Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Duration of protective immunity following COVID-19 vaccination (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

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
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 October 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 90% 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 and to identify any evidence of waning of effect in particular populations.
- 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, whereas effectiveness studies provide data on how well a treatment works in the real world setting.
- Fifty-seven papers reporting 49 unique studies were included in this evidence summary: five randomised clinical trials (RCTs) and 44 observational studies, of which 32 were cohort studies and 12 were case control studies.
- Five RCTs met the criteria for inclusion in this evidence summary. Study size ranged from 1,467 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; one study enrolled a mixture of healthcare workers (HCWs), healthy adults and those at increased risk of SARS-CoV-2 infection; and one study enrolled only healthy adults. One trial reported subgroup analysis for those aged 12 to 15 years.

- All five RCTs were peer reviewed and considered to be at low risk of bias.

- Forty-four observational studies reported on vaccine effectiveness; the number of participants within studies ranged from 324 to 4.8 million with a maximum follow-up period of up to six months. Of these 44 studies:
  - Twenty-nine studies included the general population; nine exclusively enrolled HCWs and other frontline workers; three exclusively enrolled residents of long term care (LTC) facilities; one exclusively enrolled staff and residents of LTC facilities and older people and two studies exclusively enrolled those with an immunocompromising condition or co-morbidity.
  - The quality varied; 11 were considered good quality, 22 fair quality and 11 of poor quality. The primary reasons for concern were bias relating to measurement of the outcome and lack of adjustment for confounding factors. The majority of the observational studies (30/44) included in this review 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.

- For the general population, the estimated duration of protective immunity by outcome is presented below.

  General Population - Mortality:

  - The identified RCTs were not designed or powered to examine efficacy against COVID-19 related mortality.
  - A large observational study from Public Health England found there was some evidence to suggest waning vaccine effectiveness against the Delta variant although effectiveness for mortality exceeded 78% at all time points examined up to 20 weeks post-vaccination. Additional analyses suggested that effectiveness for mortality did not differ by age. An observational study from Qatar provided similar results for the Pfizer/BioNTech vaccine in the total adult population.

  General Population - Severe Disease:

- Estimates of vaccine efficacy for severe disease exceeded 95% in two RCTs with six months follow-up; however, neither trial reported changes in vaccine efficacy over time.
- Conclusions regarding potential waning effectiveness in observational studies differed by study and vaccine type. Vaccine effectiveness for severe disease was high for the Pfizer, Moderna and AstraZeneca vaccines with estimates of at least 75% at every time point examined across all studies up to six months after dose two. No evidence of waning was identified for the Janssen vaccine in the two studies that assessed effectiveness over time. However, there was variability observed for the Janssen vaccine, with vaccine effectiveness for severe disease ranging from 60% to 91%.

General Population - Symptomatic disease and any infection:

- Three RCTs examined vaccine efficacy over time. No decline in efficacy was identified up to 12 weeks after vaccination for the Janssen vaccine for moderate to severe-critical COVID-19, or up to six months for the Moderna vaccine for symptomatic disease. While estimates for the Pfizer/BioNTech vaccine suggest a possible decline over time, there are concerns that the trial design may have led to biased measurement of the change in vaccine efficacy. However, vaccine efficacy exceeded 83% for symptomatic disease up to six months after vaccination.
- While some differences were observed between the various vaccines, there was evidence of waning effectiveness across almost all observational studies in the general population which examined effectiveness up to six months after the final regimen dose. Data from five studies for any infection comparing early and late vaccinees also suggested waning effectiveness over time.
- It is unclear whether the inconsistency between randomised and observational study results is due to differences in populations across studies, unmeasured confounders or differences in the prevalence of disease or variants of concern. Outcomes such as infection or self-reported symptomatic disease are more prone to bias from unmeasured confounders than severe disease outcomes and mortality.

- For people aged 65 years or older:

- Evidence from two observational studies suggested that vaccine effectiveness for mortality did not differ from the general population.
- For those aged 65 years or older without co-morbidities, overall point estimates for effectiveness against severe disease tended to be lower for older (particularly those aged more than 65 years) compared with younger adults, but this was not consistent across all studies. There was also a trend for the point estimates to be lower when comparing longer with shorter durations of follow-up. However, vaccine effectiveness still exceeded 74% up to six months after the second dose in studies where effectiveness over time was measured in this cohort. Lower point estimates were reported for individual vaccines or limited subgroups, in a number of studies that did not report changes in effect over time. For example, one study estimated effectiveness of 68% in those aged over 60 years for the Janssen vaccine while another estimated effectiveness of 64% for the Moderna vaccine for those aged 70 years and older. Similar to the general population, there was evidence of waning effect for symptomatic disease, with vaccine effectiveness as low as 36% after six months for the AstraZeneca vaccine.

- For those with co-morbidities or an immunocompromising condition:
  - Two observational studies found that vaccination was significantly less effective in preventing COVID-19 related hospitalisations in those with immunocompromising conditions compared to those without. A third found that vaccination was also less effective in those in clinically extremely vulnerable groups compared to the general population.
  - Two studies found no evidence of waning immunity in those with immunocompromising conditions, but there was substantial uncertainty associated with the estimates, thus the potential for waning effectiveness over time cannot be excluded.
  - A Public Health England study that included individuals with severe immunocompromising conditions, reported vaccine effectiveness for hospitalisation in those aged 65 years or older in the clinically extremely vulnerable group with follow-up for the period up to at least 20 weeks following vaccination. While effectiveness declined over time for both the AstraZeneca and Pfizer/BioNTech vaccines, the levels of decline were not statistically significant.

- For HCWs, no evidence (efficacy or effectiveness estimates) for mortality or severe disease was identified. There was evidence to suggest that vaccine efficacy for symptomatic disease for HCWs does not differ to that of the general population. For any infection, all studies reported effectiveness exceeding 80% up to five months after vaccination. One study reported effectiveness beyond five months (>150 days) with a small decline in vaccine effectiveness observed.

- The change in effectiveness for mortality and infection over time for residents or staff of long term care facilities was reported on by one study. Data were limited to follow-up for ≥61 days after the second dose with no evidence of waning of effectiveness over time observed for either the Pfizer/BioNTech or AstraZeneca vaccines. Effectiveness estimates for any infection from this study and two additional studies are lower than those observed in other studies from the general population. This suggests that residents in long term care facilities may have a lower baseline level of vaccine effectiveness for any infection compared to that observed in the general population in other studies. No evidence (efficacy or effectiveness over time) was identified for staff of long term care facilities.

- 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 those at highest risk (due to either higher risk of exposure or higher risk of severe disease outcomes) typically 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 emergence of a new variant of concern, other unmeasured confounding or a combination of all of these factors.

- Overall, the evidence suggests that vaccination against COVID-19 continues to provide protection for at least six months post-vaccination. However, there are limited data to suggest potential waning of vaccine effectiveness for severe disease in individuals at higher risk of poor disease outcomes. Given the lower initial vaccine efficacy and effectiveness in these populations, any reduction 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.

1 Background

As of October 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 was 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 21 December 2020.[3] Moderna's COVID-19 vaccine (mRNA-1273 or Spikevax) was approved on 6 January 2021,[4, 5] followed by the ChAdOx1 vaccine, developed by AstraZeneca in collaboration with the University of Oxford, on 29 January 2021.[6, 7] More recently, the Janssen vaccine (Ad26.COV2.S) was authorised on 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 28 May 2021 and 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 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 thereafter based on age and existing medical conditions. As vaccine availability increased, through the approval and acquisition of additional vaccines, the rollout accelerated. As of 23 September 2021, 7.2 million vaccine doses have been administered in Ireland, with an estimated 90.6% 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 5.2 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. 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 types of vaccines leads 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 their respective vaccination schedule's second or final dose 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	• ChAdOx1 • ChAdOx1-SARS-CoV-2 • Vaxzevria® • 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 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?"

2 Methods

This review aimed to examine the change in efficacy and effectiveness of COVID-19 vaccination over time and to identify groups where vaccine efficacy or effectiveness may be waning. A detailed summary of the methods used for this evidence summary is provided in the protocol, available here.[23]

A systematic search of published peer-reviewed articles and non-peer-reviewed preprints was undertaken. The databases Medline and Embase were searched up to 30 September 2021. A preprint search on Europe PMC was also conducted up to 30 September. The preprint server MedRxiv was examined on 31 August 2021. 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. Quality appraisal of RCTs was completed using the Cochrane risk of bias tool version 1.[24] The relevant National Institutes of Health (NIH) Quality Assessment Tool was used for the quality appraisal of observational studies.[25] For selected analyses, vaccine effectiveness data 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 running R software version 3.6.2.

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), health care 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. **Excluded:** 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).[26] Outcomes were extracted for study-defined time points since vaccination.[26] Changes in absolute and relative efficacy or effectiveness were noted. Disaggregated data by variant were extracted where 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 reported 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.

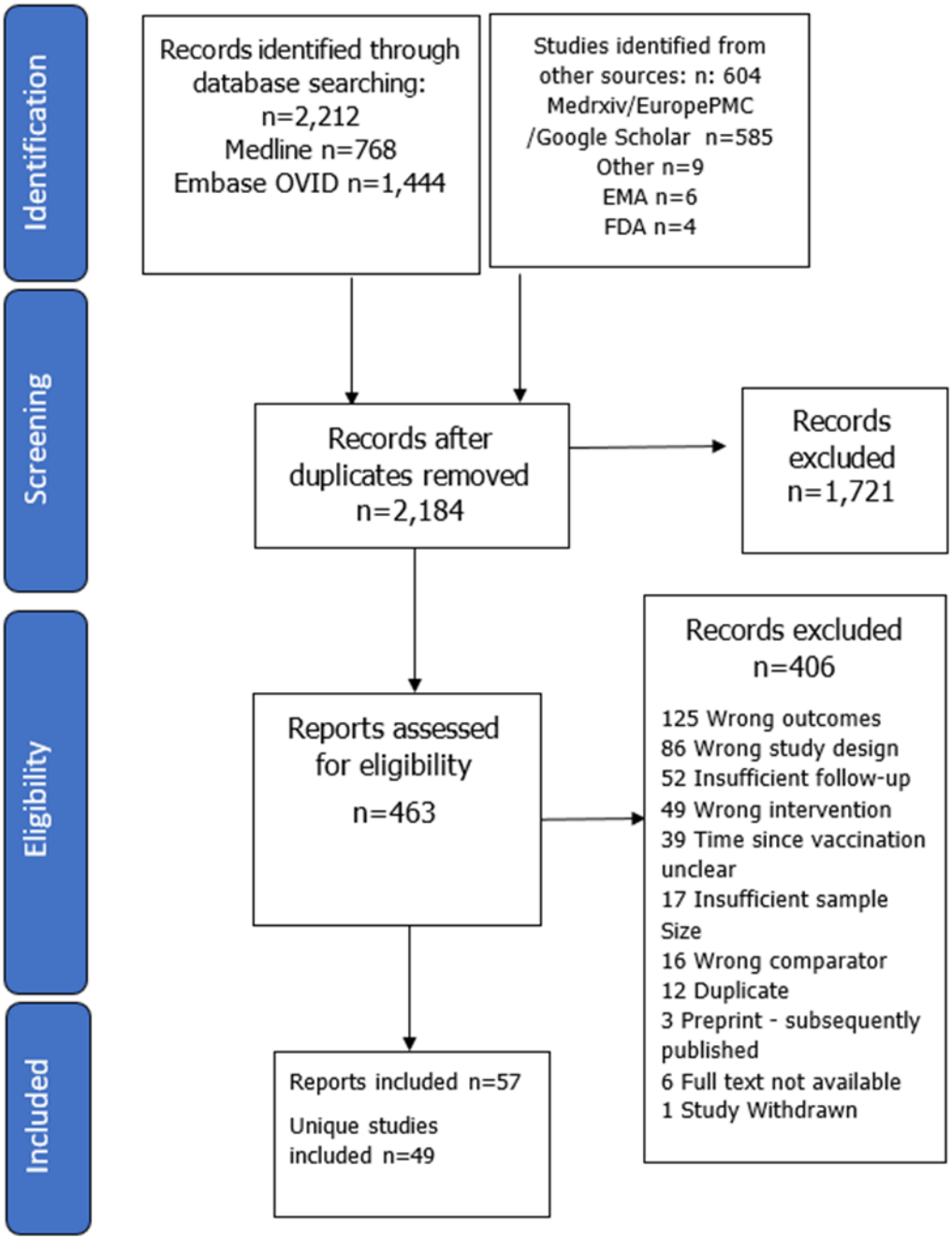
~Where median is not reported, the mean time was used to assess eligibility.

3 Results

An overview of the search findings are presented in the PRISMA diagram (Figure 1). The 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 were identified that met the inclusion criteria.[5, 21, 27-78] Thirty of the included papers were only available as preprints.[35, 36, 38-40, 42-45, 49, 51-54, 56-60, 62, 70, 73-76, 78-82]

Of the studies identified, five were RCTs,[27-34, 55] and the remaining 44 were observational study designs.[35-54, 56-61] Characteristics of included studies and study findings are described separately for vaccine efficacy (RCTs) and effectiveness (observational studies) in Sections 3.1 and 3.2, respectively.

Figure 1 PRISMA diagram of study selection



3.1 Vaccine efficacy

3.1.1 Characteristics of included studies

Eight papers describing the results of five RCTs were identified (summarised in Table 3).[27-34, 55] Studies were identified for each of the four vaccines available in Ireland: ChAdOx1 (AstraZeneca), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech). For simplicity of reporting, the pooled analysis of four RCTs by Voysey et al. are presented as a single study.[28, 29] Additional data (primarily for subgroup analysis) are provided in reports published by the EMA,[5] and the FDA.[21] All five included RCTs have been peer-reviewed.[27-34, 55, 83] 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.

Two studies enrolled individuals in good health and those with co-morbidities,[30, 32-34] one study included adults at high risk of infection or severe COVID-19,[31] one study enrolled a mixture of HCW, healthy adults and those at increased risk of SARS-CoV-2 infection,[28, 29] and one study only enrolled healthy adults aged between 18 and 65 years.[27] One RCT reported subgroup analysis for those aged 12 to 15 years.[33]

Studies required at least eight weeks of follow-up before authorisation could be approved. Hence, most of the studies initially published interim results with median cut-offs close to this date [84]. Updated analyses with up to six months of follow-up have been published for the pivotal BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) trials.[55] Updated analysis for the ChAdOx1 (AstraZeneca) vaccine trials has a mean follow-up of 12.5 weeks.[84] Most of the trials were set across multiple countries; however, the Janssen trial and a paediatric sub-study of the BNT162b2 (Pfizer/BioNTech) trial were set in the US.

All five studies 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 and described in Sections 3.1.2 to 3.1.6.

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	Primary outcomes: overall follow up		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
Madhi,[27]^ peer-reviewed South Africa (Beta Variant)	ChAdOx1 (AstraZeneca)	**N:** 1,467 Adults aged ≥18 to ≤65	Median: 17.4 weeks (IQR 16.3, 20.4)	No cases reported	NR	VE: 26.1% (95% CI -28.7 to 58.0)	VE (mild to moderate): 21.9% (95% CI -49.9 to 59.8)	No numerical evidence presented, graphical evidence only. No evidence of waning VE against symptomatic infection apparent from Kaplan Meier plot for the 1,306 patients followed for 14.2 weeks or the 261 patients followed for 21.4 weeks post dose two.	low
Voysey a (2020)[28] and b (2021),[29]^ peer-reviewed International	ChAdOx1 (AstraZeneca)	**N:** 14,330 Intervention: 7,201 Control:7,179	Mean: 12.5 weeks Up to 17.1 weeks follow up: 1% (208 participants)	NR	NR	VE: 49.5% (95% CI 37.7 to 59.0%)	VE: 63.1% (95% CI 51.8 to 71.7)	No numerical evidence presented, graphical evidence only. No evidence of waning VE against symptomatic infection apparent from Kaplan Meier graph for the 7,382 patients followed for 12.8 weeks or 208 patients followed for 17.1 weeks post dose two.	low

Author, Country	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
Sadoff ,[30] peer-reviewed International	Ad26.COV2.S (Janssen)	**N:** 39,321 Intervention: 19,630 Placebo:19,691	Median: 8.3 weeks (range 0.1 - 17 weeks)	VE: 100% (95% CI 74.3 to 100)	VE: 75% (95% CI -25.2 to 97.4)	NR	VE 66.5% (95% CI 55.5 to 75.1)	No evidence of waning VE for moderate /severe COVID19 from Kaplan Meier plot among 30,000 participants followed for 11 weeks or the 1,000 patients followed for 15 weeks.	low
Polack, [32]* peer-reviewed International	BNT162b2 (Pfizer/BioNTech)	**N**:43,448 Intervention: 21,720 Placebo:21,728	Mean: 7.6 weeks Maximum: 14 weeks	VE: 75% (95%CI -52.0 to 99.5)	NR	NR	VE 95.0% (95% CI 90.3 to 97.6)	No evidence of waning VE against symptomatic infection in Kaplan Meier plot.	low
Frenck, [33]* peer-reviewed, 12-15 year old population of Polack. US	BNT162b2 (Pfizer/BioNTech)	Randomised: 2,264	Mean: 9.0 weeks Maximum: 17 weeks	No severe cases reported in either arm	NR	NR	VE 100% (95% CI 75.3 to 100)	VE against symptomatic infection ≥7 days after dose 2 to < 2 months: VE 100% (95% CI 74.8 to 100) ≥2 months after dose 2 to <4 months: VE 100% (95% CI –399.9, 100) (prior infection included)	
Thomas,[34]* peer-reviewed, follow-up of Polack [32] International	BNT162b2 (Pfizer/BioNTech)	**N**:44,060 Intervention: 22,030 Placebo: 22,030	Mean: 16.7 weeks 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% (95% CI 73.9 to 99.9)	NR	NR	91.3% (95% CI 89.0 to 93.2)	VE against symptomatic infection ≥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)	

Author, Country	Exposure#	Sample Size	Time since final vaccination	Primary outcomes: overall follow up		Secondary Outcomes: overall follow-up		Change in vaccine efficacy over time	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
								≥ 4 months: VE 83.7% (95% CI 74.7 to 89.9)	
Baden,[31] peer-reviewed US	mRNA-1273 (Moderna)	**N:** 28,207 Intervention: 14,134 Control:14,073	Median: 9 weeks (Range 0 – 13.9)	VE: 100% (95% CI NE to 1.0)	NR		VE 94.1% (95% CI 89.3 to 96.8%)	No evidence of waning efficacy in Kaplan Meier for the 2,381 patients followed for 12 weeks post dose 2.	low
El Sahly, (55) **US** **Follow up of Baden**[31]**~**	mRNA-1273 (Moderna)	**N:** Efficacy population - 28,451 FAS – 30,346	Median – 26.1 weeks (IQR 37.5 to 32.1).	VE: 98.2% (95% CI 92.8 to 99.6)	VE: 100% (95% CI NE to 100)	VE: 82.0% (95% CI 79.5 to 84.2)	VE: 93.2 (95% CI 90.9 to 94.8)	Symptomatic infection over time (PP) ≥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	low

^Results from Madhi[27] are also included in Voysey[28, 29] as part of their pooled analysis of four registered trials, using data from an earlier interim analysis.

*The studies highlighted yellow are part of the same trial, with Polack,[32] publishing initial results, Frenck[33] publishing results for adolescents (12-15 year olds) and Thomas[34] updating the Polack paper with longer follow-up time for trial participants.

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

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

3.1.2 BNT162b2 (Pfizer/BioNTech)

Polack et al.[32] 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).

In October 2020, the trial eligibility criteria were extended to include those aged 12 to 15 years in the US. Efficacy in this sub-population is reported by Frenck et al.[33] when the mean time since the second dose was nine weeks in the BNT162b2 (Pfizer/BioNTech) arm. No cases of severe disease or death from COVID-19 were noted in either arm. Efficacy (≥7 days after second dose) for symptomatic disease was estimated as 100% (95% CI 75.3 to 100) for seronegative patients. The estimate for efficacy between two and four months after dose two was also 100%, but there were few cases of COVID-19 to inform the analysis at this time point, so there is substantial uncertainty associated with this (95% CI -399.9 to 100).

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.[34] present updated results for all participants who were followed in the blinded portion of the trial.

VE for severe disease (regardless of previous history of SARS-CoV-2) was 95.7% (95% CI 73.9 to 99.9). Thomas et al.[34] also present information on efficacy data for symptomatic disease for the total seronegative population (≥12 years) both overall and over time. Thomas et al.[34] also present information on efficacy data for symptomatic disease for the total seronegative population (≥12 years) both overall and over time. Overall VE against symptomatic disease was 91.3% (95% CI 89.0 to 93.2).When stratified by time since the second dose was administered, VE was reported 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.

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 trial towards showing a decline in

VE 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, impact of different prioritisation policies may have been amplified. Participants who remain 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. Additionally, participants less than 16 years were only eligible to join the trial from October 2020; these individuals will have shorter follow-up and thus the longer-term efficacy data may not be applicable to the paediatric population.

Thomas et al.[34] also explicitly report data in relation to the Beta variant. In South Africa, where the Beta variant was dominant, VE was 100% (95% CI 53.5 to 100) for symptomatic disease.

