result (15%). *All VE estimates extracted here do not incorporate the adjustment applied by the authors in the primary analysis as it was not considered robust. See the statement below. "Given the expedited national vaccination effort, a sizable proportion of COVID-19 vaccinations were administered by employers, mass vaccination sites, pharmacies, and other settings where often no health insurance claims were submitted. The CDC reported that 57% of US residents 12 years and older were vaccinated as of July 22, 2021, while only 34% were recorded among the same people in our claims data, which confirms substantial under-recording (Suppl. S4). As a result, it is highly likely that a substantial proportion of the unvaccinated group in claims data was in fact vaccinated and thus observed VE estimates will appear lower than indeed true. To compensate, we conservatively assumed 40% under-recording of vaccinations and applied a correction factor to all VE estimates using standard methods for correcting exposure misclassification." **High Delta States were Arkansas, Florida, Louisiana, and Missouri. *** For June and July 2021 results within four states (Arkansas, Florida, Louisiana, and Missouri) with high prevalence of the Delta variant of concern, incident rate ratios (IRR) after PS matching are reported instead of hazard ratios and VE is estimated using (1-IRR)x100 for patients contributing follow-up time from June 1, 2021 through July 31, 2021				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results

Author (Year): Robles-Fontán (2021) **Title:** Time-Varying Effectiveness of Three Covid-19 Vaccines in Puerto Rico **DOI:** doi.org/10.1101/2021.10.17.21265101 **NCT:** N/A **Study Design**: Retrospective Cohort study **Country**: Puerto Rico **Setting**: Two Department of Health databases **Time Period**: December 15, 2020 to October 1, 2021 **Variants of Concern:** Delta variant became dominant in Puerto Rico during the analysis time periods, before and after June 15,2021 **Publication status**: Preprint	**Intervention/Exposure**: ▪ mRNA-1273 (Moderna) ▪ BNT162b2 (Pfizer/BioNTech) ▪ Ad26.COV2.S (Janssen) **Comparator/Control:** Unvaccinated **Mean Time since final vaccination dose:** *Against hospitalisation, infections and death* ▪ mRNA-1273 (Moderna) – 20.78 weeks ▪ BNT162b2 – 19.27 weeks (Pfizer/BioNTech) - ▪ Ad26.COV2.S (Janssen) - 20.49 weeks *Against infection* ▪ mRNA-1273 (Moderna) – 18.52 weeks ▪ BNT162b2 – 19.52 weeks (Pfizer/BioNTech) - ▪ Ad26.COV2.S (Janssen)	**Description:** Two Puerto Rico Department of Health databases were integrated: the BioPortal, which stores test results, most hospitalizations, and deaths, and the Puerto Rico Electronic Immunization System (PREIS), which stores vaccination related data. These daily counts were stratified by gender, age group (12- 85+) and vaccination status (unvaccinated, mRNA-1273, BNT162b2, or Ad26.COV2.S). Fully vaccinated was defined as 14 days after the final dose in the vaccine series. Cases in which the infection occurred after the first dose but before being fully vaccinated were removed from the analysis. **N:** Total: 3,285,874 Vaccinated: 2,217,547 BNT162b2 (Pfizer/BioNTech - 1,243,969 - mRNA-1273 (Moderna) – 844,065 - Ad26.COV2.S (Janssen) – 129,513	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* Presented by subgroup, see below. **Adjustments** age, gender, and, since many more tests were performed on weekdays than weekends, day of the week. **Mortality** Presented by subgroup, see below. **Variants of Concern** NR **Subgroups**: * COVID-19 related Hospitalisation by age (Vaccinated vs unvaccinated) All results here represent Risk Reduction (95% CI) 45 – 74 years mRNA-1273 –	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose** NR **Adjustments:** age, gender, and, since many more tests were performed on weekdays than weekends, day of the week. **Variants of Concern:** NR **Subgroups** By age: Authors did not observe substantial differences in effectiveness against infections by age, except for those 85 and older for whom the waning appears worse **Efficacy/effectiveness over time.** mRNA-1273 (Moderna) Peak VE - 90% (95% CI 88% - 91%)

Supplementary Appendix: No	- 22.51 weeks	**Age:** NR **Male:** NR **Co-morbidities/Special Populations:** NR **Outcome measurement:** Estimates obtained from fitting these models that accounted for age, gender, and day of the week were used to quantify effectiveness and relative risks For the analysis in this study we used daily counts of laboratory-confirmed SARS-CoV-2 infections, hospitalizations, and deaths	Risk reduction (RR) = 18 (15, 22) BNT162b2 – RR = 8.0 (7, 9.2) Ad26.COV2.S – RR = 3.9 (3, 5.0) <u>75-84 years</u> mRNA-1273 – RR = 8.5 (6, 11) BNT162b2 – RR = 6.7 (5, 8.7). Ad26.COV2.S – RR = 2.0 (1, 3.3) 85+ Mrna-1273 – RR = 2.8 (2, 4.0) BNT162b2 – RR = 2.9 (2, 4.2) Ad26.COV2.S – RR = 0.8 (0.5, 1.4) COVID-19 related Mortality by age	End of follow up – VE - 71% (95% CI 68% - 74%), BNT162B2 (Pfizer/BioNTech) Peak - 87% (95% CI 85% - 89%) End of follow up – VE 56% (95% CI 53% - 59%) Ad26.COV2.S (Janssen) Peak – VE 58% (51% - 65%), End of follow up – VE - 27% (95% CI 17% - 37%)