3.1.3 mRNA-1273 (Moderna)

Baden et al.[31] 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. VE for symptomatic infection was estimated at 94.1% (95% CI 89.3 to 96.8). The trial was not powered to estimate VE for severe disease, no conclusions regarding efficacy for this outcome can be drawn. Estimates of vaccine efficacy for severe disease were lower for those ≥65 years compared with those aged less than 65 years, but the confidence intervals of the estimates overlap.

El Sahly et al. published an updated analysis of the mRNA-1273 (Moderna) trial originally published by Baden et al.[31] with a median follow-up of 26 weeks (IQR 24 to 28) after dose two.[55] The mRNA-1273 (Moderna) overall vaccine efficacy estimates were VE 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 health care 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).

3.1.4 Ad26.COV2.S (Janssen)

Sadoff et al.[30] 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).[30] 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 >28 days post-vaccination. The trial was not powered to estimate VE for mortality and no conclusions regarding efficacy for this outcome can be drawn. VE 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), VE 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.

Sadoff et al.[30] 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. Furthermore, there were no moderate to severe-critical cases in either arm after 12 weeks.[30]

3.1.5 ChAdOx1(Astra Zeneca)

Voysey et al.[28, 29] published the pooled efficacy of the ChAdOx1 (AstraZeneca) vaccine across four phase three RCTs conducted in three different countries; COV001 (UK), COV002 (UK), COV003 (Brazil) and COV005 (South Africa). For the purpose of this review, the results are considered as one RCT (n=14,330) as only pooled results are presented here. Results for COV005 are presented by Madhi et al. below.[27] All patients were seronegative at baseline with no evidence of previous SARS-CoV-2 infection. COV001 and COV005 enrolled healthy adults. COV002 and COV003 enrolled HCWs and other adults at an increased risk of exposure to SARS-CoV-2 infection. The trial primary efficacy analysis included 2,741 participants in

COV002 who received a low dose of vaccine for their first dose followed by a standard dose for their second vaccination. The results presented here reflect those who received two standard doses only.

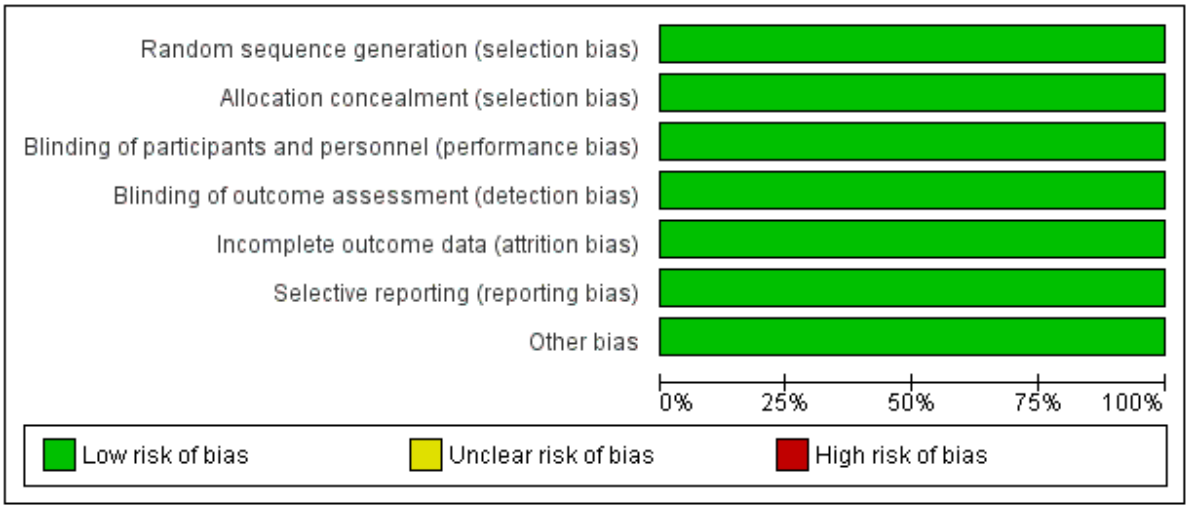
Mean follow-up time since the second dose was 12.5 weeks, with outcomes reported ≥14 days after the second dose. Changes in efficacy over time were not reported. There was limited evidence for hospitalisation, with nine hospitalisations in the placebo group and no hospitalisations in the ChAdOx1 (AstraZeneca) vaccine arm, therefore VE for severe disease was not reported. However, visual inspection of Kaplan Meier plots does not suggest any decline in efficacy for symptomatic infection for the approximately 7,400 participants who were followed for 12.8 weeks or the 208 patients followed for 17.1 weeks post-dose two. VE for symptomatic disease was estimated as 63.1% (95% CI 51.8 to 71.7).

Madhi et al.[27] report the efficacy of a phase three, double blind RCT of ChAdOx1 (AstraZeneca) in South Africa. Only adults aged ≥18 and ≤65 years of age with well-controlled or no chronic medical conditions were included. Efficacy was assessed ≥14 days after the second dose. The trial did not meet its primary efficacy endpoint versus symptomatic disease. Two doses of ChAdOx1 (AstraZeneca) vaccine were not found to be effective at preventing mild to moderate COVID-19 with an estimated VE of 21.9% (95% CI -49.9 to 59.8). Over 95.1% of sequenced cases during the trial were caused by the Beta variant. As there were no cases of severe COVID-19 in either arm, the trial is inconclusive as to whether ChAdOx1 (AstraZeneca) is effective against severe disease. The absence of severe cases may partly reflect the young and healthy demographic and clinical profile of patients enrolled in the trial.

3.1.6 Risk of bias of randomised controlled trials

The risk of bias assessment of the RCTs included in this evidence summary is presented in Figure 2. Collectively, the five studies were considered at low risk of bias across all the domains examined.[27-34, 39, 55, 85-101]

Figure 2 Risk of bias summary across RCTs



3.2 Vaccine effectiveness

3.2.1 Characteristics of included studies

Of the 44 observational studies, 32 were cohort studies,[36-40, 42-54, 58, 59, 61, 62, 64, 67, 70, 71, 73, 74, 76, 78-81] and 12 were case-control studies,[35, 38, 56, 60, 65-68, 72, 102, 103] of which six were a test-negative case-control design.[35, 56-58, 65, 66, 72] Twenty-nine studies examined vaccine effectiveness in the general population,[35-40, 42, 56-62, 64-70, 76, 78-81, 102, 104] of which six studies looked at hospitalised patients,[65-69, 102] five examined the difference in vaccine effectiveness between late and early vaccinees,[38, 42, 70, 80, 104] and four examined the difference between natural- and vaccine-derived immunity.[36, 76, 78, 81] Nine studies exclusively enrolled healthcare and other frontline workers,[44-47, 49, 50, 71-73, 105] three exclusively enrolled residents of LTC facilities,[52, 53, 74] and one study presented data from a mixture of HCWs, residents of LTC facilities and older people.[51] Two studies were conducted exclusively in populations with immunocompromising conditions or comorbidities.[54, 103] However, a number of other studies also presented information on a subgroup with immunocompromising conditions or comorbidities.[41, 56, 62, 82] The maximum follow-up reported was six months.

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	
General Population studies								
Andrews,[56] 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 100.0) 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)	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
	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) 20+ weeks 77.0 (70.3 to 82.3)	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	
	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)	
Bajema, [65] Peer reviewed US Test negative case control	BNT162b2 (Pfizer-BioNTech): Cases: 79.6%, Controls: 64.0% mRNA-1273(Moderna): Cases: 20.4% Controls: 36.0%	**N**: 1,175 Positive SARS-CoV-2 test – 388 (13.9% fully vaccinated) Negative SARS-CoV-2 test 787 (48% fully vaccinated)	Median – 11.8 weeks (IQR = 7.0–18.34 weeks)	COVID-19 associated Hospitalisation VE: 86.8 (80.4 to 91.1) During Delta variant predominance (1 July to 6 August) VE: 89.3 (80.1 to 94.3)	NR	NR	NR	Fair
Bruxvoort (a), [57] Preprint US Matched Prospective observational cohort study	mRNA-1273 (Moderna)	**N:** Vaccinated 352,878 Unvaccinated 352,878	Mean 15.44 weeks Max five months (22 weeks).	VE : 95.8 (92.5 to 97.6)	COVID-19 Hospital death VE: 97.9 (84.5 to 99.7).	VE: 87.4 (85.6 to 89.1).	VE: 88.3 (86.5 to 89.9)	Good
Bruxvoort (b), [58] Preprint US Test-negative case-control study	mRNA-1273 (Moderna)	**N:** Delta cases: 2,027 232 (11.4%) fully vaccinated	Up to 26 weeks after dose two.	Delta variant VE: 97.6 (92.8 to 99.2)	NR	*Any infection (Delta)* VE: 86.7 (84.3 to 88.7)		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	
		Controls: 10,135 4,588 (45.3%) fully vaccinated						
Chemaitelly (b),[(35)] Preprint Qatar Observational test-negative, case-control study design	BNT162b2 (Pfizer/BioNTech)	**N:** Cases: 173,496 Controls: 1,422,333	NR	VE by weeks after dose 2 0-4 weeks 95.4 (93.4 to 96.9) 5-9 weeks 94.2 (91.0 to 96.5) 10-14 weeks 91.8 (86.0 to 95.5) 15-19 weeks 86.4 (69.9 to 94.8) 20-24 weeks 95.3 (70.5 to 99.9) ≥25 weeks 71.5 (9.2 to 93.2)	VE by weeks after dose 2 0-4 weeks 93.9 (84.5 to 98.1) 5-9 weeks 90.0 (74.0 to 97.0) 10-14 weeks 93.4 (73.1 to 99.2) 15-19 weeks 80.4 (0.0 to 99.6) 20-24 weeks NR ≥25 weeks 0.0 (0.0 to 0.0)	VE by weeks after dose 2 0-4 weeks 72.1 (70.9 to 73.2) 5-9 weeks 65.8 (63.8 to 67.7) 10-14 weeks 55.5 (52.0 to 58.8) 15-19 weeks 29.7 (21.7 to 36.9) 20-24 weeks 0.0 (0.0 to 0.0) ≥25 weeks 0.0 (0.0 to 0.4)	VE by weeks after dose 2 0-4 weeks 79.6 (77.9 to 81.2) 5-9 weeks 70.8 (67.8 to 73.6) 10-14 weeks 60.6 (55.2 to 65.4) 15-19 weeks 49.6 (39.1 to 58.4) 20-24 weeks 0.0 (0.0 to 19.1) ≥25 weeks 0.0 (0.0 to 8.0)	Poor
De Gier, [(59)] preprint Preprint The Netherlands Cohort study	BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna), ChAdOx1-S (AstraZeneca), or Ad26.COV2-S (Janssen).	**N:** Total, 15,571 Fully vaccinated, 887, Partially vaccinated, 1,111 Unvaccinated, 13,574.	At least 20 weeks	*Hospitalisation** VE in Alpha period: 94 (93 to 95). VE in Delta period: 95 (94 to 95). *ICU admissions** VE in Alpha period: 93 (87 to 96). VE in Delta period: 97 (97 to 98).	NR	NR	NR	Fair
McKeigue,[(60)] **Preprint** **Scotland**	Vaccination with AstraZeneca or mRNA vaccine	**N:** 226,678 (23,467 fully vaccinated).	Median = 9.6 weeks. IQR = 6 – 12.7 weeks.	Delta dominant: After 19 May: **RR for severe disease:** 0.10 (0.08 to 0.14)	Delta dominant : After 19 May: **RR for hospitalisation**	NR	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	
Case control	(Pfizer or Moderna).				**or mortality:** 0.15 (0.13 to 0.17)			
	ChAdOx1 (AstraZeneca)			**RR for severe disease:** 0.14 (0.11 to 0.19).	**RR for hospitalisation or mortality:** 0.21 (0.18 to 0.23).			
	BNT162b2 (Pfizer/BioNTechOrmRNA-1273 (Moderna)			**RR for severe disease:** 0.09 (0.06 to 0.13).	**RR for hospitalisation or mortality:** 0.10 (0.08 to 0.12).			
Nunes, [61] Peer reviewed **Portugal** Cohort Study with crossover	mRNA vaccine: Comirnaty (BNT162b2 Pfizer.BioNTech) Spikevax (mRNA-1273)	65-79 years n = 878,489	Median 11.1 weeks IQR (10.1 – 13.4)	VE: 94 (88 to 97)	VE: 96 (92 to 98)	NR	NR	good
		N: 80+ years n = 460,820	Median 17.9 weeks IQR (16.0 – 20.9)	VE: 82 (72 to 89)	VE: 81 (74 to 87)			
Pawlowski,* [37] Peer-reviewed US (Mayo clinic and hospitals) Retrospective matched cohort study	BNT162b2 (Pfizer/BioNTech)	**N:** vaccinated 51,795 Unvaccinated 51,795	Median 10.0 weeks, IQR NR	VE: 88.3 (72.6 to 95.9)	NR	VE: 88.0 (84.2 to 91.0)	NR	Fair
	mRNA-1273 (Moderna)	**N:** vaccinated : 16,471 Unvaccinated: 16,471	Median 8.3 weeks, IQR (3.9, 11.1)	VE: 90.6 (76.5 to 97.1)	NR	VE: 92.3 (82.4 to 97.3)	NR	
Puranik,* [38], Preprint US (Mayo clinic and associated hospitals)	BNT162b2 (Pfizer/BioNTech)	**N:** vaccinated 22,064 Unvaccinated: 24,990	Mean 17.1 weeks standard deviation NR	VE: 85 (73.9 to 93.0)	NR	VE: 76.0 (69.0 to 81.0)	NR	Fair
	mRNA-1273 (Moderna)	**N:** vaccinated: 21,179	Mean 16.9 weeks	VE: 91.6 (81.0 to 97.0)	NR	VE: 86.0 (81.0 to 90.6)	NR	

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	
Retrospective matched cohort study		Unvaccinated: 24,990	standard deviation NR					
Polinski, [62] 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)	NR	VE: 69 (67 to 71)	NR	Poor
Pouwels,[39] preprint UK National longitudinal survey from UK National statistics agency.	BNT162b2 (Pfizer/BioNTech)	**N**: 743,526 individuals 384,543 (alpha dominant phase)	Median (IQR) weeks 8.43 (5 to 12.29)	NR	NR	Alpha: VE: 78 (68 to 84) Delta: VE: 80 (77 to 83)	Alpha: VE: 97 (96 to 98) Delta: VE: 84 (82 to 86)	Good
	ChAdOx1 (AstraZeneca)	358,983 (delta dominant phase)	5.86 (3.86 to 8.14)	NR	NR	Alpha: VE: 79 (56 to 90%) Delta: VE: 67 (62 to 71)	Alpha: VE: 97 (93 to 98) Delta: VE: 71 (66 to 74)	
Saciuk,[40] preprint preprint Israel Retrospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech)	**N:** 1,650,885	Median: 10.1 weeks 98 days (maximum)	VE: 93.4 (91.9 to 94.7)	VE: 91.1 (87 to 94)	VE: 93 (92.6 to 93.4)	NR	Fair
Sharma, [79] **Preprint** US Retrospective cohort study	mRNA-1273 (Moderna) **Comparators** Ad26.COV2.S (Janssen)	**N:** 1,511,382 mRNA-1273, 1,511,382 Ad26.COV2.S. 227,570	Median ~21 weeks 2% are followed for up to 28.57 weeks.	COVID-19 Hospitalisation Adjusted hazard ratio 0.27 (0.23 to 0.32)	NR	Documented SARS-CoV-2 infection: Adjusted hazard ratio 0.36 (0.33 to 0.38)	NR	Fair
	Exposure	**N:** 1,293,609	Median ~21 weeks	Adjusted hazard ratio 0.51 (0.43 to 0.60)	NR	Adjusted hazard ratio 0.54 (0.51 to 0.58)	NR	

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	
	BNT162b2 (Pfizer/BioNTech) **Comparators** Ad26.COV2.S (Janssen)	BNT162b2 (Pfizer/BioNTech) 1,293,609 Ad26.COV2.S.(Janssen) 227,570	2% are followed for up to 28.57 weeks.					
Tartof, [64] Peer reviewed US Retrospective cohort study	BNT162b2 (Pfizer-BioNTech)	**N:** Unvaccinated, 2,290,189 Fully vaccinated (2 doses plus ≥7 days), 1,043,289	Mean 14.7 weeks (range 0 to 26.0 weeks post-vaccination) SD – 7.8 weeks	VE (age 12 years and over): 90 (89 to 92)	NR	VE (age 12 years and over): 73 (72 to 74)	NR	Good
Hospitalised patients								
Grannis, [66] Peer reviewed US Test-negative case-control	BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2 (Janssen)	**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	To hospital admission Pfizer-BioNTech – 17.66 weeks Moderna – 17.09 weeks Janssen – 15.39 weeks	*Hospitalisation* VE = 86 (82 to 89) *Emergency/urgent care* VE = 82 (81 to 84 Vaccine type Pfizer-BioNTech VE :80 (73 to 85) Moderna 95 (92 to 97) Janssen 60 (31 to 77)	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	
Griffin,[67] Peer reviewed US Cohort study	1-dose Janssen (Ad26.COV2.S); 2-dose series of Moderna (mRNA-1273) OR Pfizer-BioNTech vaccine (BNT162b2)	**N:** Janssen (Johnson & Johnson): 1,830 (16.8%), Moderna: 3,047 (28%) Pfizer –BioNTech: 6,018 (55.2%) Unvaccinated: 30,801 (71.4%)	Median (IQR) 14 (10.57-17.14) weeks	Admitted to hospital ≤14 days after positive SARS-CoV-2 test date A significantly lower percentage of fully vaccinated (1.2%) persons were admitted to a hospital after their SARS-CoV-2 positive test result date compared with unvaccinated persons (4.2%) (p<0.001).	All Cause/COVID-19 $ A significantly lower percentage of deaths (0.2%) occurred among fully vaccinated persons than among partially vaccinated (0.5%) and unvaccinated (0.6%) persons (p<0.001)..	NR	NR	Poor
Self,[68] MMWR Early Release. US Case Control	Moderna – 476 (12.9%) Pfizer-BioNTech – 738 (20.0%) Janssen – 113 (3.1%)	**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%)	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	Full Surveillance Period Moderna 93 (91 to 95) Pfizer BioNTech 88 (85 to 91) Janssen 71 (56 to 81)	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	
Tenforde,[102] Published report (CDC) US Case-control	BNT162b2 (Pfizer/BioNTech) 59% MRNA-1273 (Moderna) 41%	**N:** Cases: 1,194 Controls: 1,895	Median 9.3 weeks, (IQR 5.84 to 13.25 weeks)	VE: 86 (82 to 88)	NR	NR	NR	Fair
Thompson (b), [69] 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	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)	Hospitalisation: BNT162b2 vaccine 87% (85 to 90) mRNA1273 vaccine 91 (89 to 93) Ad26.COV2.S vaccine 68 (50 to 79) ICU admissions: BNT162b2 or mRNA1273 vaccine 90 (86 to 93) Emergency department or urgent care visit: BNT162b2 vaccine 89 (85 to 91) mRNA1273 vaccine 92 (89 to 94)	NR	NR	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	
				Ad26.COV2.S vaccine 73 (59 to 82)				
General Population (Early vs Late)								
Goldberg[§],[(70)] Preprint Israel Retrospective cohort study	**Exposure**: Early vaccinees (BNT162b2 (Pfizer/BioNTech) vaccination in Jan 16-31) **Control:** Late vaccinees (BNT162b2 (Pfizer/BioNTech) in Feb, Mar, Apr and May.	**N:** Total – 9,395,923 Vaccinated - 4,785,245 Positive PCR test n=12,927 Severe COVID 19 n=348	Jan 16-31 – 27.92 weeks Feb 1-15 – 25.64 weeks Feb 16 – 28 – 23.5 weeks Mar 1 – 15 – 21.65 weeks Mar 16-31 – 19.52 weeks April – 17.24 weeks May – 12.96 weeks	Incidence Rate ratio (IRR) denoting **protection** against severe COVID-19 [95% CI] compared to the first period (January 16-31) <u>40 – 59 years</u> Feb: 2.2 (0.8 to 6.1) Mar: 2.8 (0.7 to 10.9) <u>60+ years</u> Feb: 1.2 (0.9 to 1.5) Mar: 1.7 (1.0 to 2.7)	NR	Incidence Rate ratio (IRR) denoting **protection** against documented SARS-CoV-2 infection [95% CI] compared to the first period (January 16-31) <u>16-39 years</u> Feb 1-15: 0.9 (0.8 to 1) Feb 16-28: 1.2 (1 to 1.3) Mar 1-15: 1.3 (1.1 to 1.4) Mar 16-31: 1.5 (1.4 to 1.7) April: 2.0 (1.7 to 2.3) May: 2.0 (1.6 to 2.5) <u>40 – 59 years</u> Feb 1-15: 1.1 (1 to 1.1) Feb 16-28: 1.1 (1 to 1.2) Mar 1-15: 1.2 (1.1 to 1.4) Mar 16-31: 1.6 (1.4 to 1.8)	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	
						April: 1.9 (1.6 to 2.4) May: 2.3 (1.6 to 3.3) <u>60+ years</u> Feb 1-15: 1 .1 (1.1 to 1.2) Feb 16-28: 1.3 (1.1 to 1.5) Mar 1-15: 1.6 (1.3 to 2) Mar 16-31: 1.6 (1.3 to 2) April: 2.1 (1.5 to 2.9) Mar: 2.1 (1.2 to 3.4)		
Israel,[(42)] preprint Israel (Country) Retrospective cohort study	**Exposure** ≥146 days since BNT162b2 (Pfizer/BioNTech) vaccination **Control** <146 days since BNT162b2 (Pfizer/BioNTech) vaccination	N = 33,993	Median: 20.9 weeks	NR	NR	aOR early v. late vaccinees <u>Pooled</u>: 2.06 (1.69 to 2.51)	NR	Fair
Kertes, [(80)] Preprint Israel Retrospective cohort study	**Exposure:** Participants vaccinated between January - February **Control:** Participants vaccinated	**N:** 1,432,098 Participants vaccinated between January –February: 821,231	Maximum follow up period: 21.6 weeks	NR	NR	OR early vs. late vaccinees 1.61 (1.45 -1.79)	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	
	between March - May	Participants vaccinated between March – May: 601,867						
Mizrahi,[104] preprint Israel Retrospective cohort study	**Exposure:** Early vaccinees **Control** Late vaccinees	**N:** 658,354	At least 13.1 weeks for early vaccinees.	NR	NR	aOR early vs. late vaccinees. 1.53 (1.40 to 1.68)		Fair
Puranik, [75] US Test-negative case-control study	**Exposure** Later vaccination **Control** Early vaccination BNT162b2 (Pfizer/BioNTech)	**N:** **Cases:** 652 ≥1positive symptomatic test after full vaccination (BioNTech, Pfizer vaccine (BNT162b2)) **Controls:** 5,946 (analysable data for primary analysis) *≥1 negative symptomatic test after full vaccination*	Median follow-up time since vaccination for cases: 17.8 weeks max follow up: 23.71 weeks	NR	NR	NR	Adjusted OR of symptomatic infection after full vaccination (Time relative to full vaccination) aOR (95% CI): 30 days 1.81, (0.68 to 4.82) 60 days 2.32, (0.97 to 5.52) 90 days 3.5, (1.47 to 8.35) 120 days3.21, (1.33 to 7.74)	Poor
General Population (SARS-cov2 infection derived versus Vaccine Derived immunity								
Gazit,[36] Pre-print Israel	BNT162b2 (Pfizer/BioNTech)	**N:** Fully vaccinated: 673,676	At least 12.9 weeks	OR exposure v. control	NR	aOR: exposure v. control 13.06 (8.08 to 21.11)	aOR: exposure v. control 27.02 (12.7 to 57.5)	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	
Retrospective observational study		Analysis 1 16,215 matched in each group		OR 8.06 (1.01 to 64.55)				
		Analysis 2 40,035 matched in each group		OR 6.7 (1.99 to 22.56)		aOR 5.96 (4.85 to 7.33)	aOR 7.13 (5.51 to 9.21)	
Kojima,[76] Preprint US Retrospective cohort study	**Control:** (Group 1) SARS-CoV-2 naïve and unvaccinated# (Group 2) previous SARS-CoV-2 infection, unvaccinated **Exposure (Group 3)** fully vaccinated (either the BNT162b2 (Pfizer/BioNTech) or mRNA-1273 vaccines (Moderna))	**N:** **(**1) SARS-CoV-2 naïve and unvaccinated# (n=4,313) (2) previous SARS-CoV-2 infection, unvaccinated~ (n=254) (3) fully vaccinated (either the BNT162b2 or mRNA-1273 vaccines) & (n=739)	Maximum follow up: Group 1 and 2: 31.57 weeks Group 3: 59.85 weeks	NR	NR	*Relative risk of reinfection* The IRR of those vaccinated compared to SARS-CoV-2 naïve was 0.06 (95% CI: 0.02 to 0.16). The IRR of those vaccinated compared to prior SARS-CoV-2 was 0 (95% CI: 0 to 4.98)	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	
Shrestha,[81] Preprint US **Retrospective cohort study**	**Exposure** Previously infected and vaccinated (Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) or Johnson & Johnson vaccines/Janssen (Ad26.COV2-S).	Vaccinated: 1,220 of 2,579 (47%) Unvaccinated 1,359 of 2,579 (53%)	Median follow up: 8.77-11.43 weeks	NR	NR	NR	In a Cox proportional hazards regression model, vaccination was not associated with a significantly lower risk of SARS-CoV-2 infection among those previously infected (HR 0.313, 95% CI 0 to Infinity).	Fair
	Exposure: Not previously infected and vaccinated (Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) or Johnson & Johnson vaccines/Janssen (Ad26.COV2-S).	Vaccinated: 28,855 of 49,659 (58%) Unvaccinated: 20,804 of 49,659 (42%)	Median follow up: 8.77-11.43 weeks	NR	NR	NR	In a cox proportional hazards regression model, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI: 0.015 to 0.061)	

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	
YoungXu, [78] Preprint US Retrospective cohort study	mRNA-1273 (Moderna)	N: 14,458 fully vaccinated with Moderna	At least three months	Age ≥65: HR 0.76 (95% CI: 0.31-1.83) Age <65: HR<65: 1.46 (95% CI: 0.55-3.88)	Age ≥65: HR 0.70 (95% CI: 0.04-11.79) Age <65: N/A	Age ≥65: HR 0.34 (95% CI: 0.14,0.78) Age <65: HR 0.35 (95% CI: 0.11, 1.13)	NR	Poor
	BNT162b2 (Pfizer/BioNTech)	N: 23,105 fully vaccinated with Pfizer	At least three months	Age ≥65: 0.82 (95% CI: 0.36 to 1.88) Age <65: 2.33 (95% CI: 0.92-5.93)	NR	Age ≥65: HR 0.32 (95% CI: 0.14 to0.70) Age <65: HR 0.64 (95% CI: 0.24 to 1.69)	NR	
Health care and frontline workers								
Alali,[44] Preprint Kuwait Retrospective Cohort Study (crossover)	BNT162b2 (Pfizer/BioNTech)	**N:** 3,246 Vacc: 28.% unvacc 18% (at end study)	Mean 15.0 weeks, maximum: 20.7 weeks	NR	NR	NR	VE: 94.5 (89.4 to 97.2).	Poor
Bianchi,[45] Preprint Italy Matched cohort study	BNT162b2 (Pfizer/BioNTech)	**N:** 6,136 HCWs Vaccinated group 5,351 (87.2%) Unvaccinated group 787 (12.8%)	Median 19.9 weeks IQR (19.3, 20.4)	9 hospitalisations reported, including 8 (1.0%) HCWs in the unvaccinated group and 1 (0.02%) HCW in the vaccinated group (p<0.0001).	NR	VE: 14–41 days 94.8 (87.0 to 97.8) 42–69 days 83.0 (.0 to 92.0) >69 days 81.0 (42.0 to 94.0)	14–41 days: 97.2 (90.3 to 99.2) 42–69 days: 85.0 (63.0 to 94.2) >69 days 88.0% (42.0 to 97.6)	Poor

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	
Thompson,[47]& Peer-reviewed US prospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech) 67% mRNA-1273 (Moderna) 33%	vaccinated 2,510 (161,613 person days) Unvaccinated 3,964 (127,971 person days)	Median 11.9 weeks IQR (9.6, 13.6)	NR	NR	VE: 91 (76 to 97)	NR	Fair
Fowlkes,[105]&published report (CDC), (update of Thompson) US published report (CDC), (update of Thompson) US prospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech) 65% mRNA-1273 (Moderna) 33% Ad26.COV2.S (Janssen) 2%	Unvaccinated 4,135 (181,357 person days) vaccinated 2,976 (455,175 person days)	Median 27 weeks (fully vaccinated) IQR (18.4 to 29.9 weeks)	NR	NR	VE: 80 (69 to 98)	NR	Fair
Ghosh,[46] Peer-reviewed India Cohort Study with crossover	ChAdOx1 (AstraZeneca) (Covishield®)	**N:** 1,595,630 End study: 82.2% fully vaccinated.	Mean 8.4 weeks, range NR	NR	VE: 98.53 (0.00 to 99.99)	VE: 91.81 (88.79 to 94.02)	NR	Poor
Giansante, [71] Peer reviewed Italy Retrospective cohort study	mRNA vaccine	**N:** 9,839	Mean 11.67 weeks (sd NR	15 cases hospitalised in unvaccinated, 0 cases in fully vaccinated.	NR	VE: 84.8 (73.2 to 91.4)	VE: 87.1 (69.3 to 94.6	Poor
Issac,[49] Preprint India Prospective cohort study	ChAdOx1 (AstraZeneca)	324 healthcare workers Vaccinated: 243 Unvaccinated: 80	At least 15 weeks, range NR	NR	NR	VE: 84.95 (NR p<0.05).	NR	Poor
Katz,[73] Preprint	BNT162b2 (Pfizer/BioNTech)	N: Total – 1,250	Median – 11.11 weeks	NR	NR	VE: 94.5 (82.6 to 98.2%)	VE: 97.0 (72.0 to 99.7).	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	
Israel, Prospective Cohort Study Covid-19 Vaccine Effectiveness in Healthcare Personnel in six Israeli Hospitals (CoVEHPI)		Vaccinated – 998 (79.8%) Unvaccinated – 252 (20.2%)	(10.54 to 10.82 weeks)					
Pilishvili, [72] 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)	Good
Yassi,[50] Peer-reviewed Canada , Cohort study crossover	BNT162b2 (Pfizer/BioNTech) (93.3%) mRNA-1273 (Moderna) (6.6%)	**N:** 25,116 HCWs (7,328 fully vaccinated)	Median 7.7 weeks (IQR 6.3, 8.9)	NR	NR	VE: 79.2 (64.6 to 87.8)	NR	Poor
Hcws/LTC/Homecare								
Emborg,[51] Preprint Denmark Retrospective cohort study	BNT162b2 (Pfizer/BioNTech) (all subgroups) LTC residents	Total (vaccinated) 46,101 (40,061)	Median 10.2 weeks (IQR 10.0;11.0)	VE: 75 (46 to 89)	(Covid-19 related) VE: 89 (81 to 93)	VE: 53 (29 to 69)	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	
	65PHC (65 years old, requiring practical help and care)	61,805 (45,924)	Median 8.6 weeks (IQR 4.3, 9.3)	VE: 87 (70 to 95)	VE: 97 (88 to 99)	VE: 86 (78 to 91)		
	HCWs	425,799 (112,824)	Median 9.6 weeks (IQR 8.3, 10.3)	VE: not estimated due to small numbers	VE: not estimated - small numbers	VE: 80 (77 to 83)		
Lefèvre,[52] Preprint France Retrospective cohort study	BNT162b2 (Pfizer/BioNTech)	**N**: 378 Vaccinated: 279 Unvaccinated: 40	mean 8.7 weeks, sd NR	VE 86 (67 to 94)	NR	VE: 49 (14 to 69)	NR	Fair
Muhsen,[53] Preprint Israel Prospective cohort study	BNT162b2 (Pfizer/BioNTech)	vaccinated 6,960 unvaccinated 2,202	Median 11.4 weeks IQR NR	NR	NR	VE: 89 (83 to 93)	NR	Fair
Subbarao, [74] Preprint England Observational population study (cohort study with crossover)	BNT162b2 (Pfizer/BioNTech) ChAdOx-1 (AstraZeneca)	N: 219,733 19,056 (8.7%) remained unvaccinated, 22,074 (10%) one dose of vaccine 178,603 (81.2%) received two doses of vaccine	Mean 11.0 weeks, no measure of spread	NR	Death within 28 days of positive SARS-CoV-2 test Both vaccines combined VE 1-14 days VE: 87 (68 to 95) 15+ days VE: 78 (36 to 92)	Both vaccines combined VE 15-28 days VE: 70 (56 to 80) 29-60 days VE: 73 (6 to 80) 61+ days VE: 65 (50 to 76)	NR	Fair
	BNT162b2 (Pfizer/BioNTech)				*VE* 15+ days VE: 72 (23 to 90)	VE 15-28 days VE: 71 (53 to 82) 29-60 days		

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: 78 (65 to 86) 61+ days VE: 72 (52 to 83)		
	ChAdOx-1 (AstraZeneca)				*VE* 15+ days VE: 89 (47 to 98)	VE 15-28 days VE:71 (53 to 83) 29-60 days VE: 69 (53 to 79) 61+ days VE: 58 (35 to 73)		
Individuals with co-morbidities or immunocompromising conditions								
Chemaitelly,[54] 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
McKeigue, [82] Preprint Scotland Case control	Vaccination with AstraZeneca or mRNA vaccine (Pfizer or Moderna).	**N*:** 226,678 (23,467 fully vaccinated).	Median = 9.57 weeks. IQR = 6 – 12.71 weeks (from ref	*Severe Disease*** No risk condition RR# 0.07 (95% CI 0.05 to 0.10) VE: 93 (90 to 95) Moderate risk condition RR 0.11 (0.08 to 0.15) VE: 89 (85 to 92)	*Hospitalisation or mortality**** No risk condition RR# 0.13 (0.11 to 0.15) VE = 87% (85 to 89) Moderate risk condition RR 0.15 (0.13 to 0.17)	NR	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	
				Condition eligible for shielding RR 0.34 (0.24 to 0.48) VE: 66 (52 to 76)	Condition eligible for shielding RR 0.33 (0.28 to 0.39) VE: 67 (61 to 72%)			
	ChAdOx1 (AstraZeneca)			*RR for severe disease:* No risk condition RR# 0.06 (0.04, 0.10) Moderate risk condition RR 0.14 (0.10, 0.19) Condition eligible for shielding RR 0.37 (0.25, 0.54) VE: 63 (46 to 75)	*RR for hospitalisation or mortality*: No risk condition RR# 0.16 (0.14, 0.19) Moderate risk condition RR 0.20 (0.17, 0.24) Condition eligible for shielding RR 0.37 (0.31, 0.45)			
	BNT162b2 (Pfizer/BioNTech) Or mRNA-1273 (Moderna)			*RR for severe disease:* No risk condition RR# 0.08 (0.04, 0.15) Moderate risk condition RR 0.06 (0.04, 0.10) Condition eligible for shielding RR 0.28 (0.16, 0.49) VE: 72 (51 to 84).	*RR for hospitalisation or mortality:* No risk condition RR# 0.09 (0.07, 0.11) Moderate risk condition RR 0.08 (0.07, 0.11) Condition eligible for shielding RR 0.28 (0.20, 0.38)			

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	
Tenforde (sub-group analysis),[102] Published report (CDC) US Case-Control	BNT162b2 (Pfizer/BioNTech): 59% mRNA-1273 (Moderna): 41%	**N:** Cases: 205 Controls: 447 (21% of the overall study population)	Median 9.3 weeks (IQR 5.8 to 13.3 weeks) - in study overall	VE: 63 (44 to 76)	NR	NR	NR	Fair

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.

Further details on Quality Appraisal is provided in Appendix B.

Analyses from Pawloski et al.[37] and Puranik et al.[38] are based on an overlapping patient cohort.

& - Shaded studies represent multiple reports of the same study.

§Goldberg et al. also reported results for vaccine effectiveness against severe disease and infection comparing vaccinated with unvaccinated individuals, results available in Appendix C.

Key: CDC - Centers for Disease Control and Prevention, CI – confidence interval, HCW – health care worker, IQR inter-quartile range, LTC – long-term care, sd – standard deviation, NR - not reported, US – United States, 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	Quality appraisal
General population					
Andrews, [56] 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	VE against **hospitalisation** by weeks after second dose (Delta): 2-9 weeks: 98.4% (95% CI 97.9 to 98.8) 10-14 weeks: 96.5% (95% CI 95.9 to 97.1) 15-19 weeks: 94.4% (95% CI 93.4 to 95.2) 20+ weeks: 92.7% (95% CI 90.3 to 94.6) VE against **mortality** by weeks after second dose (Delta) 2-9 weeks: 98.2% (95% CI 95.9 to 99.2) 10 to 14 weeks: 95.2% (95% CI 93.0 to 96.7) 15 to 19 weeks: 93.9% (95% CI 91.1 to 95.8) 20+ weeks: 90.4% (95% CI 85.1 to 93.8) VE against **symptomatic infection** by weeks after second dose (Delta) week 1: 92.4 (95% CI 92.1 to 92.7) 2 to 9 weeks: 89.8 (95% CI 89.6 to 90.0) 10 to 14 weeks: 80.3 (95% CI 79.9 to 80.6) 15 to 19 weeks: 73.4 (95% CI 72.9 to 73.9) 20+ weeks: 69.7 (95% CI 68.7 to 70.5)	Good
	ChAdOx1 (AstraZeneca)		Up to 20+ weeks	VE against **hospitalisation** by weeks after second dose (Delta): week 1: 93.9 (95% CI 91.3 to 95.7) 2 to 9 weeks: 95.2 (95% CI 94.6 to 95.6) 10 to 14 weeks: 91.4 (95% CI 90.5 to 92.2) 15 to 19 weeks: 86.8 (95% CI 85.1 to 88.4) 20+ weeks: 77.0 (95% CI 70.3 to 82.3) 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)	

Author, Country Study Design	Exposure#	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
				VE against **symptomatic infection** by weeks after second dose (Delta) Week 1: 62.7 (95% CI 61.7 to 63.8) 2 to 9 weeks: 66.7 (95% CI 66.3 to 67.0) 10 to 14 weeks: 59.3 (95% CI 58.8 to 59.9) 15 to 19 weeks: 52.6 (95% CI 51.7 to 53.5) 20+ weeks: 47.3 (95% CI 45.0 to 49.6)	
	mRNA-1273 (Moderna)		Up to 14 weeks	VE against **hospitalisation** by weeks after second dose (Delta): Week 1: 97.5 (95% CI 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 (95% CI 94.4 to 95.9) 2-9 weeks: 94.5 (95% CI 94.1 to 95.0) 10-14 weeks: 90.3 (95% CI 67.2 to 97.1)	
Bajema, (65) Peer-reviewed US Test negative case control	BNT162b2 - Pfizer-BioNTech (Cases: 79.6%, Controls–64.0%) mRNA-1273 – Moderna (Cases: 20.4% Controls: 36.0%)	**N**: 1,175 Positive SARS-CoV-2 test – 388 (13.9% fully vaccinated) Negative SARS-CoV-2 test 787 (48% fully vaccinated)	Median – 11.8 weeks (IQR = 7.0–18.34 weeks)	VE against **hospitalisation** by days after dose <90 days VE = 86.1 (95% CI 76.5 to 91.8) ≥90 days VE = 87.2% (95% CI 78.2 to 92.5)	Fair
Bruxvoort, (57) Pre-print USA Matched Prospective observational cohort study	mRNA-1273 (Moderna)	**N:** Vaccinated 352,878 Unvaccinated 352,878	Mean 15.44 weeks Maximum 22 weeks.	Kaplan Meier presented for each outcome but these results are not adjusted for confounding factors	Good
Bruxvoort, , (58) Pre-print USA	mRNA-1273 (Moderna)	**N:** Delta cases: 2,027	Up to 26 weeks after dose two.	VE against any **infection** by days after dose 2 Delta variant	Good

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
Test-negative case-control study		232 (11.4%) fully vaccinated Controls: 10,135 4,588 (45.3%) fully vaccinated		14-60 94.1 (90.5-96.3) 61-90 88.7 (85.0, 91.5) 91-120 85.9 (81.1, 89.5) 121-150 77.0 (69.1, 82.9) 151-180 80.0 (70.2-86.6) >180 days Not Estimable	
Chemaitelly,[(35)] Preprint Qatar Observational test-negative, case-control study design	BNT162b2 (Pfizer/BioNTech)	N: Cases: 173,496 Controls: 1,422,333	NR	VE against **hospitalisation** by weeks after dose 2 0-4 weeks: 95.4 (95% CI 93.4 to 96.9) 5-9 weeks: 94.2 (95% CI 91.0 to 96.5) 10-14 weeks: 91.8 (95% CI 86.0 to 95.5) 15-19 weeks: 86.4 (95% CI 69.9 to 94.8) 20-24 weeks: 95.3 (95% CI 70.5 to 99.9) ≥25 weeks: 71.5 (95% CI 9.2 to 93.2) VE against **mortality** by weeks after dose 2 0-4 weeks 93.9 (95% CI 84.5 to 98.1) 5-9 weeks 90.0 (95% CI 74.0 to 97.0) 10-14 weeks 93.4 (95% CI 73.1 to 99.2) 15-19 weeks 80.4 (95% CI 0.0 to 99.6) 20-24 weeks NR ≥25 weeks NR VE against any **infection** by weeks after dose 2 0-4 weeks 72.1 (95% CI 70.9 to 73.2) 5-9 weeks 65.8 (95% CI 63.8 to 67.7) 10-14 weeks 55.5 (95% CI 52.0 to 58.8) 15-19 weeks 29.7 (95% CI 21.7 to 36.9) 20-24 weeks 0.0 (95% CI 0.0 to 0.0) ≥25 weeks 0.0 (95% CI 0.0 to 0.4) VE against symptomatic **infection** by weeks after dose 2 0-4 weeks 79.6 (95% CI 77.9 to 81.2) 5-9 weeks 70.8 (95% CI 67.8 to 73.6) 10-14 weeks 60.6 (95% CI 55.2 to 65.4) 15-19 weeks 49.6 (95% CI 39.1 to 58.4) 20-24 weeks 0.0 (95% CI 0.0 to 19.1)	Poor