			(Vaccinated vs unvaccinated) 45-74 mRNA-1273 RR = 31 (21, 48) BNT162b2 RR = 14 (11, 19) AD26.COV2.S RR = 6.2 (4, 10) 75 to 84 mRNA-1273 RR = 13 (8, 21) BNT162b2 RR = 13 (8, 20) AD26.COV2.S RR = 3.4 (2, 8.3) 85+ mRNA-1273 RR = 3.8 (2, 6.1) BNT162b2 RR = 4.8 (3, 8.5) Ad26.COV2.S -	

			RR = 0.7 (0.4, 1.4) **Efficacy/effectiveness over time.** Vaccine effectiveness over time against hospitalisation as a curve depicting risk reduction, although authors did not have enough data to obtain as precise estimates as for infections. Waning of effectiveness against hospitalisation is observed over time, though very imprecise estimates	
* probabilities of hospitalisation and mortality by age and vaccine are also available.				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Rosenberg (2021) **Title:** COVID-19 Vaccine Effectiveness by Product and Timing in New York State **DOI:** 10.1101/2021.10.08.21264595 **NCT:** N/A **Study Design**: Prospective cohort study **Country**: US **Setting:** Surveillance-based cohort of adults residing in New York State **Time Period**: 1 May 2021 – 3 September 2021 **Variants of Concern:** Prevalence of Delta	**Exposure**: ▪ BNT162b2 (Pfizer–BioNTech) ▪ mRNA-1273 (Moderna) ▪ Ad26.COV2.S (Janssen) **Comparator/Control:** ▪ Unvaccinated **Time since final vaccination dose:** ▪ BNT162b2 (Pfizer–BioNTech) – maximum 34.47 weeks ▪ mRNA-1273 (Moderna) – maximum 32.9 weeks ▪ Ad26.COV2.S (Janssen)-	**Description:** Adults aged ≥18 years residing in New York state. Vaccination data for persons, excluding those in settings that report directly to the federal system such as veterans, military, and first nations tribal healthcare facilities are captured. Persons who received non-FDA authorized vaccines were excluded from the full vaccination definition and were analytically classified unvaccinated, but comprise an estimated 0.03% of persons fully vaccinated in the registries by May 2021. Persons with a positive laboratory result within 90 days before May 1 were considered not susceptible for either outcome and excluded, per the CDC case-definition **N:** Total - 8,834,604 Fully-Vaccinated - 5,787,817 (65.5%) ▪ BNT162b2 (Pfizer–BioNTech) – 48.6% ▪ mRNA-1273 (Moderna) – 41.5% ▪ Ad26.COV2.S (Janssen) – 10.0% **Age:** Total -	**Severe Disease:** **≥14 days after second/final dose** See below **Adjustments:** **Mortality :** *NR* **Variants of Concern.** Incident laboratory-confirmed COVID diagnosis and hospitalization were ascertained during the pre- vs. post-Delta variant period from May 1 (<2%) to August 28, 2021 (>99%)	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection:** *See below* **Adjustments:** NR **Mortality :** NR **Variants of Concern** Incident laboratory-confirmed COVID diagnosis and hospitalization were ascertained during the pre- vs. post-Delta variant period from May 1 (<2%) to August 28, 2021 (>99%)

increased from <2% on week commencing 1 May to >99% by week commencing 28 August 2021. **Publication status**: Preprint	maximum 26.1 weeks	18-49 years – 4,079,407 50-64 years – 2,261,421 >65 years- 2,493,776 **Male** NR **Co-morbidities and Special Populations** NR		

Table 1 Estimated vaccine effectiveness for laboratory-confirmed COVID-19 hospitalisations by age and vaccine.

		Month of outcome ascertainment			
		Week commencing May-21 VE (95% CI)	Week commencing Jun-21 VE (95% CI)	Week commencing Jul-21 VE (95% CI)	Week commencing Aug-21 VE (95% CI)
Month of full vaccination	**Vaccine Cohort 18- 49 years**				
	Pfizer-BioNTech	96.4 (94.5, 97.7)	94.7 (90.8, 97.2)	95.9 (93.0, 97.7)	95.5(94.0, 96.7)
	January/February	97.9 (93.9,99.6)	98.3 (90.4,100.0)	96.3 (89.1,99.2)	93.1 (88.9,96.0)
	March	99 (94.3,100.0)	97.4 (85.7,99.9)	96.3 (86.7,99.6)	95.2 (90.5,97.9)
	April	95.1 (92.2,97.1)	92.5 (86.4,96.3)	95.6 (91.5,98.0)	96.6 (94.8,97.9)
	Moderna	96.8 (94.7,98.2)	92 (86.6,95.5)	96.1(92.9,98.2)	97.5(96.1,98.5)
	January/February	96.8 (92.6,99.0)	98.4 (91.1,100.0)	98.9(93.6,100.0)	97.4(94.6,98.9)
	March	98.2 (93.5,99.8)	91.1 (77.1,97.6)	92(81.2,97.4)	97.9(94.6,99.4)
	April	95.9 (92.0,98.2)	87.3 (76.5,93.9)	96.3(90.6,99.0)	97.3(94.9,98.8)
	Janssen	95.9(91.6,98.4)	88.3(76.9,95.0)	94.8(87.7,98.3)	93.8(90.2,96.3)
	March	90.7(72.9,98.1)	53.7(0.0,83.1)	94.4(69.0,99.9)	92.7(81.3,98.0)
	April	97.1(92.6,99.2)	96.4(87.0,99.6)	94.8(86.7,98.6)	94.1(90.0,96.8)