Author, Country Study Design	Exposure#	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
				≥25 weeks 0.0 (95% CI 0.0 to 8.0) Additional results over time presented in the data extraction table.	
De Gier, [59] Preprint The Netherlands Cohort study	BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna), ChAdOx1-S (AstraZeneca), or Ad26.COV2-S (Janssen).	**N:** Total, 15,571 Fully vaccinated, 887, Partially vaccinated, 1,111 Unvaccinated, 13,574.	at least 20 weeks	VE against **hospitalisation** by weeks after fully vaccinated 0-4 weeks: Age 15-49: 99% (95% CI: 97-99); Age 50-69: 98% (95% CI: 97-98); Age 70+: 90% (95% CI: 85-93) 5-9 weeks: Age 15-49: 93% (95% CI: 88-96); Age 50-69: 97% (95% CI: 96-98); Age 70+: 92% (95% CI: 90-93) 10-14 weeks: Age 15-49: 75% (95% CI: 56-86); Age 50-69: 90% (95% CI: 85-93); Age 70+: 90% (95% CI: 88-92) 15-19 weeks: Age 15-49: 97% (95% CI: 76-100); Age 50-69: 92% (95% CI: 84-96); Age 70+: 91% (95% CI: 88-92) 20+ weeks: Age 15-49: 97% (95% CI: 87-99); Age 50-69: 98% (95% CI: 94-99); Age 70+: 91% (95% CI: 87-94) VE against **ICU admission** by weeks after fully vaccinated 0-4 weeks: Age 15-49: 100% (95% CI: --); Age 50-69: 99% (95% CI: 98-99); Age 70+: 99% (95% CI: 93-100) 5-9 weeks: 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: Age 15-49: 82% (95% CI: 29-96); Age 50-69: 93% (95% CI: 85-96)	Fair

Author, Country Study Design	Exposure#	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
				Age 70+: 96% (95% CI: 93-98) 15-19 weeks Age 15-49: 100% (95% CI: --) Age 50-69: 89% (95% CI: 70-96) Age 70+: 97% (95% CI: 89-99) 20+ weeks Age 15-49: 100% (95% CI: --) Age 50-69: 100% (95% CI: --) Age 70+: 90% (95% CI: 57-98)	
McKeigue, [60] Preprint Scotland Case control	Vaccination with ChAdOx1-S (AstraZeneca) or mRNA vaccine (that is, BNT162b2 (BioNTech/Pfizer) or mRNA-1273 (Moderna)	**N:** Total, 226,678 Fully vaccinated, 23,467	Median (IQR) wks: 9.6 (6-12.7) wks.	For severe disease: Modelled waning effect half-life of 27 (95% CI 14 to 143) days, constant efficacy 82%; (weak evidence favouring this model over the best-fitting model with waning to zero efficacy). For hospitalised or fatal COVID-19: Modelled waning effect half-life of 17 (95% CI 9 to 39) days, constant efficacy of 83%.	Good
Nunes, [61] peer reviewed Portugal Cohort Study with crossover	mRNA vaccine: Comirnaty (BNT162b2 Pfizer.BioNTech) Spikevax (mRNA-1273)	65-79 years n = 878,489	Median 11.1 weeks IQR (10.1 – 13.4)	NR	Good
		N: 80+ years n = 460,820	Median 17.9 weeks IQR (16.0 – 20.9)	**Hospitalisation** 14-41 days VE: 82% (95%CI 64% to 91%) 42-69 days VE: 81% (95%CI 61% to91%)	

Author, Country Study Design	Exposure#	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
				70-97 days VE: 78% (95%CI 57% to 88%) 98+ days VE: 89% (95%CI 71% to 96%) **Mortality** 14-41 days VE: 86% (95%CI 68% to 93%) 42-69 days VE: 84% (95%CI 70% to 91%) 70-97 days VE: 87% (95%CI 77% to 92%) 98+ days VE: 74% (95%CI 60% to 83%)	
Polinski,[62]	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.	Poor
Pouwels,[39] preprint 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: 8.4 (5 to 12.3)	OR for **testing positive** per 30 days after ≥14 days after dose 2 v. unvaccinated OR 1.22 (95% CI 1.06-1.41) (p=0.007)	Good
	ChAdOx1 (AstraZeneca)		5.86 (3.86 to 8.14)	(Measure as above) OR 1.07 (95% CI 0.98-1.18, p=0.15)	
Tartof, [64] peer reviewed	BNT162b2 (Pfizer-BioNTech)	**N:** Unvaccinated, 2,290,189	Mean 14.7 weeks (Range 0 to 26.0 weeks post-	VE against (any) infection (aged 12 years and over)	Good

<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</th><th>Quality appraisal</th></tr>
<tr><td>US
Retrospective cohort study</td><td></td><td>Fully vaccinated (two doses plus ≥7 days), 1,043,289</td><td>vaccination) SD: 7.8 weeks</td><td>2 - < 3months 78 (76-79)
3 - <4months 68 (65-70)
4 - <5 months 61 (58-64)
>=5 months 47 (43-51)

VE against (any) hospitalisation (aged 12 years and over)
2 - < 3months 92 (89-95)
3 - <4months 93 (89-95)
4 - <5 months 91 (87-93)
>=5 months 88 (82-92)</td><td></td></tr>
<tr><td colspan="6">Hospitalised patients</td></tr>
<tr><td>Self,[68]
MMWR Early Release.
US
Case Control</td><td>Moderna – 476 (12.9%)

Pfizer-BioNTech – 738 (20.0%)

Janssen – 113 (3.1%)</td><td>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%)</td><td>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</td><td><table><tr><th>Days after full vaccination</th><th>Moderna</th><th>Pfizer</th><th>Janssen</th></tr><tr><td>>28</td><td>-</td><td>-</td><td>68% (49 to 80)</td></tr><tr><td>14-120</td><td>93% (90 to 95)</td><td>91% (88 to 93)</td><td>-</td></tr><tr><td>>120</td><td>92% (87 to 96)</td><td>77% (67 to 84)</td><td>-</td></tr></table></td><td>Fair</td></tr>
<tr><td>Tenforde,[102]
published report (CDC),
US
Case-control</td><td>BNT162b2 (Pfizer/BioNTech) 59%
MRNA-1273 (Moderna) 41%</td><td>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>
Weeks 2-12: VE 86% (95% CI 82% to 90%)
Weeks 13-24: VE 84% (95% CI 77% to 90%)</td><td>Fair</td></tr>
<tr><td>Thompson, [69]
US</td><td>BNT162b2 (Pfizer/BioNTech)
mRNA-1273 (Moderna)
Ad26.Cov2.S (Janssen)</td><td>Hospitalisations:
BNT162b2 (Pfizer/BioNtech) 8,500</td><td>Hospitalisation – Median - 53 IQR (33 to 75)</td><td><u>VE against hospitalisation</u></td><td>Good</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</th><th>Quality appraisal</th></tr>
<tr><td>Test negative case control</td><td></td><td>mRNA-1273 (Moderna)
6,374

Ad26.COV2.S (Janssen)
707

Unvaccinated
20,406</td><td>ICU admission – Median - 52 (IQR 34 to 73)
Emergency department/Urgent Care – Median 50 (IQR 31 to 73)</td><td>
<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</td><td>(91% (85% to 94)</td><td>≥ 56</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 colspan="2"></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 colspan="2"></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 colspan="2">-</td></tr>
<tr><td>≥112</td><td>83% (64 to 92)</td><td>≥112</td><td>95% (79 to 99)</td><td colspan="2"></td></tr>
</table>

VE against emergency department and urgent care (ED/UC) medical events
<table>
<tr><th>Days post dose 2</th><th>Pfizer-BioNTech</th><th>Days post dose 2</th><th>Moderna</th><td>Days post dose</td><th>Janssen</th></tr>
</table>
</td><td></td></tr>
</table>

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
				14-27 days 93% (87 to 96) **28 to 41** 94% (90 to 97) **42-55 days** 93% (81 to 87) **56 to 69 days** 82% (68 to 90) **70 to 83 days** 80% (66 to 88) **84 to 97 days** 91% (82 to 96) **98 to 111 days** 78% (61 to 87) **≥112 days** 83% (64 to 92) **14-27** 90% (81 to 95) **28 to 41** 96% (92 to 98) **42-55** 93% (85-96) **≥ 56** 90% (79-95) **59 to 69** 91%(79 – 96) **70-83** 91% (79 – 97) **84-97** NR - no breakthrough cases **≥112** 90% (52 to 98) **14-27** 67% (30 to 84) **28 to 41** 80% (52 to 92) **42-55** 58% (5 to 81) **≥ 56** 87% (71 to 94)	
General Population (Early vs Late)					
Goldberg[§],[(70)] **Preprint** **Israel** **Retrospective cohort study**	**Exposure**: Early vacinees (BNT162b2 (Pfizer/BioNTech) vaccination in Jan 16-31) **Control:** Late vaccinees (BNT162b2 (Pfizer/BioNTech) in Feb,Mar,Apr and May.	**N:** Total – 9,395,923 Vaccinated - 4,785,245 Positive PCR test n=12,927 Severe COVID 19 n=348	Jan 16-31 – 27.92 weeks Feb 1-15 – 25.64 weeks Feb 16 – 28 – 23.5 weeks Mar 1 – 15 – 21.65 weeks Mar 16-31 – 19.52 weeks April – 17.24 weeks	Incidence rate ratio; protection against severe COVID-19 compared to being vaccinated in the first period (January 16-31) by month of vaccination 40 – 59 years Feb 2.2 (0.8 to 6.1) Mar 2.8 (0.7 to 10.9) 60+ Feb 1.2 (0.9 to 1.5) Mar 1.7 (1.0 to 2.7)	Fair

Author, Country Study Design	Exposure#	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
			May – 12.96 weeks	Incidence rate ratio; protection against documented SARS-CoV-2 infection compared to the first period (16-31 January) by month of vaccination <u>16-39</u> Feb 1-15 0.9 (0.8 to 1) Feb 16-28 1.2 (1 to 1.3) Mar 1-15 1.3 (1.1 to 1.4) Mar 16-31 1.5 (1.4 to 1.7) April 2 (1.7 to 2.3) May 2 (1.6 to 2.5) 40 – 59 Feb 1-15 1.1 (1 to 1.1) Feb 16-28 1.1 (1 to 1.2) Mar 1-15 1.2 (1.1 to 1.4) Mar 16-31 1.6 (1.4 to 1.8) April 1.9 (1.6 to 2.4) May 2.3 (1.6 to 3.3) 60+ Feb 1-15 1.1 (1.1 to 1.2) Feb 16-28 1.3 (1.1 to 1.5) Mar 1-15 1.6 (1.3 to 2) Mar 16-31 1.6 (1.3 to 2) April 2.1 (1.5 to 2.9) Mar 2.1 (1.2 to 3.4)	
Israel,[42] preprint Israel (Country) Retrospective cohort study	**Exposure** ≥146 days since BNT162b2 (Pfizer/BioNTech) vaccination **Control** <146 days since BNT162b2 (Pfizer/BioNTech) vaccination	N = 33,993	Median: 20.9 weeks	aOR early vs. late vaccinees <u>Pooled</u>: 2.06 (95% CI 1.69 to 2.51)	Fair
Kertes, [80] Preprint Israel	**Exposure:** Participants vaccinated between January - February	**N:** 1,432,098 Participants vaccinated	Maximum follow up period 21.6 weeks	OR early v.v late vaccinees 1.61 (95% CI: 1.45 -1.79)	Fair

Author, Country Study Design	Exposure#	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
Retrospective cohort study	**Control:** Participants vaccinated between March - May	between January – February: 821,231 Participants vaccinated between March – May: 601,867			
Mizrahi,[104] preprint Israel Retrospective cohort study	**Exposure:** Early vaccinees **Control** Late vaccinees	**N:** 658,354	At least 13.1 weeks for early vaccinees.	aOR early vs. late vaccinees. 1.53 (95% CI 1.40 to 1.68)	Fair
Puranik,[75] US test-negative case-control study	**Exposure** Later vaccination **Control** Early vaccination Vaccination with BNT162b2 (Pfizer/BioNTech)	**N:** **Cases:** 652 At least 1 positive symptomatic test after full vaccination **Controls:** 5,946 At least 1 negative symptomatic test after full vaccination	Median follow-up time since vaccination for cases: 17.8 weeks max follow up: 23.7 weeks	Adjusted Odds Ratio of symptomatic infection after full vaccination Time relative to full vaccination aOR (95% CI) 30 days 1.81, (0.68-4.82) 60 days 2.32, (0.97-5.52) 90 days 3.5, (1.47-8.35) 120 days 3.21, (1.33-7.74)	Poor
Health care and frontline workers					
Bianchi,[45] preprint Italy	BNT162b2 (Pfizer/BioNTech)	**N:** 6,136 HCWs Vaccinated group 5,351 (87.2%) Unvaccinated	Median 19.9 weeks IQR (19.3, 20.4)	VE against **symptomatic infection** 14–41 days: 97.2% (95% CI 90.3 to 99.2%) 42–69 days: 85.0% (95% CI 63.0 to 94.2%) >69 days: 88.0% (95% CI 42.0 to 97.6%)	Poor

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
Matched cohort study		group 787 (12.8%)			
Fowlkes,[105] published report (CDC), (update of Thompson) US, prospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech) 65% MRNA-1273 (Moderna) 33% Ad26.COV2.S (Janssen) 2%	unvaccinated 4,135 (181,357 person days) vaccinated 2,976 (455,175 person days)	Median 27 weeks (fully vaccinated) IQR 18.4 to 29.9 weeks)	VE against **any infection** days after dose 2 14–119: 85% (95% CI 68 to 93) 120–149 days: 81% (95% CI 34 to 95) 150+ days 73% (95% CI 49 to 86)	Fair
Pilishvili, [72] 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** 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)	Good
Yassi,[50] peer-reviewed Canada, Cohort study crossover	BNT162b2 (Pfizer/BioNTech) 93.3% MRNA-1273 (Moderna) 6.6%	**N:** 25,116 HCWs (7,328 fully vaccinated)	Median 7.7 weeks (IQR 6.3, 8.9)	Graph presented of VE against **any infection** over time - No decline observed but confidence intervals are very wide.	Poor
Healthcare and Frontline workers					
Subbarao, [74] preprint England observational population study (cohort study with crossover)	BNT162b2 (Pfizer/BioNTech) ChAdOx-1 (AstraZeneca)	N: 219,733 19,056 (8.7%) remained unvaccinated, 22,074 (10%) one dose of vaccine 178,603 (81.2%)	Mean 11.0 weeks, no measure of spread	Both vaccines combined VE against mortality (Death within 28 days of positive SARS-CoV-2 test) 1-14 days 87% (95%CI 68-95%) 15+ days 78% (95%CI 36 – 92) VE against **any infection**	Fair

Author, Country Study Design	Exposure[#]	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time	Quality appraisal
		received two doses of vaccine		15-28 days 70% (95% CI 56 – 80) 29-60 days 73% (95% CI 62-80%) 61+ days 65% (95% CI 50 – 76)	
	BNT162b2 (Pfizer/BioNTech)			VE against **any infection** 15-28 days 71% (95% CI 53 – 82) 29-60 days 78% (95% CI 65 - 86) 61+ days 72% (95% CI 52 – 83)	
	ChAdOx-1 (AstraZeneca)			VE against **any infection** 15-28 days 71% (95% CI 53 – 83) 29-60 days 69% (95% CI 53 - 79) 61+ days 58% (95% CI 35 – 73	
Immunocompromised					
Chemaitelly,[(54)] preprint Qatar, Retrospective cohort study with crossover	BNT162b2 (Pfizer/BioNTech): 93% MRNA-1273 (Moderna): 7%	**N:** 782	Mean 10.5 weeks (max = 24 weeks)	VE against **hospitalisation** ≥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)	Fair
Tenforde (sub-group analysis), [(102)] **published report** (CDC) US, Case-Control	BNT162b2 (Pfizer/BioNTech): 59% MRNA-1273 (Moderna): 41%	**N:** Cases: 205 Controls: 447 (21% of the overall study population)	Median 9.3 weeks, (IQR 5.8 to 13.3 weeks) in study overall	VE against **hospitalisation** 2-12 weeks: 64.3 (95% CI 48.5 to 79.6) 13-24 weeks: 53.6 (95%CI 12.8 to 77.8)	Fair

[§]Goldberg also reported results for vaccine effectiveness against severe disease and infection comparing vaccinated with unvaccinated individuals, results available in appendix

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

3.2.2 General population and hospital based studies

This section describes studies of vaccine effectiveness in the general population or in hospitalised patients. Studies comparing early versus late vaccines or naturally acquired immunity are described in later sections. Of the 20 studies in the general population or hospitalised patients, 13 were conducted in the US,[37, 38, 57, 58, 62, 64-69, 79, 102] three studies were conducted in the UK,[39, 56, 60] and one each in Qatar,[35] Portugal,[61] the Netherlands,[59] and Israel.[40] Of the 20 studies, 11 were only available as preprints.[35, 38-40, 56-60, 62, 79] Studies are described below grouped by country given that many studies conducted in the same country contain overlapping participants.

UK

Three UK studies, from Public Health England,[56] Public Health Scotland,[60] and the UK Office for National Statistics/Oxford[39] provide important information for the review question.

Public Health England

In a preprint, Andrews et al.[56] 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.

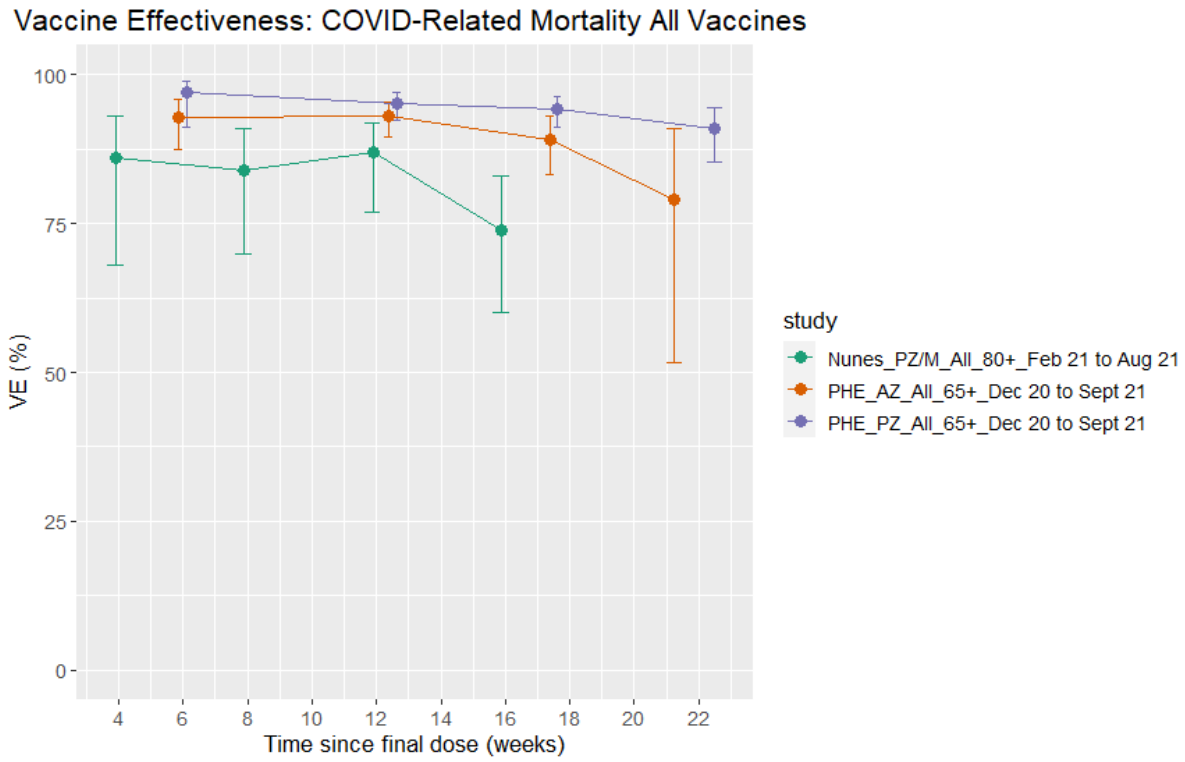
Vaccine effectiveness over time for both the Alpha and Delta dominant periods was presented for three outcomes (symptomatic disease, hospitalisation and death). Results were stratified by vaccine, age and clinical risk group status. Results from the Delta period are summarised here. No statistical tests 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 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, effectiveness 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; these are shown in Figure 3 alongside results from another study (Nunes et al.) that examined mortality over time in older adults.

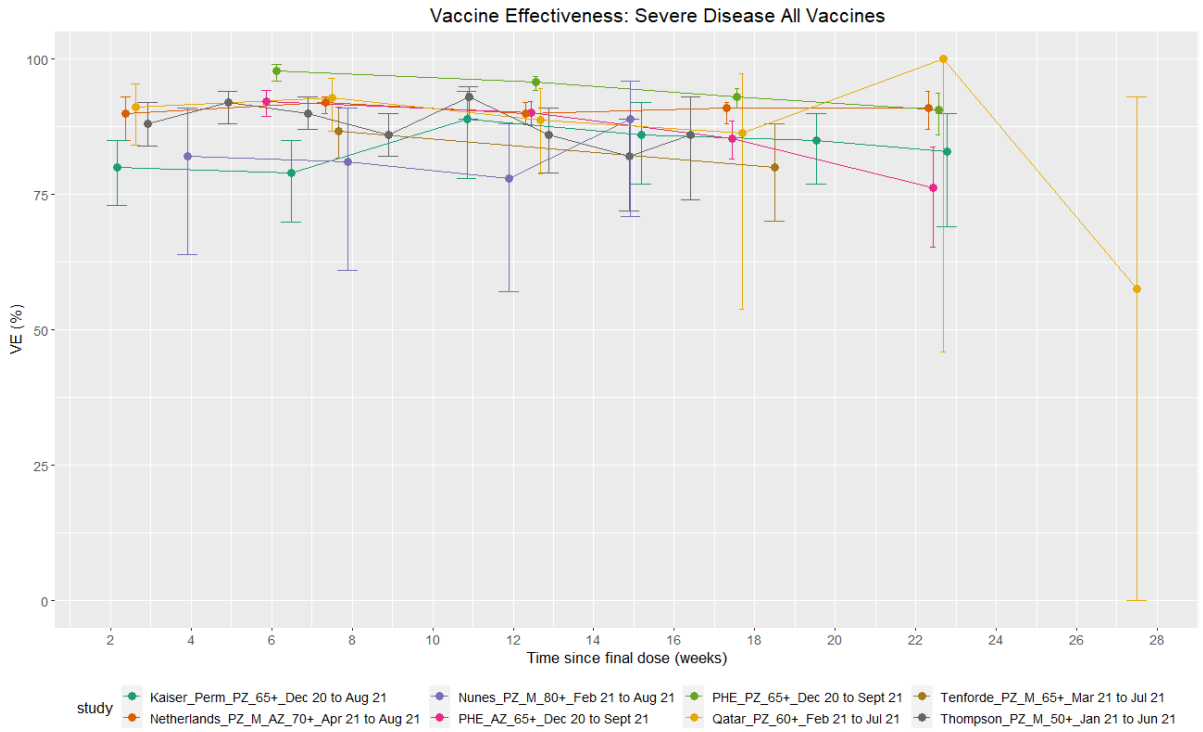
Figure 3 Vaccine effectiveness against mortality over time for older adults from Public Health England and Nunes et al.



Abbreviations: AZ – AstraZeneca, M – mRNA-1273 (Moderna), PHE – Public Health England, PZ – BNT162b2 (Pfizer/BioNTech).

Similar patterns were observed for hospitalisations for both vaccines. For the BNT162b2 (Pfizer/BioNTech) vaccine, vaccine effectiveness was 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 older and 65 years and older, respectively. For the ChAdOx1 (AstraZeneca) vaccine, effectiveness 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 time periods from 2-9 weeks to ≥20 weeks after the second dose. When limited to those aged 65 years or older, vaccine effectiveness ranged from 92.2% (95% CI 89.4 to 94.3) to 76.3% (95% CI 65.3 to 83.8) over the same time periods (pink line, Figure 4). Results for those aged 65 years and older from this study and from other studies which examine severe disease over time in older adults are plotted in Figure 4.

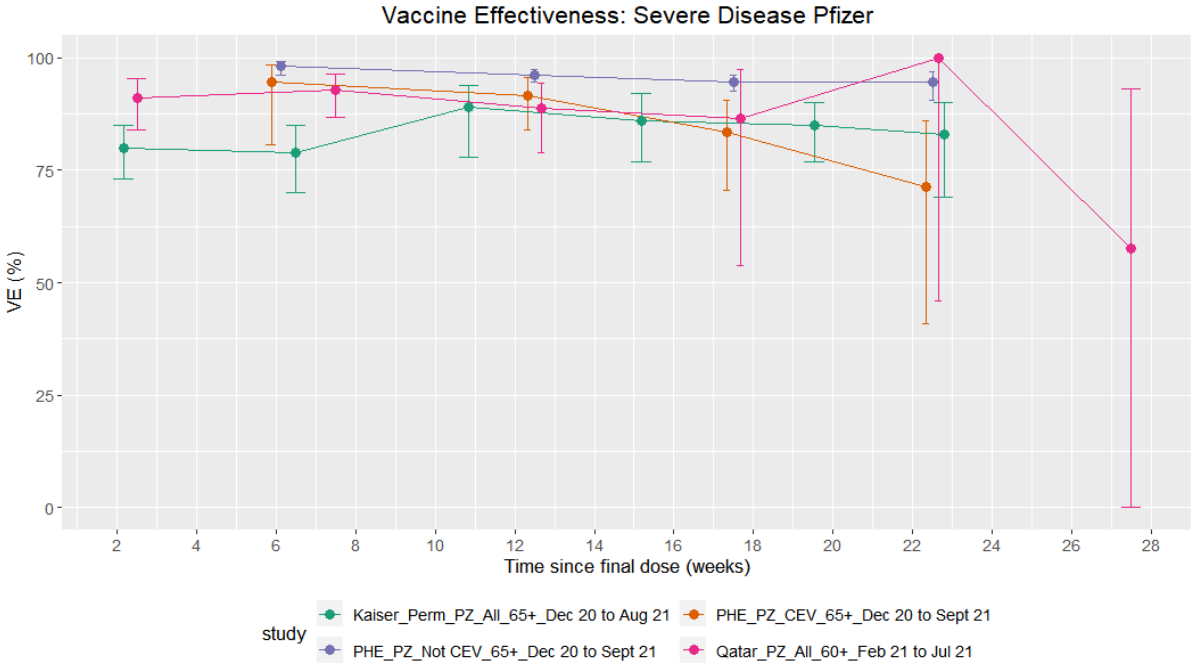
Figure 4 Vaccine effectiveness against severe disease presented over time across observational studies for all vaccines in older adults.



Abbreviations: AZ – AstraZeneca, M – mRNA-1273 (Moderna), PHE – Public Health England, PZ – BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness

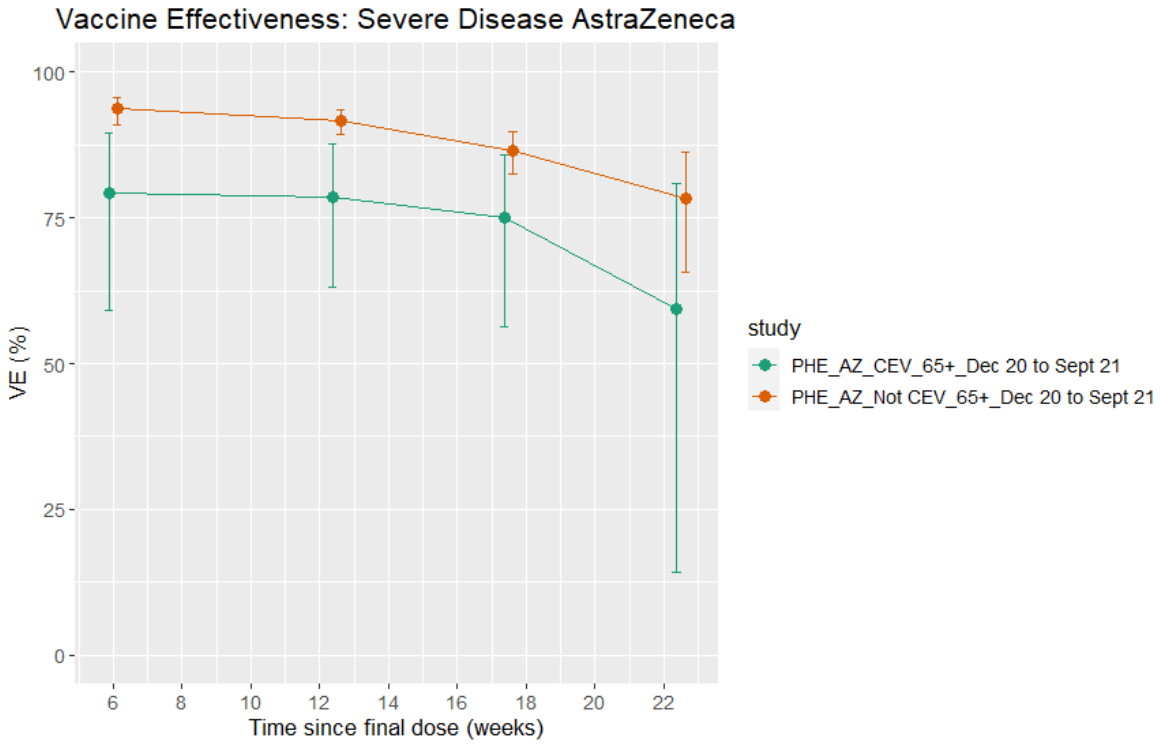
Effectiveness over time for those not in a clinically extremely vulnerable group was presented for those aged 65 years or older. Vaccine effectiveness at 20+ weeks was 94.6% (95% CI 90.5 to 97.0) and 78.4% (95% CI 65.7 to 86.4) for those who received BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) vaccines. These results are plotted in Figure 5 (purple line) and Figure 6 (orange line) for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca), respectively along with the results of other studies which estimated vaccine effectiveness of BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) for severe disease over time.

Figure 5 Vaccine effectiveness against severe disease presented over time across observational studies for BNT162b2 (Pfizer/BioNTech) vaccine in older adults.



Abbreviations: CEV – Clinically Extremely Vulnerable, Kaiser Perm – Kaiser Permanente, PZ – Pfizer/BioNTech, PHE – Public Health England, VE – Vaccine Effectiveness.

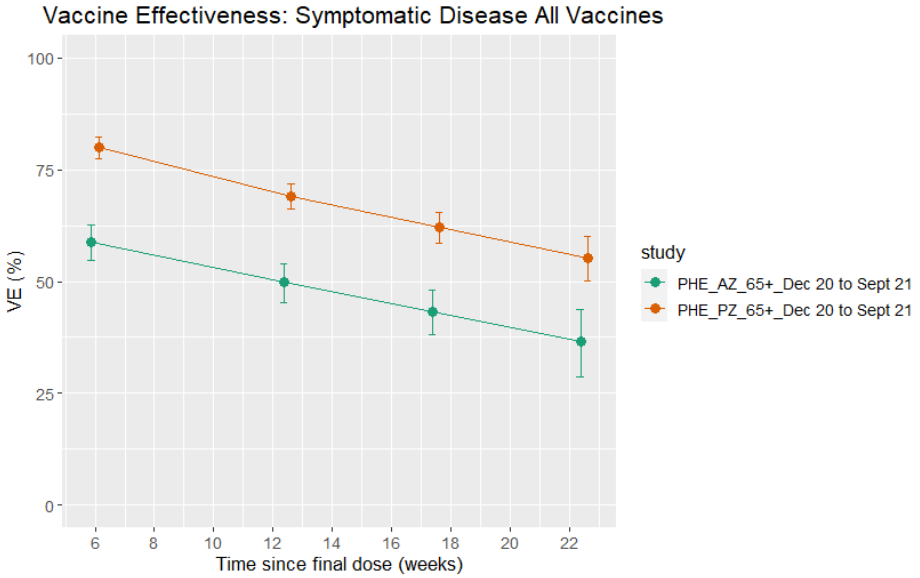
Figure 6 Vaccine effectiveness against severe disease presented over time for ChAdOx1 (AstraZeneca) vaccine in older adults by clinical extremely vulnerable group from Public Health England



Abbreviations: AZ – ChAdOx1 (AstraZeneca), CEV – clinically extremely vulnerable, PHE – Public Health England, VE – Vaccine Effectiveness.

Greater variation over time was observed for the symptomatic disease endpoints. ChAdOx1 (AstraZeneca) vaccine 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) vaccine 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. Similar patterns were observed for the subgroup aged 65 years and older (Figure 7). There was shorter follow-up for those who received the mRNA-1273 (Moderna) vaccine; the estimated vaccine effectiveness was 90.3% (95% CI 67.2 to 97.1) 10-14 weeks after the second dose with no longer-term data presented.

Figure 7 Vaccine effectiveness against symptomatic disease over time in for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) in adults 65 years or older from Public Health England



Abbreviations: AZ – ChAdOx1 (AstraZeneca), PHE – Public Health England, PZ – BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness.

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.

Vaccine effectiveness results for those with clinical risk conditions from this study are reported in section 3.2.4.

REACT-SCOT – Public Health Scotland.

REACT-SCOT is an ongoing matched case-control study by Public Health Scotland. Data from 1 December 2020 to 19 August 2021 were examined to estimate the effectiveness of ChAdOx1 (AstraZeneca) and mRNA vaccines (Pfizer or Moderna) for severe disease and hospitalisation or fatal COVID-19.[60] Potential cofounders were accounted for by matching each case (severe disease n = 5,168; hospitalisation/fatal disease n= 17,121) to ten controls 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 0.21 (95% CI 0.18 to 0.23) and 0.10 (95% CI 0.08 to 0.12) respectively.

Vaccine effectiveness over time was also reported up to approximately 26 weeks after the second dose. Vaccine effectiveness decreased (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 thereafter. While the mRNA vaccines were initially more effective for the severe disease outcome than ChAdOx1 (Astra Zeneca), this difference diminished over time.

Further analyses were undertaken to model the rate of waning for the three vaccines combined.[82] 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 two 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.

In a separate paper, Public Health Scotland also examine vaccine effectiveness in individuals with risk conditions or who were categorised as clinically extremely vulnerable.[103] This is described in Section 3.2.4.

Pouwels et al.

One general population study by Pouwels et al. using data from the UK Office for National Statistics COVID-19 infection survey was identified.[39] This analysis of the effectiveness of BNT162b2(Pfizer/BioNTech) and ChAdOx1(AstraZeneca)[39] is available as a preprint. 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 to71) 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).

Pouwels et al.[39] 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.[39]

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). 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 conditions and age was not accounted for, these results should be interpreted with caution.

In those aged 18 to 64 years, there was evidence of a reduction in effectiveness over time against new RT-PCR-positive infections. Effectiveness was measured by the odds ratios of fully vaccinated compared with unvaccinated per 30 days longer after being fully vaccinated in the delta dominant period. The OR of testing positive was 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 (AstraZeneca).

Pouwels et al.[39] 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, long term health conditions, prior infection, dosing interval).[39] Data were presented graphically with no interpretation of subgroup interaction effects. Graphs for the odds of any infection over time appear to suggest greater vaccine waning in those with long term conditions and older individuals, less waning over time in those with evidence of prior infection and no apparent difference in vaccine waning by dosing interval. However, it is not possible to interpret these graphs as evidence of an effect.

Portugal

One study from Portugal was identified. Nunes et al. is a large retrospective cohort study using comprehensive data from eight national electronic health registries of mRNA vaccine effectiveness (BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) in community-dwelling individuals aged 65 years or older in mainland Portugal.[61] Results were adjusted for a wide range of confounders including, sociodemographic and socioeconomic characteristics, co-morbidities, number of SARS-CoV-2 tests and previous vaccine uptake.

For those aged 65 to 79 years (n=878,489) who were followed for a median of 11 weeks after dose two (IQR 10 to 13), overall vaccine effectiveness was 94% (95% CI: 88 to 97) for COVID-19-related hospitalisation and 96% (95% CI 92 to 98) for COVID-19-related mortality.

Adults aged 80 years and older (n=460,820) were followed for a median duration of 18 weeks (IQR 16 to 21) after dose two. Overall vaccine effectiveness for

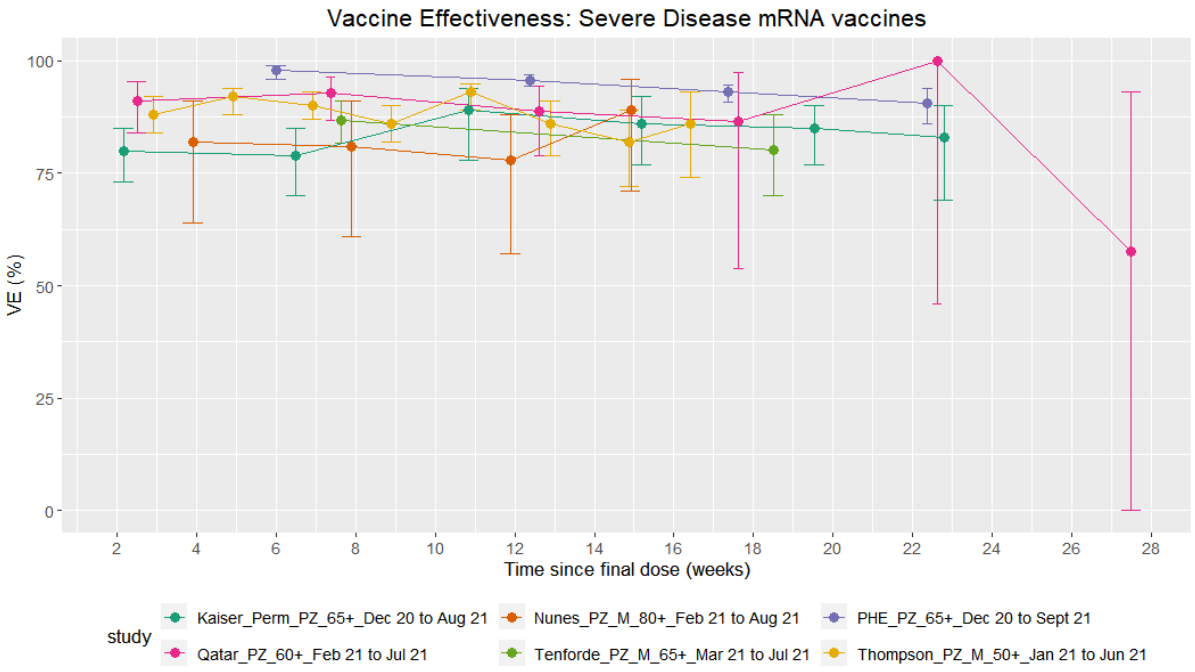
hospitalisation was 82% (95% CI 72 to 89) and 81% (95% CI 74 to 87) for mortality.

Effectiveness over time was only reported for the cohort aged 80 years and older. For COVID-19 related mortality, vaccine effectiveness was 86% (95% CI 69 to 93) and 74% (95% CI 60 to 83) for the intervals 14-41 days and ≥98 days after dose two, respectively (green line, Figure 3).

Results from this and other studies that examined effectiveness versus severe disease over time in older adults are plotted in Figure 8. Vaccine effectiveness for hospitalisation in the cohort age 80 years and older were 82% (95% CI 64 to 91) and 89% (95% CI 71 to 96), for the intervals 14-41 days and ≥98 days after dose two, respectively (orange line, Figure 8).

Evidence for waning was examined by comparing the rate of infection ≥ 98 days to 14 to 41 days after the dose two. While no evidence of waning was seen for either outcome, confidence intervals in both analyses were very wide. (HR 1.8 (95% CI 0.77 to 4.25) and 0.62 (95% CI 0.20 to 1.93) for mortality and hospitalisation, respectively).

Figure 8 Vaccine effectiveness against severe disease presented over time across observational studies for mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) vaccines in older adults



Abbreviations: Kaiser_Perm – Kaiser Permanente, M – mRNA-1273 (Moderna), PHE – Public Health England, PZ – BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness.