	Pfizer-BioNTech	95.8(94.5,96.9)	95.2(92.6,97.0)	93.9(91.4,95.8)	95.1(94.1,96.0)
	January/February	93.1(88.5,96.1)	93.4(84.3,97.9)	96.8(90.6,99.3)	94.6(91.7,96.7)
	March	94(89.7,96.8)	96(88.2,99.2)	91.5(83.1,96.4)	95.9(93.3,97.7)
	April	97(95.5,98.0)	95.4(92.2,97.5)	93.8(90.6,96.0)	95(93.8,96.1)
	Moderna	97.3(96.1,98.3)	97(94.5,98.6)	96.7(94.4,98.2)	96.9(95.9,97.7)
	January/February	98.3(95.7,99.5)	100(95.5,100.0)	98.1(93.0,99.8)	97(94.8,98.4)
	March	100(98.1,100.0)	98.5(91.7,100.0)	97.6(91.4,99.7)	98(95.8,99.2)
	April	95.9(93.8,97.5)	95.2(90.8,97.8)	95.7(92.1,98.0)	96.5(95.1,97.6)
	Janssen	88.2(83.3,91.8)	91(82.6,95.9)	90.4(83.0,95.1)	92.8(90.1,95.0)
	March	90.7(81.6,96.0)	93.3(75.6,99.2)	86.6(68.5,95.7)	92.2(86.4,96.0)
	April	87(80.9,91.6)	90(79.1,96.0)	92(83.3,96.8)	93.1(89.7,95.5)
	Vaccine Cohort 18- 49 years				
	Pfizer-BioNTech	95(94.2,95.7)	93.8(92.3,95.1)	89.6(87.4,91.4)	89.2(88.1,90.2)
	January/February	93.2(91.1,94.9)	92.8(89.0,95.6)	89.3(84.6,92.8)	86.2(83.6,88.5)
	March	95.8(94.5,96.8)	94.1(91.5,96.1)	89(85.5,91.8)	89.6(87.9,91.1)
	April	95.2(94.0,96.2)	94.1(91.8,95.9)	90.1(87.1,92.6)	90.3(88.8,91.6)
	Moderna	97.2(96.7,97.7)	96.4(95.3,97.4)	95.2(93.9,96.3)	94.1(93.3,94.8)
	January/February	97.4(95.7,98.6)	96.2(92.5,98.4)	91.8(86.7,95.3)	93.2(91.0,95.0)
	March	97.5(96.6,98.2)	97.5(95.9,98.6)	95.8(93.8,97.3)	94.1(93.0,95.1)
	April	96.9(96.0,97.7)	95.5(93.4,97.0)	95.7(93.7,97.2)	94.3(93.2,95.3)
	Janssen	85.5(81.5,88.8)	80.9(72.7,87.1)	82.4(74.5,88.4)	82.8(79.0,86.1)
	March	90.4(85.0,94.2)	80.5(67.0,89.4)	83(70.1,91.3)	82.9(76.9,87.7)

	April	81.8(75.7,86.6)	81.2(70.0,88.9)	82(70.8,89.6)	82.7(77.6,86.9)
	Vaccine Cohort over 65 years				
	Pfizer-BioNTech	95(94.2,95.7)	93.8(92.3,95.1)	89.6(87.4,91.4)	89.2(88.1,90.2)
	January/February	93.2(91.1,94.9)	92.8(89.0,95.6)	89.3(84.6,92.8)	86.2(83.6,88.5)
	March	95.8(94.5,96.8)	94.1(91.5,96.1)	89(85.5,91.8)	89.6(87.9,91.1)
	April	95.2(94.0,96.2)	94.1(91.8,95.9)	90.1(87.1,92.6)	90.3(88.8,91.6)
	Moderna	97.2(96.7,97.7)	96.4(95.3,97.4)	95.2(93.9,96.3)	94.1(93.3,94.8)
	January/February	97.4(95.7,98.6)	96.2(92.5,98.4)	91.8(86.7,95.3)	93.2(91.0,95.0)
	March	97.5(96.6,98.2)	97.5(95.9,98.6)	95.8(93.8,97.3)	94.1(93.0,95.1)
	April	96.9(96.0,97.7)	95.5(93.4,97.0)	95.7(93.7,97.2)	94.3(93.2,95.3)
	Janssen	85.5(81.5,88.8)	80.9(72.7,87.1)	82.4(74.5,88.4)	82.8(79.0,86.1)
	March	90.4(85.0,94.2)	80.5(67.0,89.4)	83(70.1,91.3)	82.9(76.9,87.7)
	April	81.8(75.7,86.6)	81.2(70.0,88.9)	82(70.8,89.6)	82.7(77.6,86.9)

Table 2 Estimated vaccine effectiveness for laboratory-confirmed COVID-19 cases by age and vaccine.