US

Thirteen studies conducted in the US were identified within this review.[37, 38, 57, 58, 62, 64-69, 79, 102]

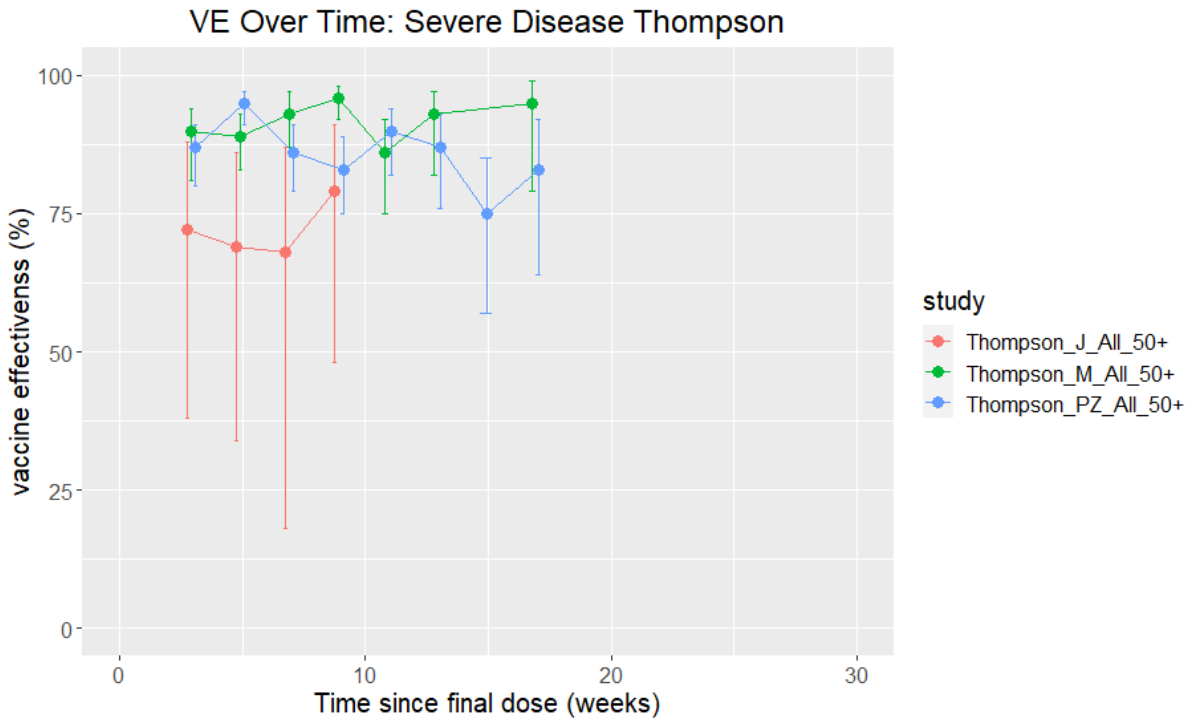
Vision Network

Thompson et al.[69] 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 vaccines combined) for hospitalisation was 88% (95% CI 84 to 92) and 86% (95% CI 74 to 93) 14-27 days and ≥112 days after vaccination, respectively. Vaccine effectiveness over time is presented in Figure 9 by vaccine. Similar results were observed with VE 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) (blue line, Figure 9) and mRNA-1273 (Moderna)(green line, Figure 9), respectively. Data for Ad26.COV.S (Janssen) were limited to ≥56 days after vaccination (VE 79% (95% CI 48 to 91), red line, Figure 9).

Vaccine effectiveness (vaccines combined) for emergency or urgent care visits was 92% (95% CI 88 to 95) and 86% (95% CI 74 to 93) 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.

Figure 9 Vaccine effectiveness against severe disease over time for all vaccines in older adults, from Thompson et al.



Abbreviations: J – Ad26.COV2.S (Janssen), M - mRNA-1273 (Moderna), PZ – BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness

Subgroup analysis over a median follow-up of 12 weeks showed VE for hospitalisation of 84% (95% CI 73 to 91) in patients 85 years of age or older and 90% (95% CI 86 to 93) in those with one or more chronic respiratory condition. No difference in effectiveness for these groups was apparent compared to the total cohort.

Grannis et al. published an updated analysis from this dataset, including data from June to August 2021 when the Delta variant was predominant.[66] Median time since vaccination for the vaccines was 17.7 weeks, 17.1 weeks and 15.4 weeks for the BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna) and Ad26.COV2.S (Janssen) vaccines, respectively. Vaccine effectiveness for hospitalisation differed by vaccine, and was highest among mRNA-1273 (Moderna) vaccine recipients (95%; 95% CI 92 to 97), followed by BNT162b2 Pfizer-BioNTech (80%; 95% CI 73 to 85) and Ad26.COV2.S (Janssen) (60% 95% CI 31 to 77).

Data were also stratified by age. In contrast to the findings by Thompson et al.,[69] vaccine effectiveness against COVID-19 hospitalisation was lower among adults aged 75 years or older compared with those aged less than 75 years (VE: 76% (95% CI 64 to 84) vs. 89% (95% CI 85 to 92), respectively). Although caution is warranted in

interpreting these findings given the uncertainty as to whether this decline related to changes in SARS-CoV-2 or waning of vaccine-induced immunity over time, or a combination of factors.

IVY Network

Two studies (Tenforde et al,[102] and Self et al.[68]) present results from the IVY networks' case control study across 21 academic medical centres in the US.

Tenforde et al.[41] 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 time 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 (82.1%), with 26% and 21.1% having a history of pulmonary disease or an immunocompromising condition, respectively. A small proportion of patients were 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 adjustment for socioeconomic variables or comorbidities. 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. VE versus 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 the 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 were extracted for this review using WebPlotDigitiser (Version 4.4) software.[106] These extracted 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.[106] Results for those aged 65 years and older are plotted with other studies which examined vaccines effectiveness for older adults over time (lime green line, Figure 8). For those with multiple morbidities, VE 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.

Results for those with an immunocompromising condition are described in section 3.2.4.

Self et al.[68] is a US case-control study conducted by the CDC in adults 18 years or older (without immunocompromising conditions) examining VE for hospitalisation with COVID-19. A total of 476,738 participants with a median (IQR) time since second dose of 79 (46–112), 86 (51–119), 68 (36–111) days for the mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNTech) and Ad26.COV2.S (Janssen), respectively, were included in the analysis. The study population overlaps with that analysed by Tenforde et al.[107] and included a large proportion of individuals with co-morbidities (60% had chronic cardiovascular disease including hypertension and 25.1% had chronic lung disease). Results were adjusted for a wide range of confounders.

For the mRNA-1273 (Moderna) vaccine, no evidence of waning effectiveness was observed. Vaccine effectiveness for hospitalisation was 93% (95% CI 90 to 95) and 92% (95% CI 87 to 96) at 14-120 days and >120 days after full vaccination, respectively (for 25% of patients the interval from second dose was >112 days). In contrast, the vaccine effectiveness for the BNT162b2 (Pfizer/BioNTech) vaccine reduced, from 91% (95% CI 88 to 93) to 77% (95% CI 67 to 84), over the same period. The time since vaccination was shorter for those who received the Ad26.COV2.S (Janssen) vaccine, vaccine effectiveness after 28 days after full vaccination was 68% (95% CI 49 to 80).

Kaiser Permanente Healthcare System

Three studies present analysis of vaccine effectiveness in individuals from the Kaiser Permanente healthcare system in California with up to six months follow-up data.[57, 58, 64] Tartof et al. measured the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine while two separate studies by Bruxvoort et al., both published as preprints, measured the effectiveness of mRNA-1273 (Moderna).

Tartof et al.[64] was a large (n=3.4 million) retrospective cohort study of the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine in individuals aged 12 years or older. Vaccine effectiveness by age over time was presented for both COVID-19 hospitalisation and any SARS-CoV-2 infection. Results were adjusted for a wide range of potential confounders, and suggested sustained effectiveness for

hospitalisation up to six months after being fully vaccinated but waning effectiveness for any SARS-CoV-2 infection.

In individuals aged 12 years or older, vaccine effectiveness for hospitalisation ranged from 92% (95% CI 89 to 95) to 88% (95% CI 82 to 92) for the periods two to three months and ≥ five months after being fully vaccinated, respectively. VE for any infection for the same periods was 78% (95% CI 76 to 79) and 47% (95% CI 43 to 51), respectively (green line, Figure 10). The observed decline in effectiveness over time was greater than that observed for the symptomatic disease outcome in the pivotal Pfizer clinical trial by Thomas et al.[34]

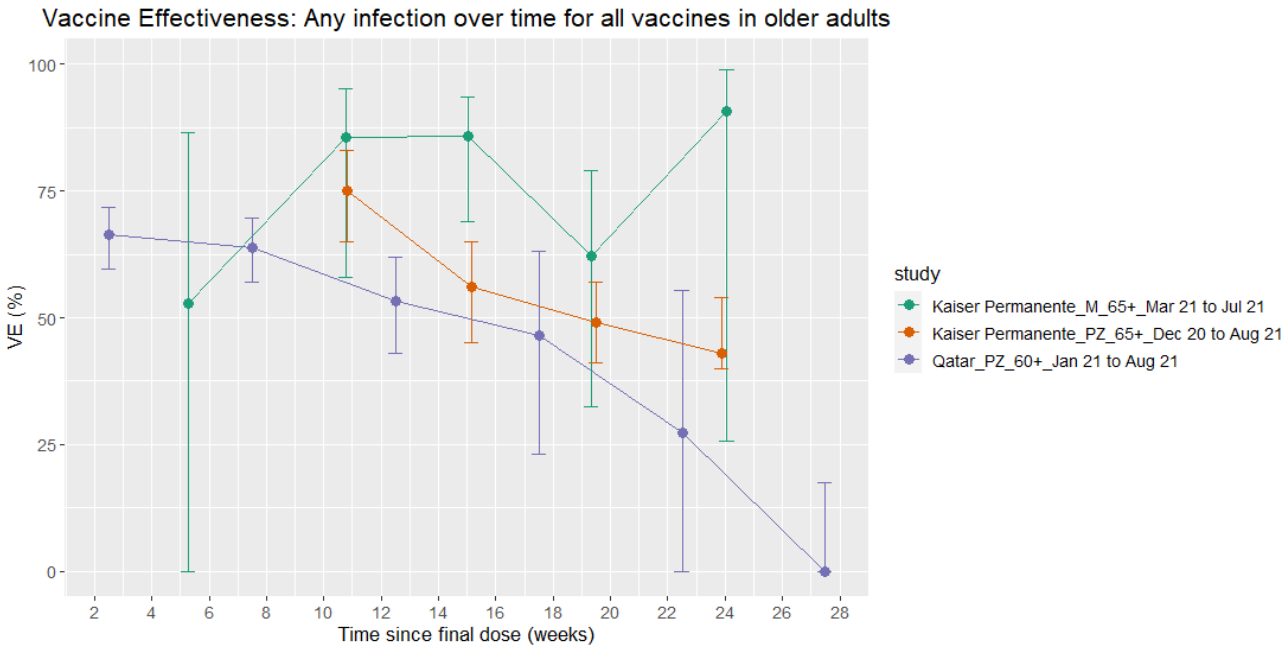
Figure 10 Vaccine efficacy and effectiveness against any infection or symptomatic disease for the BNT162b2 (Pfizer/BioNTech) vaccine in the general population

Abbreviations: PZ – BNT162b3 (Pfizer/BioNTech), VE – Vaccine Effectiveness/efficacy

Note: Outcome in Kasier Permanente study was any infection, whereas in the RCT by Thomas this was symptomatic disease.

When the analysis in Tartof et al. is limited to individuals aged 65 years or older, vaccine effectiveness for hospitalisation was 89% (95% CI 78 to 94) at two to three months and 83% (95% CI 69 to 90) ≥ five months after being fully vaccinated (green line, Figure 5). VE for any infection for the same periods was 75% (95% CI 65 to 83) and 43% (95% CI 30 to 54), respectively (orange line, Figure 11).

Figure 11 Vaccine effectiveness against any infection over time for all vaccines in older adults



Abbreviations: M – mRNA-1273 (Moderna), PZ – BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness

Delta variant specific results were also presented. For any infection, VE for Delta was lower than non-Delta variants, but VE for hospitalisation was comparable for both subtypes.

Bruxvoort et al. (a) is a matched prospective observational cohort study examining mRNA-1273 (Moderna) effectiveness.[57] Vaccine recipients (n=352,878) were matched 1:1 to unvaccinated cohort (n=352,878). Results were adjusted for a large range of confounding factors including sociodemographics, healthcare resource use, and socioeconomic variables. Mean follow-up after dose two was 15 weeks with a maximum follow-up of five months. Overall vaccine effectiveness for COVID-19 hospital death and COVID-19 hospitalisation ≥14 days after dose two were 97.9% (95% CI 84.5 to 99.7%) and 95.8% (95% CI 92.5 to 97.6%), respectively. When stratified by age, no significant difference in vaccine effectiveness for any infection was observed. In those aged 75 years or older, vaccine effectiveness was 83% (95% CI 76.8 to 87.6).

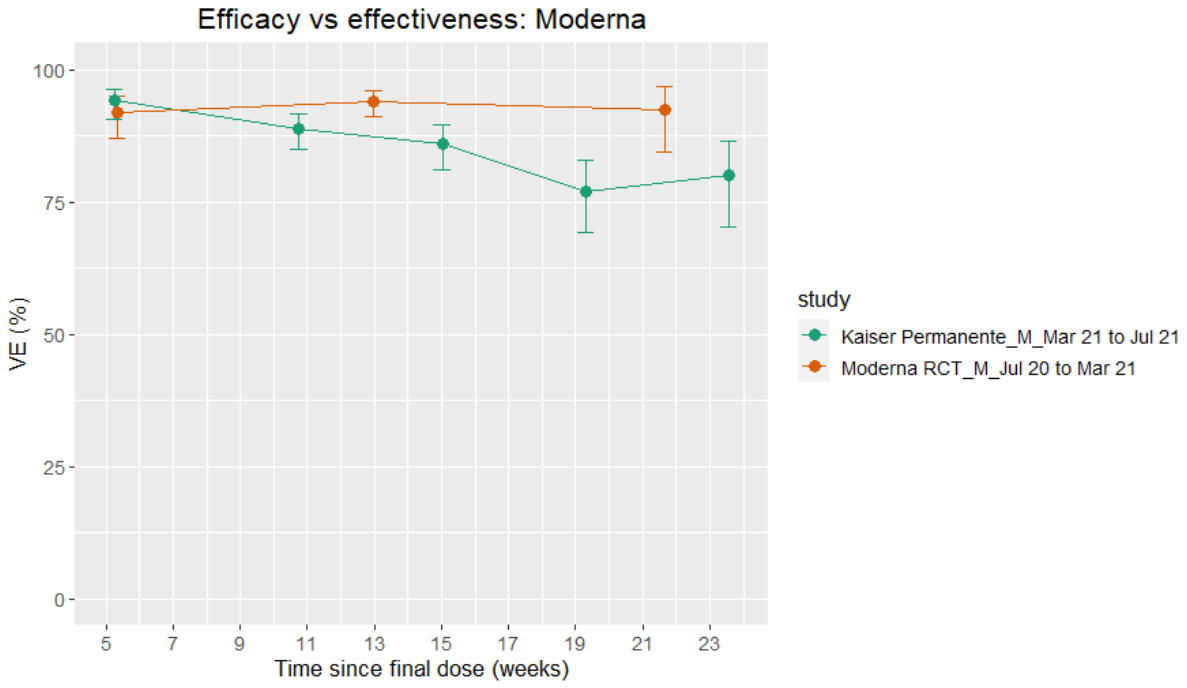
Bruxvoort et al. (b) also report an analysis using a test-negative case-control study design.[58] While the study design and follow-up periods differ from Bruxvoort et al (a), most of the individuals in this study are likely be included in both analyses. In this study, sequenced test positive cases (n=8,153) collected from 1 March to 27

July 2021 were matched 1:5 to test negative controls on age, sex, race/ethnicity and specimen collection date. Results were also adjusted for additional confounders including co-morbidities and healthcare resource use. The maximum time since vaccination was 26 weeks (six months).

Vaccine effectiveness for Delta variant COVID-19 hospitalisation was 97.6% (95% CI 92.8 to 99.2).

As shown in Figure 12 (green line), vaccine effectiveness against any infection for the Delta variant declined from 94.1% (90.5-96.3%) to 80.0% (70.2-86.6%) between the intervals 14-60 days to 151-180 days after vaccination. The observed decline in effectiveness over time was greater than that observed for the symptomatic disease outcome in the pivotal Moderna clinical trial by El Sahly et al. (orange line, Figure 12).[55]

Figure 12 Vaccine efficacy and effectiveness against any infection or symptomatic disease for the mRNA-1273 (Moderna) vaccine in the general population



Abbreviations: M – mRNA-1273 (Moderna); VE – Vaccine Effectiveness. Note: Outcome in Kaiser Permanente study was any infection, whereas in the Moderna RCT, the outcome examined was symptomatic disease.

Bruxvoort et al. also stratified results by age group up to 180 days after dose two.[58] Similar reductions in effectiveness for any infection over time were observed among individuals aged 18-64 years compared to those aged 65 years or older, but

estimates for the latter were associated with substantial uncertainty as indicated by the wide 95% confidence intervals. Results over time for those aged 65 years or older are plotted in Figure 11 (green line). Across the total follow-up period, vaccine effectiveness for any Delta infection was lower among individuals aged 65 years or older (75.2%; 95% CI 59.6 to 84.8) than those aged 18-64 years (VE 87.9%; 95% CI 85.5 to 89.9%).

Veterans Affairs

Two studies were identified which examined vaccine effectiveness in members of the US veteran health association.[65, 79] In both studies, the populations are predominantly male (over 90%) and of older age (median 68 and 70 years). Therefore, the results from these studies may not be generalisable to the general population.

Sharma et al. is a large retrospective cohort study of 3 million veterans.[79] Over a median follow-up of 21 weeks, the effectiveness of mRNA-1273 (Moderna) and BNT162b2 (Pfizer) was compared to that of Ad26.COV2.S (Janssen). Cox proportional hazard models were used to estimate cumulative incidence of infection. Results were adjusted for a wide range of confounders including sociodemographics, co-morbidities, previous documented SARS-CoV-2 infection, regional COVID-19 and vaccine-related variables.

Overall vaccine breakthrough occurrence was 0.37%. Compared to the Ad26.COV2.S (Janssen) vaccine, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) had lower occurrence of COVID-19 hospitalisation (adjusted Hazard Ratio (aHR) 0.51 (95% CI 0.43 to 0.60) and 0.27 (95% CI 0.23 to 0.32), respectively) and documented SARS-CoV-2 infection (aHR 0.54 (95% CI 0.51 to 0.58) and aHR 0.36 (95% CI 0.33 to 0.38), respectively). It was not reported if there were differences in the characteristics of individuals who received the different vaccines.

Bajema et al. is a US test-negative case-control study of mRNA vaccine effectiveness (BNT162b2 or mRNA-1273) in hospitalised veterans aged 18 years or older.[65] Patients with a COVID-19 like illness who received a positive SARS-CoV-2 test result were included as cases (n=388) and those with negative test results were included as controls (n=787). The median time since the final vaccination dose was 12 weeks (IQR 7 to 18).

Vaccine effectiveness for COVID-19 associated hospitalisation was estimated at 86.8% (95% CI 80.4 to 91.1%). Vaccine effectiveness differed by age with higher effectiveness in those aged 18 to 64 years (VE 95.1%; 95% CI 89.1 to 97.8) compared to those aged 65 years or older (VE 79.8%; 95% CI 67.7 to 87.4%).

Vaccine effectiveness also differed by vaccine, and was higher for mRNA-1273 (Moderna) VE = 91.6% (95% CI 83.5 to 95.7) compared to BNT162b2 (Pfizer/BioNTech) VE = 83.4% (95% CI 74.0 to 89.4).

There was no evidence of waning effectiveness. Vaccine effectiveness in those who were vaccinated <90 days (VE 86.1%; 95% CI 76.5 to 91.8) was similar to those who were fully vaccinated ≥90 days (VE 87.2%; 95% CI 78.2 to 92.5).

Mayo Clinic

Three studies (Pawlowski et al.[37] Puranik et al. (a), [38] and Puranik et al. (b),[75] used data from the same patient cohort, one which compared early and late vaccinees is described in section 3.2.3, [75] the other two are described here. Both included people aged 18 years and older who underwent RT-PCR testing at the Mayo clinic and affiliated hospitals. Patients who had a previous positive test before their first vaccine dose were excluded. Although published only as a preprint, the paper by Puranik et al.[38] had a longer duration of follow-up than the Pawlowski study[37](mean 17 weeks post final dose for both vaccines versus eight and ten weeks for the mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) vaccines, respectively), so is described in preference here.[37, 38]

There were differences in the statistical approach used by the two studies, with Pawlowski et al.[37] using propensity scores to match vaccinated and unvaccinated individuals, while Puranik et al.[38] triple matched patients on criteria associated with exposure (BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), unvaccinated). The risk of biased estimates was noted for both approaches, and particularly the potential bias due to a failure to match on unobserved variables, for example, socio-economic status and date of vaccination.

All VE estimates presented here are ≥14 days after second dose. The vaccine effectiveness estimates for mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) against hospitalisation were 91.6% (95% CI 81 to 97) and 85% (95% CI 73 to 93), respectively. Similar estimates were observed for ICU admission, but confidence intervals were wider due to fewer events to inform the analysis.

VE estimates were not computed by the authors for the mortality endpoint, with no deaths in either of the vaccinated cohorts. There were four COVID-19 associated deaths in 6,951 person years in the unvaccinated group. Follow-up was similar for vaccinated groups. For confirmed RT-PCR infection, VE for mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) were 86% (95% CI 81 to 90.6, p <0.001) and 76% (95% CI 69 to 81, p<0.001), respectively.

Puranik et al.[38] also presented analysis on how VE changed over calendar time, with VE point estimates declining with time. Care must be taken when interpreting this analysis as the cohort is dynamic and the mean time since vaccination in each analysis may increase or decrease each month as the composition of the cohort changes. The authors noted that the decline in effectiveness observed with calendar time coincided with the arrival of the Delta variant.

Other studies

In the US, Griffin et al, found that fully vaccinated persons,[67] were less likely to be hospitalised, admitted to ICU, or require mechanical ventilation, but there was limited adjustment for confounders. No estimates of vaccine effectiveness were presented.

Polinski et al. examined the effectiveness of the Ad26.COV2.S (Janssen) vaccine in a matched cohort study with cross over.[62] Vaccinated individuals were matched 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 the 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). The authors report that no difference in effectiveness for either hospitalisation or any infection was observed over time.