		Month of outcome ascertainment		
Month of full vaccination		**Week commencing May 1 VE % (95% CI)**	**Week commencing July 10 (VE 95% CI)**	**Week commencing August 28 (VE 95% CI)**
	Vaccine Cohort 18- 49 years			
	Pfizer-BioNTech	93.6 (92.6, 94.6)	65.8 (62.2, 69.5)	69.0 (67.4, 70.6)

	January/February	90.5 (88.0, 93.0)	64.2 (56.9, 71.5)	67.4 (64.2, 70.6)
	March	90.8 (87.9, 93.8)	64.7 (55.9, 73.4)	66.2 (62.3, 70.1)
	April	95.6 (94.5, 96.7)	66.8 (62.3, 71.4)	70.4 (68.5, 72.4)
	Moderna	96.5 (95.6, 97.3)	77.2 (73.9, 80.5)	78.4 (77.0, 79.9)
	January/February	94 (92.1, 95.9)	79.8 (74.5, 85.0)	72.1 (69.3, 74.9)
	March	97.8 (96.5, 99.2)	74.9 (68.1, 81.8)	79.2 (76.3, 82.0)
	April	97.7 (96.6, 98.7)	76.4 (71.3, 81.5)	83.1 (81.2, 85.1)
	Janssen	89.4 (87.0, 91.8)	51.7 (43.8, 59.6)	70.2 (67.4, 73.0)
	March	90.3 (85.0, 95.6)	19.8 (0.0, 42.7)	66.2 (59.5, 73
	April	89.2 (86.5, 91.9)	59.2 (51.2, 67.1)	71.1 (68.1, 74.2)
	Vaccine Cohort 18- 49 years			
	Pfizer-BioNTech	95.3 (94.3, 96.2)	71.5 (66.5, 76.5)	76.2 (74.5, 78.0)
	January/February	89.7 (86.3, 93.1)	70.6 (59.7, 81.5)	73.4 (69.3, 77.5)
	March	93.4 (90.7, 96.1)	71.6 (60.9, 82.3)	74.2 (70.1, 78.2)
	April	97.1 (96.2, 98.0)	71.7 (66.0, 77.5)	77.4 (75.4, 79.4)
	Moderna	97.4 (96.6, 98.2)	85.8 (82.1, 89.5)	82.9 (81.3, 84.6)
	January/February	96.1 (94.1, 98.1)	77.9 (69.0, 86.8)	76.4 (72.8, 80.1)
	March	97.1 (95.2, 99.0)	83.6 (75.1, 92.0)	78.2 (74.3, 82.0)

April	98 (97.1, 99.0)	90.2 (86.2, 94.1)	87.6 (85.8, 89.3)	
Janssen	86.8 (83.4, 90.2)	72.6 (63.4, 81.8)	76 (72.6, 79.4)	
March	88.5 (82.8, 94.1)	75.3 (59.9, 90.8)	70.3 (63.6, 77.1)	
April	86.1 (81.9, 90.2)	71.4 (60.3, 82.5)	78.4 (74.6, 82.2)	
Vaccine Cohort ≥65 years				
Pfizer-BioNTech	91.9 (90.6, 93.2)	79.2 (74.5, 83.8)	77.8 (75.9, 79.6)	
January/February	85.1 (81.4, 88.8)	72.1 (61.9, 82.3)	75.9 (72.3, 79.5)	
March	91.8 (89.7, 93.9)	81 (74.5, 87.5)	77.2 (74.4, 79.9)	
April	95.1 (93.7, 96.6)	81 (75.1, 87.0)	79.1 (76.7, 81.5)	
Moderna	96.2 (95.3, 97.0)	87.2 (83.8, 90.5)	84.3 (82.8, 85.7)	
January/February	97.2 (95.4, 99.0)	80 (70.1, 89.9)	79.1 (75.2, 82.9)	
March	96.1 (94.8, 97.4)	86.3 (81.4, 91.2)	84.5 (82.5, 86.5)	
April	95.9 (94.7, 97.2)	90.4 (86.4, 94.4)	85.8 (83.9, 87.7)	
Janssen	81.7 (76.3, 87.1)	79.3 (68.1, 90.5)	70.8 (65.7, 76.0)	
March	85.5 (78.3, 92.7)	86.2 (72.6, 99.8)	67 (58.9, 75.1)	
April	78.9 (71.3, 86.4)	74.1 (57.7, 90.5)	73.7 (67.4, 80.0)	

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Self (2021) Title: Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021 **DOI:** 10.15585/mmwr.mm7038e1 **NCT:** N/A **Study Design***:* Case Control[@] **Country**: USA **Setting***:* 21 hospitals across 18 states. **Time Period***:* 11 March to 15 August, 2021.	**Intervention/Exposure**: Vaccinated, 1,327 (36.0%) • Moderna – 476 (12.9%) • Pfizer-BioNTech – 738 (20.0%) • Janssen – 113 (3.1%) **Comparator/Control:** Unvaccinated, 2,362 (64.0%) **Time since final vaccination dose and symptom onset/hospitalisation:** Median (weeks) - Moderna – 11.25 (IQR 6.55 to 15.95) Pfizer-BioNTech – 12.25 (IQR 7.26 to 16.95) Janssen – 9.68 (IQR 5.12 to 15.81) Maximum follow up time was approximately 29 weeks	**Description:** Adults ≥18 years who were hospitalized with or without COVID-19. Patients with immunocompromising conditions and those who received ≥1 vaccine dose but were not fully vaccinated were excluded. 226 (6.1%) participants self-reported prior laboratory-confirmed SARS-CoV-2 infection **N:** Total - 3,689 Case – 1,682 Control – 2,007 Unvaccinated – 2,362 (64.0%) Patients hospitalised with COVID-19: Total: 1,682 Vaccinated: 219 (13.0%) Unvaccinated: 1,463 (87.0%) **Age:** Overall, median age, yrs (IQR) 58 (44-69) Unvaccinated, median age, yrs (IQR) 53 (40–64). **Male:** Overall, 51.8%% Unvaccinated, 52.3% **Co-morbidities:** • Overall Chronic CVD – 59.7% Chronic lung disease – 25.1%	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* NR *Hospitalisation* See below *ICU admissions* NR **Adjustments:** Admission date, geographic region, age, sex, and race and Hispanic ethnicity. A separate model added an interaction term between product type and time since vaccination. **Mortality** NR **Variants of Concern** NR **Efficacy/effectiveness over time:** See below	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥14 days after second/final dose** NR

Variants of Concern: NR **Publication status**: On 17 September 2021, this report was posted online as an MMWR Early Release.		Diabetes mellitus – 29.6% Obesity (by BMI) – 50.1% • Unvaccinated Chronic CVD – 51.6% Chronic lung disease – 22.1% Diabetes mellitus – 26.2% Obesity (by BMI) – 53.2%	Moderna VE (93%) was significantly higher than Pfizer-BioNTech (88%); p=0.011. VE for both mRNA vaccines was higher than that of Janssen (71%); (p<0.001).	

Primary outcomes (hospitalisations)				
Vaccine	Full Surveillance Period VE (95% CI)	>28 days after full vaccination£ VE (95% CI)	14-120 days after full vaccination VE (95% CI)	>120 days after full vaccination VE (95% CI)
Moderna	93% (91 to 95)	-	93% (90 to 95)	92% (87 to 96)
Pfizer BioNTech	88% (85 to 91)	-	91% (88 to 93)	77% (67 to 84)
Janssen	71% (56 to 81)	68% (49 to 80)	-	-

£ - Because a limited number of patients received Janssen vaccine >120 days before illness onset (19 total), VE for the Janssen vaccine was not stratified by time

BMI, Body mass index

CVD, Cardiovascular disease

@ Case- illness† patients were admitted to a hospital with COVID-19–like and a positive SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) or antigen test result. Control-patients were adults admitted to a hospital§ who received a negative SARS-CoV-2 RT-PCR test result.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Sharma (2021) **Title:** COVID-19 Vaccine Breakthrough Infections in Veterans Health Administration **DOI:**https://doi.org/10.1101/2021.09.23.21263864 **NCT:** NA **Study Design***:* Retrospective cohort study **Country**: US **Setting:** Persons in Veterans Health Administration **Time Period***:* January 1, 2021 to August 31, 2021 **Variants of Concern:** Regional proportion of delta variant were predictors of vaccine breakthrough events,Prevalence not provided.	**Time since final vaccination:** Median ~21 weeks 2% are followed for up to 28.57 weeks.	**Description:** Eligibility criteria included Veterans at least 18 years or older who received two doses of mRNA-1273 or BNT162b2 vaccines within the recommended timeframe listed in FDA approvals, or received Ad26.COV2.S vaccine during January 1, 2021 to August 31, 2021; residents of nursing home facilities were excluded. Previous SARS-CoV-2 infection was defined as a PCR or antigen positive specimen collected at least 90 days before date of final vaccination. **N:** Vaccinated: 3,030,561 mRNA-1273, 1,511,382 BNT162b2 1,293,609 Ad26.COV2.S. 227,570 **Age:** median 70 (interquartile range [IQR]: 58-76) **Male** = 91.5% **Co-morbidities:**	**Severe Disease:** **≥14 days after second dose** See below by vaccine **Adjustments:** estimates are adjusted for age, sex, race/ethnicity, Charlson Comorbidity Index, previous documented SARS-CoV-2 infection, population density in county of residence, county-level COVID-19 incidence, county-level vaccine coverage and regional proportion of delta variant **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** At 200 days, the unadjusted cumulative incidence of documented COVID-19 hospitalization was 0.16% (95% CI 0.15-0.18%)	**Confirmed RT-PCR or antigen SARS-CoV-2 infection ≥14 days after second dose of mRNA-1273 (Moderna)** **See below by vaccine** **Adjustments:** estimates are adjusted for age, sex, race/ethnicity, Charlson Comorbidity Index, previous documented SARS-CoV-2 infection, population density in county of residence, county-level COVID-19 incidence, county-level vaccine coverage and regional proportion of delta variant **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time:** At 200 days, the unadjusted cumulative incidence of documented SARS-CoV-2 infection breakthrough infections was 0.84% (95% CI 0.81-0.87%).

Publication status: Preprint		Solid Tumor, Leukemia, or Lymphoma: 484,311 (16.0%)		
	Exposure BNT162b2 (Pfizer/BioNTech) **Comparators** Ad26.COV2.S (Janssen)	**N:** BNT162b2 (Pfizer/BioNTech) 1,293,609 Ad26.COV2.S.(Janssen) 227,570	**Severe Disease:** **≥14 days after second dose of BNT162b2 (Pfizer/BioNTech)** *COVID-19 Hospitalisation Adjusted hazard ratio (95% CI)* 0.51 (0.43, 0.60)	**Confirmed RT-PCR or antigen SARS-CoV-2 infection ≥14 days after second dose of BNT162b2 (Pfizer/BioNTech)** *Documented SARS-CoV-2 infection Adjusted hazard ratio (95% CI)* 0.54 (0.51, 0.58)
	Exposure mRNA-1273 (Moderna) **Comparators** Ad26.COV2.S (Janssen)	N mRNA-1273, 1,511,382 Ad26.COV2.S. 227,570	**Severe Disease:** **≥14 days after second dose of mRNA-1273 (Moderna)** *COVID-19 Hospitalisation Adjusted hazard ratio (95% CI)* 0.27 (0.23, 0.32)	**Confirmed RT-PCR or antigen SARS-CoV-2 infection ≥14 days after second dose of mRNA-1273 (Moderna)** *Adjusted hazard ratio (95% CI)* 0.36 (0.33, 0.38)