Israel

One study from the general population was identified from Israel where, to date, the immunisation programme has primarily been based on the BNT162b2 (Pfizer/BioNTech) vaccine.[40] Four studies comparing early versus late vaccinees are described in Section 3.2.3.

Saciuk et al.[40] 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

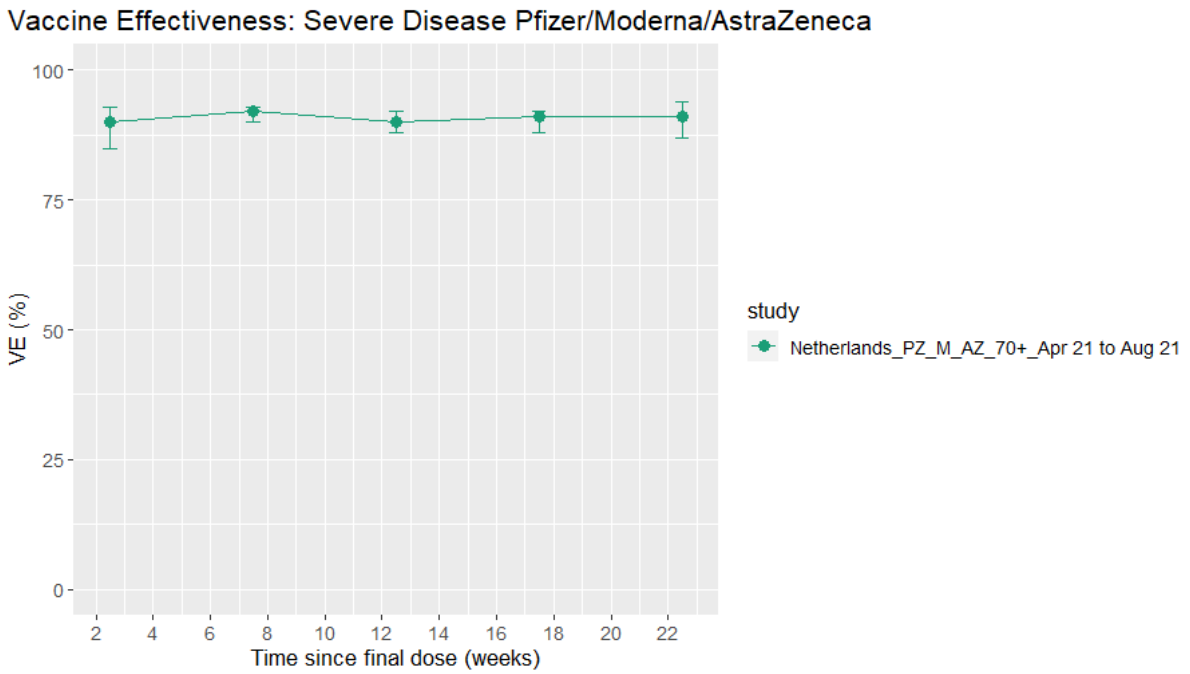
time since final vaccination dose was ten weeks. Effectiveness estimates were adjusted for gender, age, co-morbidity, geographical statistical area and calendar week. VE estimates were 93.4% (95% CI 91.9 to 94.7) and 91.1% (95% CI 86.7 to 94.1) for hospitalisation and COVID-19 related mortality, respectively. VE versus any infection was 93% (95% CI 92.6 to 93.4).

Netherlands

In a preprint, De Gier et al. examined COVID-19 vaccine effectiveness against hospitalisations and ICU admission in the Netherlands from April to August 2021 using linked nationwide registries of COVID-19 hospitalisations and vaccinations.[59] Results were calculated for the Alpha and Delta dominant periods adjusted for age group and calendar time.

Similar overall vaccine effectiveness (all vaccines combined) was observed for the Alpha and Delta dominant periods for ICU admission (93% (95% CI 87 to 96) vs. 97% (95% CI 97 to 98), respectively) and severe disease/hospitalisation (94% (95% CI 93 to 95) and 95% (95% CI 94 to 95), respectively). For both outcomes, vaccine effectiveness exceeded 89% for all time points up to 20 or more weeks after dose two for the 50 to 69 and ≥70 year age groups. Vaccine effectiveness estimates for those aged 15 to 49 years exceeded 75% at every time point, but the estimates were associated with considerable uncertainty given that there were fewer events in this age group. Results over time for severe disease/hospitalisation for those aged 70 or older are plotted in Figure 13.

Figure 13 Vaccine effectiveness against severe disease over time for Pfizer/Moderna/AstraZeneca combined in older adults from De Gier et al.



Abbreviations: AZ – ChAdOx1 (AstraZeneca), M - mRNA-1273 (Moderna), PZ – BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness

Vaccine effectiveness by age and vaccine type was also presented. Vaccine effectiveness for hospitalisation across all age groups was 96% (95% CI 95 to 96); 84% (95% CI 80 to 87); 94% (95% CI 92 to 95) and 91% (95% CI 88 to 94) for BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna), ChAdOx1 (AstraZeneca) and Ad26.COV2-S (Janssen), respectively. When limited to those aged 70 years or older, vaccine effectiveness was estimated at 92% (95% CI 90 to 93), 64% (95% CI 47 to 76) and 78% (95% CI 63 to 86) for BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna), and ChAdOx1 (AstraZeneca), respectively. No data for those aged ≥70 years were available for Ad26.COV2-2 (Janssen).

Qatar

Chemaitelly et al.[35] examined the persistence of BNT162b2 (Pfizer/BioNTech) vaccine effectiveness in Qatar. The study population included the entire resident population of Qatar and employed data from integrated national SARS-CoV-2 databases, which include all records of RT-PCR testing, vaccinations and COVID-19 hospitalisations.[35]

The primary analysis used a matched test-negative, case-control study design. Cases (RT-PCR-positive persons) and controls (RT-PCR-negative persons) were matched

one-to-one by sex, ten-year age group, nationality, the reason for testing, and calendar week of testing. Multiple sensitivity analysis were conducted by adjusting the inclusion and exclusion criteria or by incorporating additional matching factors. The authors also conducted scenario analysis adjusting for prior infection and matching factors in logistic regression (they were, sex, age, nationality, the reason for RT-PCR testing, and calendar week of RT-PCR).

The authors report that while all records were included in the study, only samples of matched cases and controls were included in the analysis. As the authors do not report how the composition or size of these samples were chosen, the potential for bias cannot be assessed.

Between 21 December 2020 and 15 August 2021, a total of 891,481 individuals completed the two-dose regimen of BNT162b2 (Pfizer/BioNTech). In total, 173,496 individuals with a RT-PCR positive confirmed SARS-CoV-2 (cases) and 1,422,333 individuals with a RT-PCR negative SARS-CoV-2 test (controls) were eligible for matching. The population characteristics of cases and controls were representative of the young diverse demographics in that 9% of residents were ≥50 years of age, and 89% were expatriates from over 150 countries.

The data reported reflect effectiveness versus the Beta variant, as this was the primary variant in circulation during the study time period. However, variant-specific effectiveness results for Alpha, Beta and Delta are also presented. Results for most outcomes were presented by four-week intervals starting from administration of the second dose of BNT162b2 (Pfizer/BioNTech) to ≥25 weeks after the second dose.

VE point estimates for the composite outcome of any severe, critical or fatal COVID-19 infection were similar at most time points examined. For example, VE was 95.4% (95% CI 93.4 to 96.9) and 95.3% (95% CI 70.5 to 99.9) at 0-4 weeks and at 20-24 weeks after the second dose, respectively. There were very limited data to support VE at ≥25 weeks, and confidence intervals were wide (VE 71.5%, 95% CI 9.2 to 93.2). When the outcomes of severe, critical or fatal COVID-19 were examined separately, VE estimates and trends were similar to the composite outcome. There were limited data to inform the VE against the Delta variant, with 95% confidence intervals ranging from 0 to 100%. Subgroup analysis by age was also performed, with vaccine effectiveness estimates similar for those aged ≥60 years compared with those under 60 years. Results for those aged 60 years and older are plotted with other studies which measured the effectiveness of BNT162b2 (Pfizer/BioNTech) in older adults over time in Figure 5 (pink line).

Vaccine effectiveness estimate for any RT-PCR confirmed infection was 72.1% (95% CI 70.9 to 73.2) 0-4 weeks post dose two, falling to 29.7% at 15-19 weeks after the

second dose and to 0% from week 20. Results for those aged 60 years and older are plotted with other studies which examine the effectiveness of BNT162b2 (Pfizer/BioNTech) in older adults for any infection over time in Figure 11 (purple line).

Based on these results, the authors concluded that the effectiveness of BNT162b2 (Pfizer/BioNTech) against infection appears to wane rapidly after its peak, but that it persists at a robust level against hospitalisation and death for at least six months after the second dose. No statistical tests were reported to examine whether any changes over time were statistically significant. Therefore, along with consideration of the methodological concerns, no firm conclusions about the change in effectiveness over time may be drawn from the results presented.

The reliability of these results is questioned by the results of regression scenario analysis. As expected, univariate analysis suggests that a person vaccinated with BNT162b2 (Pfizer/BioNTech) is less likely to have a RT-PCR confirmed infection ≥25 weeks after dose two (OR 0.57, 95% CI 0.53 to 0.62) compared to an unvaccinated person. When this estimate is adjusted for confounders in a multivariable regression analysis, the adjusted odds ratio (aOR) changes direction with the odds of a vaccinated person testing positive 1.65 times higher than an unvaccinated person (aOR1.65, 95% CI1.51 to 1.80). The change in the direction of effect has not been investigated by the study author. However, as the result is not plausible from a clinical perspective this suggests biased estimates from unmeasured confounders. As the same data are used in the primary and scenario analysis, the primary analysis is also likely to be biased. Without further information, the cause of the bias can only be speculated. The authors highlight that vaccinated persons presumably have a higher social contact rate than unvaccinated persons and may also have reduced adherence to safety measures. Furthermore, the authors acknowledge that subtle differences in test seeking behaviour or changes in the pattern of testing with the introduction of other testing modalities such as rapid antigen testing could lead to differences in vaccine effectiveness over time. The authors also note that the same findings were reached regardless of the reason for RT-PCR testing, but these analyses were not presented.

Overall the quality of the study was determined to be poor, with numerous concerns identified. However, reasons for bias from testing behaviour are substantially less likely to affect the severe disease endpoints. Bias relating to increased exposure to COVID-19 in the vaccinated group would lead to estimates showing reduced effectiveness over time for severe disease. As the vaccine effectiveness was sustained over time, these data do not suggest a substantial waning effect for these outcomes.

3.2.3 Early versus late vaccinee studies

Four Israeli studies and one US study examined the difference in vaccines effectiveness between early and late vaccinees (as defined by each study).

Four Israeli studies by Israel et al.,[42] Mizrahi et al.,[104] Goldberg et al.,[70] and Kertes,[80] adopted similar study designs looking at differences in the odds of testing positive between early and late vaccinees. The four studies (all available as preprints) used outcome data from separate healthcare providers during a period of Delta variant prominence. All excluded individuals who previously had a positive RT-PCR test. All four studies reported lower effectiveness for those vaccinated early compared with those vaccinated late, with the adjusted odds of testing SARS-COV-2 positive ranging from 1.53 to 2.1 times higher in early vaccinees, suggesting waning effectiveness over time.

Puranik et al.(b) is a US test-negative case-control study of vaccine effectiveness in the Mayo Clinic comparing early and late vaccinees.[75] After adjustment for confounding, the adjusted odds of symptomatic infection were higher 120 days after full vaccination compared with at the date of full vaccination (aOR 3.21; 95% CI 1.33 to 7.74).

A strength of all five studies is that the assessment of outcomes in early vaccinated and late vaccinated groups was in the same calendar time, minimising bias. Furthermore, as the studies only included vaccinated individuals, there may be less bias associated with differences in health behaviours (for example mask-wearing) between vaccinated and unvaccinated groups. However, as the age groups used to adjust the analysis were very wide, there may be some residual confounding, given that older individuals were among those vaccinated first. Individuals with a greater risk of exposure (such as healthcare workers) were also among those vaccinated first and this was not controlled for in the analysis. Failure to control for these confounders may bias the results towards showing a decline in vaccine effectiveness over time.

3.2.4 Individuals with co-morbidities or an immunocompromising condition

Two studies considered vaccines effectiveness solely in those with co-morbidities or an immunocompromising condition. Three studies from the general population reported subgroup results for these cohorts.

Chemaitelly et al.[54]

In a preprint, Chemaitelly et al.[54] 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. 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. 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 have been previously reported. [54] However, care must be taken when interpreting the analysis as there were limited adjustments for potential confounders, such as calendar time.

Tenforde et al. [107]

Vaccine effectiveness in patients with immunocompromising conditions was examined in a subgroup analysis in the case-control study by Tenforde et al.[107] (section 3.2.2). 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 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 VE 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.

Public Health England

The Public Health England study reports changes in subgroup results over time for those in vulnerable groups. For ChAdOx1 (AstraZeneca), VE for hospitalisation in those aged 65 years or older in the clinically extremely vulnerable group was estimated as 79.3% (95% CI 59.2 to 89.5) and 59.4% (95% CI 14.1 to 80.8) at 2-9 weeks and ≥20 weeks after dose two, respectively (green line, Figure 6). For BNT162b2 (Pfizer/BioNTech), it was 94.6% (95% CI 80.6 to 98.5) and 71.4% (95% CI 40.9 to 86.1) at 2-9 weeks and ≥20 weeks after dose two, respectively (orange line, Figure 5).[56]

VE 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 93.7% (95% CI 92.3 to 94.8) and 69.7% (95% CI 29.7 to 86.9) at 2-9 weeks and ≥20 weeks, respectively. For BNT162b2 (Pfizer/BioNTech) it was 98.1% (95% CI 97 to 98.8) at 2-9 weeks and was not reported for ≥20 weeks.

REACT-SCOT Case Control Study – Public Health Scotland

As described earlier, REACT-SCOT is an ongoing matched case control study by Public Health Scotland.[60] In addition to the main analysis, a separate paper reports vaccine effectiveness for those with conditions that increase their risk of poor outcomes from COVID-19.[103] The statistical methods for this analysis differed from the main analysis, while they still matched for age, sex, general practice and calendar time the covariates used for further adjustment differed. In this analysis, they adjusted for care home residence, number of adults in the household, number of non-cardiovascular drug classes and recent hospital stay.

They report effectiveness for severe disease of 93% (95% CI 90 to 95) in those without risk conditions, 89% (95% CI 85 to 92) in those with moderate risk conditions, and 66% (95% CI 52% to 76%) in the clinically extremely vulnerable (CEV) category. Effectiveness against hospitalisation was also lower at 67% (95% CI 61% to 72%) in the CEV group than in the other two risk categories. 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 ranged from 0.20 (95% CI 0.13 to 0.32) for severe respiratory disease to 1.09 (95% CI 0.48 to 2.49) for those on immunosuppressants.

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 numerically lower for those who received the AstraZeneca vaccine (VE 63%; 95 CI 46% to 75%) and the mRNA vaccines (72% 95 % CI 51% to 84%), but differences were not statistically significant.

Unlike the Public Health England study,[56] vaccine effectiveness over time was not examined for this cohort.

Polinski et al.

Polinski et al. reports vaccine effectiveness of Ad26.COV2.S (Janssen) over a mean follow-up of 15 weeks in a subgroup analysis of the main study described in Section 3.2.3.[62] 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.

3.2.5 Healthcare workers

Ten papers describing nine studies were identified that examined vaccine effectiveness in healthcare workers (excluding those who specifically examined HCWs in long-term care facilities which are described below).[44-51, 71-73] Given the number of studies identified, this section focuses on studies of good or fair quality only.

HEROES-RECOVER

The US CDC examined vaccine effectiveness in the HEROES-RECOVER cohort – a prospective cohort study that enrolled HCWs, first responders and other frontline and essential workers.[47, 105] Participants were swabbed and tested for SARS-CoV-2 infection regardless of symptom or vaccination status. Vaccine effectiveness estimates were adjusted for baseline sociodemographic and health characteristics, and participant's virus exposure. Thompson et al.[47] reported results from 10 April 2021 when fully vaccinated participants had been followed for a median duration of 11.9 weeks. Two-thirds of participants had received the BNT162b (Pfizer/BioNTech) with the remaining one-third having received the mRNA-1273 (Moderna) vaccine. Against any SARS-CoV-2 infection, VE was estimated at 91% (95% CI 76 to 97) ≥14 days after the second dose. There was no evidence of a differential effect in those aged less than 50 compared with those aged 50 years and older. VE for severe disease was not reported.

Fowlkes et al.[105] published an updated analysis from 14 August 2021. The median time since vaccination had increased to 27 weeks. In the updated analysis, 2% of participants had received the Ad26.COV2.S (Janssen) vaccine. VE for any infection was 85% (95% CI 68 to 93), 81% (95% CI 34 to 95), and 73% (95% CI 49 to 86) at 14–119 days, 120-149 days and ≥150 days following the second dose, respectively. The authors highlight that as the 95% CIs are overlapping, any difference in VE over time is not statistically significant and differences could be due to poor precision. The authors consider that the observed decline in point estimates corresponded to an increase in the prevalence of the Delta variant. Pre-Delta variant

predominance, the estimated VE was 91% (95% CI 81 to 96) falling to 66% (95% CI 26 to 84) in the Delta dominant period.

Pilishvili et al.[72]

Pilishvili et al. conducted a test-negative case-control study to examine the effectiveness of mRNA vaccines in HCW across 25 US states.[72] 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 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 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 analyses were presented for the mRNA combined analysis. Vaccine effectiveness, did not differ by age (<50 versus ≥50 years), for people with asthma, or for those with underlying conditions or risk factors for severe COVID-19.

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 that was observed during weeks 3 and 4, 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) 3-4 weeks and 80.9% (95% CI 61.0 to 90.4) 13-14 weeks after dose two.

Emborg et al.

In a preprint, Emborg et al.[51] present the results of a Danish retrospective cohort study examining the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine. Data from this Danish Civil registration system were linked to national hospitalisation, vaccination and microbiological databases and registries. Results were adjusted for a wide range of potential confounders, including calendar time, age, sex, co-morbidities and hospital admission. Five separate cohorts were analysed, but only three (HCWs, LTC resident, and ≥65 years requiring practical help and person care at home (65PHC)) met the minimum time since the vaccination threshold required for inclusion in this review. Results for the cohort of HCWs included in the analysis

are presented here with results for the LTC resident and 65PHC cohorts described in the section on residents and staff of care homes for older people.

The study included 426,000 HCWs in the analysis of which 112,824 were vaccinated. The median time since vaccination for the fully vaccinated cohort was ten weeks. No information was reported regarding variants of concern in circulation at the time of the analysis from 27 December 2020 to 11 April 2021. Vaccine effectiveness against confirmed SARS-CoV-2 infection was 80%. There were no events of COVID-19 related hospital admissions or deaths in the vaccinated groups over 16,000 person years of follow-up compared to incidence rates of 0.002 and 0.004 per person year, respectively in 79,000 person years of follow-up in the unvaccinated group.

Katz et al. [73]

In an Israeli prospective cohort study of 1,250 HCWs, vaccine effectiveness for BNT162b2 (Pfizer/BioNTech) for symptomatic infection of 97.0% (95% CI: 72.0% to 99.7%) over a median follow-up of 11 weeks was observed.

Other studies

The remaining five studies were considered to be of poor quality.[44-46, 49, 50, 71]

Bianchi et al.[45] examined the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine in a cohort of HCWs in an Italian University Hospital. The median follow-up in the vaccinated group was 20 weeks. Vaccinated HCWs were matched to an unvaccinated cohort in the hospital; however, the factors used for matching were not described, nor was it clear how HCWs were chosen for inclusion in the study. The authors do not report results for the primary outcomes of this review, but results for any SARS-CoV-2 infection and symptomatic disease are reported stratified by time since the second dose. Point estimates for vaccine effectiveness for any infection were 94.8% (95% CI 87.0 to 97.8), 83.0% (95% CI 65.0 to 92.0) and 81.0% (95% CI 42.0 to 94.0) at 14-41 days, 42-69 days, and at >69 days, respectively. For the symptomatic disease outcome, VE was 97.2% (95% CI 90.3 to 99.2), 85.0% (95% CI 63.0 to 94.2) and 88.0% (95% CI 42.0 to 97.6) at the same time points, respectively. The authors did not report any analysis examining if the change over time was statistically significant.

Yassi et al.[50] examined VE in a cohort study of 25,000 HCWs in Canada. Most vaccinated participants received the BNT162b2 (Pfizer/BioNTech) vaccine (93.3%). The median time since vaccination was 54 days. VE ≥7 days after second dose against any infection was 79.2% (95% CI 64.6 to 87.8%). However, there was very limited adjustment for confounders. A graph of the cumulative vaccine effectiveness over time up to 112 days after the second dose was presented. A decline in vaccine

effectiveness was not observed, but confidence intervals were too wide to draw any conclusion.

In a preprint, Alali et al.[44] presented the results of a retrospective cohort study (with crossover) from a single hospital in Kuwait which examined the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine. The mean time since the final vaccination was 15 weeks. VE against symptomatic infection ≥ 7 days after the second dose was 94.5% (95% CI 89.4% to 97.2%).