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Thompson (2021) **Title:** Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings **DOI:** 10.1056/NEJMoa2110362 **NCT:** N/A **Study Design***:* Test negative (case-control) **Country**: USA **Setting***:* Hospital, emergency departments and urgent care clinics **Time Period***:* 01 January 2021 to 22 June 2021 **Variants of Concern:** NR **Publication status**: Peer-reviewed	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.Cov2.S (Janssen) **Comparator/Control:** *Unvaccinated* **Time in days since final vaccination dose to index date*:** Hospitalisation – Median - 53 IQR (33 to 75) ICU admission – Median - 52 (IQR 34 to 73) ED/UC – Median 50 (IQR 31 to 73)	**Description:** conducted a study involving adults (≥50 years of age) with Covid-19–like illness who underwent molecular testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) **N:** **Hospitalisations:** *BNT162b2 (Pfizer/BioNtech)* *8,500* *mRNA-1273 (Moderna)* *6,374* *Ad26.COV2.S (Janssen)* 707 *Unvaccinated* *20,406* **ED or urgent care visit:** *BNT162b2(Pfizer/BioNtech)* *3,589* *mRNA-1273 (Moderna)* *2,476* Ad26.COV2.S*(Janssen)* 456 *Unvaccinated* *11,812*	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation % (95% CI):* *BNT162b2 vaccine 87 (85–90)* *mRNA1273 vaccine 91 (89–93)* *Ad26.COV2.S vaccine 68 (50–79)* *ICU admissions:* *BNT162b2 or mRNA1273 vaccine 90 (86–93)* Emergency department or urgent care visit: *BNT162b2 vaccine 89 (85–91)* *mRNA1273 vaccine 92 (89–94)* *Ad26.COV2.S vaccine 73 (59–82)* **Adjustments:** Vaccine effectiveness was adjusted with weights based on propensity-for vaccination scores and according to age, geographic region, calendar time (days from 1 January 2021, to the index date for each medical visit), and local virus circulation. **Mortality**	**Confirmed RT-PCR SARS-CoV-2 infection** N/R **Adjustments:** N/A **Variants of Concern:** NR **Subgroups**: N/R **Efficacy/effectiveness over time:** N/R

Age:
among hospitalized patients
median age was 74 years (interquartile range, 66 to 82)

among those who visited an emergency department or urgent care clinic.

70 years (interquartile range, 61 to 78)

Age of participants in study

	Un-vaccinated	*Full, 2 Doses of mRNA Vaccine*	*Full, Ad26.COV2.S Vaccine*
50–64 yr	5,532	1898	282
65–74 yr	6,681	4,481	187
75–84 yr	*5,233*	*5,189*	*153*
≥85 yr	*2,960*	*3,306*	*85*

Male = 47%

Co-morbidities: NR

All Cause/COVID-19: NR

Variants of Concern

NR

Subgroups:

Effectiveness against hospitalization [$] *:*

≥50 yr of age	89% (95% CI: 87 to 91)
≥85 yr of age	83% (95% CI: 77 to 87)
≥50 yr of age with no chronic condition	92% (95% CI 86 to 96)
≥50 yr of age with ≥1 chronic respiratory condition	90% (95% CI: 88 to 92)
≥50 yr of age with ≥1 chronic nonrespiratory condition	88% (95% CI: 86 to 90)

Effectiveness against ICU admission

≥50 yr of age	90% (95% CI: 86–93)

Effectiveness against SARS-CoV-2 Infection Leading to an Emergency Department or Urgent Care Clinic Visit

≥50 yr of age	*91% (95% CI:89 to 93)*
≥85 yr of age	84% (95% CI:73 to 91)
≥50 yr of age with ≥1 chronic respiratory condition	90% (95% CI:86 to 93)
≥50 yr of age with ≥1 chronic nonrespiratory condition	90% (95% CI: 87 to 92)

Efficacy/effectiveness over time:

Effectiveness against hospitalization ≥50 yr of age

42–55 Days after dose 2	90% (95% CI: 87 to 93)
56–69 Days after dose 2	86% (95% CI: 82 to 90)
70–83 Days after dose 2	93% (95% CI: 89 to 95)
84–97 Days after dose 2	86% (95% CI: 79 to 91)
98–111 Days after dose 2	82% (95% CI: 72 to 89)
≥ 112 Days after dose 2	86% (95% CI: 74 to 93)

			Effectiveness against emergency department or urgent care visit ≥50 yr of age 42–55 Days after dose 2: 95% (95% CI: 91 to 97) 56–69 Days after dose 2: 88% (95% CI: 81 to 92) 70–83 Days after dose 2: 86% (95% CI: 78 to 91) 84–97 Days after dose 2: 92% (95% CI: 87 to 96) 98–111 Days after dose 2: 86% (95% CI: 77 to 92) ≥ 112 Days after dose 2: 86% (95% CI: 74 to 93)	

messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated hospitalization by days past most recent dose. VE (95% CI)

	14-27 days post dose 2	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**98 to 111 days post dose 2**	**(≥112 days post dose-2**
Pfizer-BioNTech	87% (80 to 91)	95% (91 to 97)	86% (79 to 91)_	83 (75 to 89)	90% (82 to 94)	87% (76 to 93)	75% (57 to 85)	83% (64 to 92)
	14-27 days post dose 2	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**≥ 56 days post dose 2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**(≥112 days post dose-2)**
Moderna	90% (81 to 94)	89% (83 to 93)	93% (87 to 97)	(91% (85% to 94)	96%(92 to 98)	86% (75 to 92)	93%(82 to 97)	95% (79 to 99)
	14-27 days post dose	**28 to 41 days post dose**	**42-55 days post dose**	**≥56 days post dose**				
Janssen	72% (38 to 88)	69% (34 to 86)	68%(18 – 87)	79% (48 to 91)			-	

messenger RNA (mRNA) vaccine effectiveness (VE) among COVID-19-associated emergency department and urgent care (ED/UC) medical events VE (95% CI)								
Pfizer-BioNTech	**14-27 days post dose 2**	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**98 to 111 days post dose 2**	**(≥112 days post dose-2**
	93% (87 to 96)	94% (90 to 97)	93% (81 to 87)	82% (68 to 90)	80% (66 to 88)	91% (82 to 96)	78% (61 to 87)	83% (64 to 92)
	14-27 days post dose 2	**28 to 41 days post dose 2**	**42-55 days post dose-2**	**≥ 56 days post dose 2**	**56 to 69 days post dose 2**	**70 to 83 days post dose 2**	**84 to 97 days post dose 2**	**(≥112 days post dose-2)**
Moderna	90% (81 to 95)	96% (92 to 98)	93% (85-96)	90% (79-95)	91%(79 – 96)	91% (79 – 97)	not recorded due to no breakthrough cases	90% (52 to 98)
	14-27 days post dose	**28 to 41 days post dose**	**42-55 days post dose**	≥ 56 days post dose				
Janssen	67% (30 to 84)	80% (52 to 92)	58% (5 to 81)	87% (71 to 94)				
* Index date defined for each medical visit was defined as either the date of collection of a respiratory specimen associated with the most recent positive or negative SARS-CoV-2 test result before the medical visit or the date of the medical visit (if testing occurred only after the admission or visit date).								

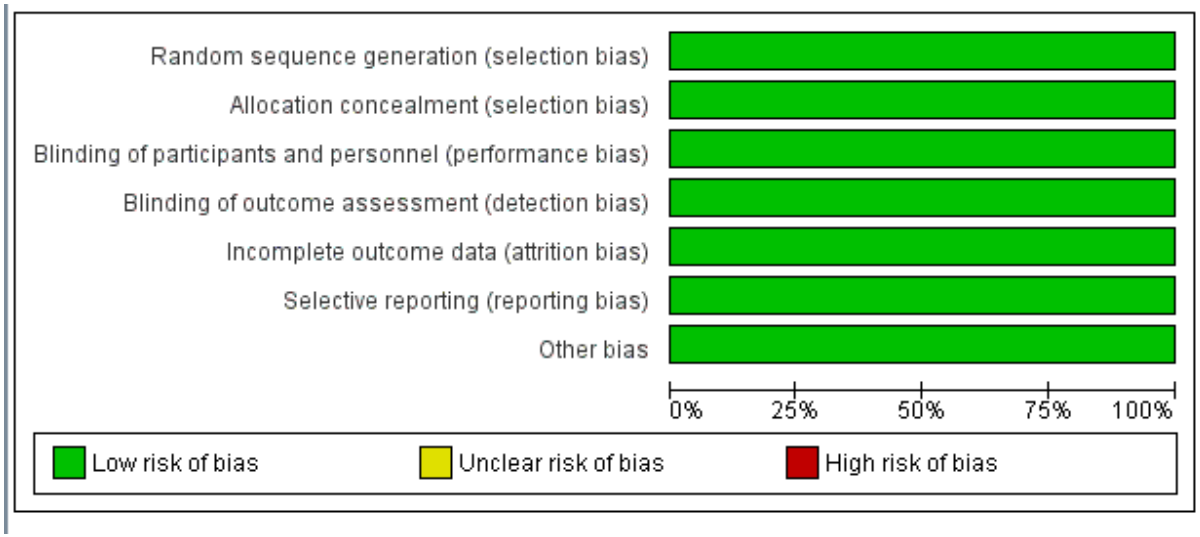
Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Uschner (2021) **Title:** Breakthrough SARS-CoV-2 Infections after Vaccination in North Carolina **DOI:** doi.org/10.1101/2021.10.10.21264812 **NCT:** NCT04342884 **Study Design***:* Prospective observational Study **Country**: US **Setting***:* Six healthcare systems **Time Period***:* January 15, 2021 to September 24, 2021 **Variants of Concern:** The study period included a statewide surge in cases driven by the Delta variant,	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2.S (Janssen) **Comparator/Control:** ▪ Age group ▪ Vaccine type ▪ Healthcare worker/non-healthcare worker **Time since final vaccination dose:** Infected participants: Median: 24 weeks (IQR 17 to 28.4) Non-infected participants: Median: 23.6, (IQR 17.4 to 29.9)	**Description:** Fully vaccinated adults 18 years and older **N:** 16,020 **Age:** 18-44 – 33% 45-64 – 47% 65+ - 20% **Male** = 26% **Co-morbidities/Special Populations:** **HCWs – 34%** **Outcome measurement:** The primary outcome was weeks until first self reported infection (positive SARS-CoV-2 antigen or nucleic acid amplification test) occurring ≥ 14 days after vaccination	**Severe Disease:** **≥14 days after second/final dose** NR	**Risk of breakthrough infection** *Any infection by vaccine type* Ad26.COV2.S vs BNT162b2 HR = 2.23 (1.40 to 3.56) mRNA-1273 vs BNT162b2 HR = 0.69 (0.50 – 0.96) **Adjustments:** Multivariate analyses were adjusted for; vaccination quarter before estimating HRs for breakthrough infection after vaccination. Age, sex, race/ethnicity, HCW status, vaccination brand, prior COVID-19 infection, Vaccination rate in county of residence (<60% or ≥60%), county classification

with a comparable number of new cases as during the winter of 2020-21 **Publication status**: Pre-print Supplementary Appendix: No				(Urban, suburban or rural), mask usage **Variants of Concern:** NR **Subgroups** **NR** **Efficacy/effectiveness over time.** Cumulative incidence curves are presented for overall estimates, by vaccine and county setting
@ 92% of infections were symptomatic infections, defined as one or more self-reported symptom suggestive of COVID-19 ± 3 days from the date of a positive test				

Quality Appraisal

Randomised Control Trial

The included RCT (ENSEMBLE) was considered at low risk of bias across all domains.



Observational studies

The quality appraisal of a cohort or a cross sectional study was assessed using tool: The National Institutes of Health (NIH) quality assessment tool for Cohort and Cross Sectional Studies, available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Table App.B1: Quality appraisal of cohort studies

Quality appraisal	Arregoces et al. (2021)	Cohn (2021)	Corchado-Garcia (2021)	De Gier (2021)	Lin (2021)	Polinski (2021)[37]	Robles-Fontan (2021)	Rosenberg (2021)	Sharma (2021)	Uschner (2021)
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	✓	✓	X	X	✓	CD
3. Was the participation rate of eligible persons at least 50%?	✓	✓	CD	✓	✓	✓	✓	✓	✓	CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

exclusion criteria for being in the study pre-specified and applied uniformly to all participants?										
5. Was a sample size justification, power description, or variance and effect estimates provided?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✓	✓	✓	✓	CD
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the	X	X	X	✓	✓	X	X	X	X	X

outcome (e.g., categories of exposure, or exposure measured as continuous variable)?										
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	X	✓	✓	✓	X
10. Was the exposure(s) assessed more than once over time?	CD	✓	X	✓	✓	✓	✓	✓	✓	X
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	CD	X	CD	X	✓	CD	X	CD	CD
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD

13. Was loss to follow-up after baseline 20% or less?	✓	✓	✓	✓	✓	✓	✓	✓	CD	CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	CD	✓	X	✓	X	✓	CD	X	✓	X
Quality Rating†	Fair	Good	Fair	Fair	Poor	Poor	Poor	Poor	Fair	Poor
Comment	Some concerns due to under-reporting of comorbidities in the database and hence potential lack of controlling for confounding	Minor concerns regarding outcome ascertainment bias as reason for testing not provided	Some concerns regarding lack of adjustment for important confounders	Underlying conditions or other cofounders not taken into account.	Hospitalisation and death status were known for only approximately 40% and 60% of Covid-19 cases, respectively. Lack of adjustment for education/socio economic status / test seeking behaviour.	Critical potential for bias by assuming that 40% are unvaccinated are actually vaccinated	Limited adjustment of variables and lack of description of population under investigation.	Underlying conditions or other cofounders not taken into account. Lack of information on demographics of participants.	Concern regarding outcome ascertainment bias, only secondary review outcomes are reported.	Self-reported vaccination status and lack of control for important confounders. Also lack of information on recruitment of participants.

The quality appraisal of a case control study was assessed using tool: The National Institutes of Health (NIH) quality assessment tool for CASE-Control studies, available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Table App.B2: Quality appraisal of case control studies

Quality appraisal criteria	Grannis (2021)	Self (2021)	Thompson (2021)
1. Was the research question or objective in this paper clearly stated and appropriate?	✓	✓	✓
2. Was the study population clearly specified and defined?	X	✓	✓
3. Did the authors include a sample size justification?	✓	X	✓
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	✓	✓	✓
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	✓	CD	✓
6. Were the cases clearly defined and differentiated from controls?	✓	✓	✓
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	NA	NA	✓
8. Was there use of concurrent controls?	CD	CD	✓
9. Were the investigators able to confirm that the exposure/risk	✓	✓	✓

Quality appraisal criteria	Grannis (2021)	Self (2021)	Thompson (2021)
occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	✓	✓	✓
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	CD	CD	CD
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	✓	✓	✓
Quality Rating†	Fair	Fair	Good
Comment	Insufficient information regarding the characteristics of the study population	Incomplete information on matching process. Most key confounding variables adjusted for. No adjustment for socioeconomic status.	

†Quality can be rated as Good, Fair or Poor**.** ✓Yes. **x** No, CD = could not be determined, NA = not applicable, NR = none repo

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