Both Indian studies of the vaccine effectiveness of Covishield (an alternative brand name of the ChAdOx1 (AstraZeneca) vaccine) in HCWs were considered to be of poor quality. Ghosh et al.[46] analysed VE in 1.6 million healthcare and frontline workers in the Indian Army over a mean of eight weeks follow-up, while the study by Issac et al.[49] analysed VE in 324 HCWs in India who had at least 15 weeks follow-up. VE against any infection was 91.8% (95% CI 88.8 to 94.0) and 84.9% (95% CI not reported) for Ghosh et al.[46] and Issac et al.,[49] respectively. There was no adjustment for age or other important confounders in either analysis.

Similar results for any infection and symptomatic infection were also observed for Giansante et al. in Italy.[71]

3.2.6 Residents and staff of long term care facilities

Four studies consider care homes for older people, with three looking at vaccine effectiveness for residents,[51, 52, 74] and one considering the effectiveness in staff.[53]

Residents

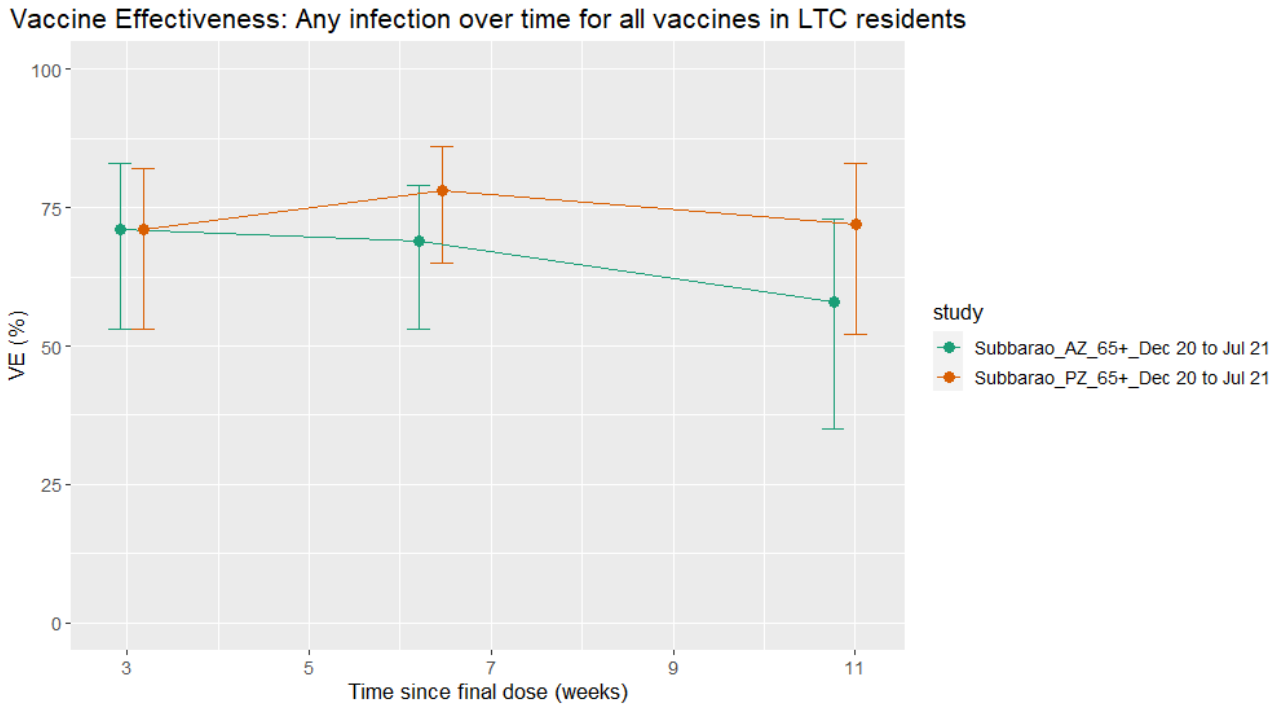
Public Health England (Subbarao et al.)

In a preprint, Public Health England reported the vaccine effectiveness of BNT162b2 (Pfizer/BioNTech) and ChAdOx-1 (AstraZeneca) in 219,733 residents of LTCF aged 65 years or older living in England from 8 December 2020 to 01 July 2021.[74] Residents with a positive result in the 90 days prior to the study start date were excluded. At the end of the study period, 8.7% remained unvaccinated, 10% received only one dose and 81.2% received two doses. The mean time since vaccination was 11 weeks. Residents were tested regularly for SARS-CoV2 infection and results were adjusted for sex, age group, index of deprivation and local authority case rate.

Vaccine effectiveness for COVID-19 associated mortality was 89% (95% CI 47 to 98) and 72% (95% CI 23 to 90) for ChAdOx-1 (AstraZeneca) and BNT162b2 (Pfizer/BioNTech), respectively. For any infection, vaccine effectiveness was reported

by time since second dose for both vaccines (Figure 14). There was no evidence of waning for BNT162b2 (Pfizer/BioNTech) (orange line); vaccine effectiveness was 71% (95% CI 53 to 82), 78% (95% CI 65 to 86) and 72% (95% CI 52 to 83) at 15-28, 29 to 60 and ≥61 days after the second dose, respectively. Point estimates were numerically lower for ChAdOx1 (AstraZeneca) over time (green line), but confidence intervals are wide and overlapping at all time points; vaccine effectiveness was 71% (95% CI 53 to 83), 69% (95% CI 53 to 79), 58% (95% CI 35 to 73) at 15-28, 29 to 60 and ≥61 days after the second dose, respectively.

Figure 14 Vaccine effectiveness against any infections as presented over time for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) in individuals residing in long term care facilities



Abbreviations: AZ - ChAdOx1 (AstraZeneca), LTC - long term care facilities, PZ - BNT162b2 (Pfizer/BioNTech), VE – Vaccine Effectiveness.

Denmark

The large Danish study conducted by Emborg et al.[51] which reported on the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine in HCWs (discussed in section 3.2.5) also reported results for LTC residents. A total of 46,101 LTC residents were included in the analysis of whom 40,061 were vaccinated by the end of the study period with a median time since vaccination of ten weeks. VE for hospitalisation and for mortality were estimated at 75% (95% CI 46 to 89) and 89%

(95% CI 81 to 93), respectively. The VE for any infection was 53% (95% CI 29 to 69).

Emborg et al.[51] also provided estimates of BNT162b2 (Pfizer/BioNTech) VE for people aged 65 years or older who require practical help and personal care at home. A total of 61,805 were included in the analysis of which 45,924 were vaccinated by the end of the study period. The median time since vaccination was nine weeks. The estimated VE was 87% (95% CI 70 to 95) for COVID-19 related hospitalisation with similar estimates observed for COVID-19-associated mortality at 97% (95% CI 88 to 99) and confirmed infection 86% (95% CI 78 to 91).

France

In a preprint, Lefèvre et al.[52] examined the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine versus the Beta variant in nursing homes in Eastern France in which any outbreak that implicated Beta during the study period was documented. The mean time since second vaccination dose was 8.7 weeks. The median age of residents was 89 (IQR 82 to 92) years. Vaccine effectiveness was estimated as 86% (95% CI 67 to 94) for severe disease and 49% (95% CI 14 to 69) for any infection.

Staff

Muhsen et al.[53] examined the effectiveness of the BNT162b2 (Pfizer/BioNTech) vaccine in an Israeli prospective cohort study of HCWs working in LTC facilities during a period of Alpha variant predominance. Participants with a previous infection or COVID-19 immunisation at the index date were excluded. The median follow-up was 11.4 weeks in the fully vaccinated group. Results were adjusted for a wide range of confounders including age, sex, residential area, socio-economic status, population group, and residential area rates of infection. The adjusted VE for any infection ≥14 days after second dose was 89% (95% CI 83 to 93). The study was limited to those who adhered to routine weekly RT-PCR screening. No information was provided on whether these participants are representative of the total cohort of HCWs working in LTC facilities as it is noted that only 50% met the adherence criterion.

3.2.7 SARS-Cov-2 infection versus vaccine derived immunity

Four studies were identified that compared outcomes following recovery from SARS-CoV-2 infection, relative to those based on vaccine-derived immunity.[36, 76, 78, 81]

Gazit et al.[36] compared the risk of COVID-19 related outcomes in fully vaccinated individuals (with no history of infection) to unvaccinated individuals with a history of

infection. The population in this study overlaps with that by Mizrahi et al.[104] as both include data from individuals enrolled in the same healthcare provider (Maccabi Healthcare Services).

The fully vaccinated group was defined as SARS-CoV-2 naive individuals who received two doses of BNT162b2 (Pfizer/BioNTech) vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive RT-PCR test result by before 1 June 2021. The unvaccinated previously infected group was defined as individuals who had a positive SARS-CoV-2 RT-PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period. These groups were matched in a 1:1 ratio by age, sex, and residential socioeconomic status.

Two of the three statistical models conducted by the authors met the eligibility criteria for this review. The most relevant model (Model 1) matched for the time of the exposure event (vaccination or initial infection), thus individuals included in the unvaccinated previously infected cohort were all SARS-CoV-2 positive between 1 January 2021 and 28 February 2021. Outcomes were evaluated from 1 June to 14 August 2021 when the Delta variant was dominant in Israel. Individuals in both groups had been vaccinated or exposed to the SARS-CoV-2 for at least three months. There were 16,215 persons in each group. After adjusting for comorbidities, the authors found an 8.06 fold (95% CI 1.01 to 64.55; p = 0.049) increased risk of hospitalisation for COVID-19 in fully vaccinated patients compared with those previously infected. Previous HIQA reviews have highlighted that re-infection is a rare event,[108] therefore the absolute difference in risk may be small, and confidence intervals for this analysis are very wide indicating substantial uncertainty.[108]

In direct response to the study by Gazit et al.,[43] a comparable retrospective cohort study was conducted by Young-Xu et al.[78] in a US Veterans population. Part of the study design was matched to that of Gazit et al., focusing on exposure (that is, infection or vaccination) during January and February 2021 and outcome assessment (that is, reinfection or breakthrough infection) during June, July, and the first half of August 2021. The study population included all Veterans enrolled under the care of Veterans Health Administration (VHA) aged 18 or older. Similar to Model 1 in the study by Gazit et al., individuals who had no SARS-CoV-2 infection prior to 1 January 2021, and then prior to 1 March 2021 were either fully vaccinated or had a documented, laboratory-confirmed, SARS-CoV-2 infection and were unvaccinated. The outcome assessment occurred between 1 June and 18 August 2021 when the Delta variant was dominant. However, unlike the study by Gazit et al., matched Cox survival models to compare time to events of interest by type of immunity were

constructed. Additionally, each previously infected Veteran was matched with up to four vaccinated individuals (Pfizer-BioNTech or Moderna), based on state and index event dates, race/ethnicity, age groups, sex, rural/urban, Charlson Comorbidity Index (CCI) and Veterans Affairs priority groups (based largely on disabilities).

This study involved a total of 47,102 US Veterans with a mean (SD) age of 62.8 (14.1) years, 91.3% of whom were male. A total of 9,539 patients with SARS-CoV-2 infection during the first two months of 2021 were matched to 14,458 and 23,105 participants fully vaccinated with mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) mRNA vaccines, respectively. Estimates based on the matched, adjusted multivariable Cox model showed that between June and August 2021, there was no significant difference in the risk of hospitalisation between vaccinated and previously infected individuals. For infection, using previously infected patients as the reference, those who received mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech) vaccines had a 66% [HR: 0.34 (95% CI, 0.14 to 0.78)] and 68% [HR: 0.32 (95% CI, 0.14 to 0.70)] significantly lower hazard of infection, respectively. Focusing on infection during July and August specifically, during which time the prevalence of Delta variant reached 100% in most of the US, no difference in the risk of infection was observed. However, there was substantial uncertainty associated with these estimates (HR 2.45 [95% CI, 0.56 to 20.66] and HR 1.89 [95% CI, 0.49 to 7.28] for mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech), respectively) as indicated by the wide confidence intervals.

The authors surmised that the differing results between the current study and that by Gazit et al. may be due to differences in population (in particular the older age profile in the study by Young-Xu et al.), statistical models or the availability of an additional vaccine (that is, mRNA-1273(Moderna)). The authors also consider the possibility that Israel had reached herd immunity at the time of the study by Gazit et al. and hence differences between vaccinated and unvaccinated individuals may have appeared to be minimal at that time.

In the study by Kojima et al.,[(76)] the relative risk of SARS-CoV-2 infection among individuals who were SARS-CoV-2 naïve (no prior infection), previously infected, or fully vaccinated was assessed in employees of a clinical laboratory in the US, where all employees were screened daily using PCR. Using an electronic laboratory information system, employees were divided into three groups:

- Group 1: no previous infection and unvaccinated (n=4,313)
- Group 2: previous SARS-CoV-2 infection and unvaccinated (n=254)
- Group 3: fully vaccinated, with either BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) (n=739) without previous infection.

The incidence rate ratio (IRR) of those fully vaccinated compared with those with no prior infection and unvaccinated was 0.06 (95% CI: 0.02 to 0.16). The IRR of those fully vaccinated compared with prior infection was not estimable due to zero events in the previously infected group. The authors concluded that previous SARS-CoV-2 infection and vaccination for SARS-CoV-2 were both associated with a decreased risk infection or reinfection in a routinely screened workforce, with a lower absolute incidence rate observed in the previously infected cohort. Important limitations of this study are its relatively small sample size, that the populations are drawn from different time periods (before and after mass vaccination) and that confounders were not adequately controlled for, making direct comparisons between groups less meaningful.

In the study by Shrestha et al.,[77] the cumulative incidence of SARS-CoV-2 infection was examined among 52,238 employees in an American healthcare system. All employees of the Cleveland Clinic Health System working in Ohio on 16 December 2020, the day COVID-19 vaccination was started, were included in this retrospective cohort study. The study period was from 16 December 2020 until 15 May 2021, with historic PCR results available from 12 March 2020. Vaccine effectiveness was examined separately in a previously infected cohort and a cohort with no history of previous infection.

In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (aHR 0.031, 95% CI: 0.015 to 0.061), but not among those previously infected (aHR 0.313, 95% CI: 0 to infinity) because there were no reinfections.

3.2.8 Quality of included effectiveness studies

Quality appraisal was conducted using the NIH Quality Assessment Tools.[25]

The quality appraisal of the 32 cohort studies,[36-40, 42-54, 58, 59, 61, 62, 64, 67, 70, 71, 73, 74, 76, 78-81] and the 12 case-control studies,[35, 38, 41, 56, 60, 65-68, 72, 102, 103] are described in Appendix B (Tables App.B1, App.B2 and App.B3). Of the 44 observational studies, eleven were rated as good quality,[39, 51, 56-58, 60, 61, 64, 69, 72, 82], 22[36-38, 40, 42, 52-54, 59, 65, 66, 68, 70, 73, 74, 76, 79-81, 104, 107] were appraised as being of fair quality and eleven[35, 44-46, 49, 50, 62, 67, 71, 73, 75, 78] of poor quality.

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 VE studies. Individuals aware of their vaccinated status may have altered their testing behaviour. Routine testing regardless of vaccination or symptom status (such as that described in the study by Pouwels et al.[39]) 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. For instance, Emborg et al.[51] was rated as good quality for this reason. Studies comparing early vaccinees with late vaccinees were not downgraded because of outcome ascertainment bias as both groups are expected to have similar propensities for testing.

Two analyses have been published of the HEROES-RECOVER study.[47, 105], which we consider as one study for the purposes of this review. The first analysis by Thompson et al.[47] was rated as of good quality. However, as insufficient information regarding loss to follow-up was presented in the updated analysis by Fowlkes et al.,[105] this study could only be considered of fair quality.

Other concerns for which studies were downgraded related to defining the population,[104] and incomplete presentation of matching methods, and spurious results suggesting that significant confounding remained in the final analysis.[35]

Thirty studies are currently published as preprints[35, 36, 38-40, 42, 44, 45, 49, 51-54, 56-60, 62, 70, 73-76, 78-82, 104] and have not yet been formally peer-reviewed, raising additional concerns about the overall quality and the potential for results to change prior to formal publication.

4 Discussion

4.1 Summary of findings

In the following sections, evidence for the duration of efficacy and effectiveness are presented by study outcome for each of the populations of interest. The World Health Organization (WHO) have recommended that the primary goal of immunisation is to protect against hospitalisation, severe disease and death which are the primary outcomes of this review.[109] This section primarily focusses on studies which report vaccine efficacy or effectiveness beyond 14 weeks post-vaccination.

4.1.1 General Population

Primary Outcome: COVID-19 related mortality

The RCTs identified in this review were not designed or powered to examine efficacy against COVID-19 related mortality.[31-33, 55, 110]

The large study by Public Health England provides the strongest evidence for vaccine effectiveness for COVID-related mortality over time in the general population.[56] In those aged 16 years and over, vaccine effectiveness against the Delta variant exceeded 78% at all-time points examined up to 20 weeks post-vaccination. There was some evidence to suggest a decline in effectiveness over time for the ChAdOx1 (AstraZeneca) vaccine with estimated vaccine effectiveness of 94.1% (95% CI 91.8 to 95.8) and 78.7% (95% CI 52.7 to 90.4) for the periods two to nine weeks, and more than 20 weeks, after the second dose, respectively. A similar decline was not observed with the BNT162b2 (Pfizer/BioNTech) vaccine which had an estimated vaccine effectiveness of 90.4% (95% CI 85.1 to 93.8) more than 20 weeks after dose two. However, the authors report that the groups who received the two vaccines differed, so it is uncertain if the differences observed can be attributed to differences in vaccine performance. Evidence from a Qatar study provides similar results for BNT162b2 (Pfizer/BioNTech) up to 14 weeks after dose two, but this study was considered of poor quality.[35]

Primary Outcome: Severe Disease

Vaccine efficacy estimates for severe disease exceeded 95% in two RCTs with six months follow-up;[34, 55] however, neither trial reported changes in efficacy over time.

Observational studies identified in this review reported effectiveness at multiple time points, with data available up to six months following the final regimen dose.

Conclusions regarding the potential waning of effectiveness differed across studies and by vaccine type.

Across five studies (three US,[64, 69, 102] one Qatar[35] and one the Netherlands[59]), with up to six months follow-up after the final dose, no evidence of a decline in vaccine effectiveness over time was noted. Overall vaccine effectiveness for severe disease exceeded 75% at all time points in these five studies for BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna).

Three analyses found evidence of waning over time, but the changes in vaccine effectiveness differed by vaccine. A large US study observed a decline in vaccine effectiveness over time for BNT162b2 (Pfizer/BioNTech) from 91% (95% CI 88 to 93) to 77% (95% CI 67 to 84) for the periods 14-120 days and >120 days after dose two, respectively.[68] This decline was not observed for mRNA-1273 (Moderna), where vaccine effectiveness was sustained at 93% (95% CI 90 to 95) and 92% (95% CI 87 to 96) over the same time periods. Conversely, a UK study by Public Health England observed that vaccine effectiveness was sustained over time for the BNT162b2 (Pfizer/BioNTech) vaccine (VE 92.7%; 95% CI 90.3 to 94.6) ≥20 weeks after dose two) with a reduction in VE observed for ChAdOx1 (AstraZeneca) from 95.2% (95% CI 94.6 to 95.6) to 77% (95% CI 70.3 to 82.3) for the periods two to nine weeks and ≥20 weeks after the second dose, respectively.[56] The REACT-SCOT study by Public Health Scotland, with up to approximately six months follow-up, found some evidence of waning during the first two months after the second dose in an analysis of the ChAdOx1 (AstraZeneca) and the mRNA vaccines combined. Effectiveness plateaued thereafter; however, the absolute fit of the model to the data was not provided, so it is difficult to assess the robustness of the approach.[60]

Compared to the mRNA vaccines, there were less long term follow-up data available for Ad26.COV2.S (Janssen) with substantial variability in the vaccine effectiveness estimates. Polinski et al. reported stable effectiveness of 73% for Ad26.COV2-S (Janssen) over a mean time since vaccination of fifteen weeks. A study from the VISION network with a median follow-up of 16 weeks observed effectiveness of 60%,[66] while effectiveness of 91% over a follow-up period of at least 20 weeks was observed by de Gier et al. (albeit noting that few people aged over 70 years were included in this latter analysis).[59] In an analysis of Veterans Affair data, recipients of Ad26.COV2.S (Janssen) had higher occurrences of COVID-19 hospitalisation compared to recipients of BNT16b2(Pfizer/BioNTech) and mRNA-1273(Moderna).[79]

A highly cited study by the US CDC (Rosenberg et al.), examined changes in age-adjusted vaccine effectiveness against hospitalisation and infection.[111] The study did not meet inclusion criteria for this review as vaccination dates and time since vaccination were not reported. While a decline in effectiveness against any infection

was noted, it coincided with an increase in the Delta variant from less than 2% to over 80% of sequenced samples. The authors highlighted the challenges in interpreting the findings in these circumstances, noting uncertainty as to whether the observed reductions in effectiveness were due to waning immunity, reduced effectiveness versus the Delta variant, other unmeasured confounding or a combination of these factors.

Secondary outcome: symptomatic and any infection

The Ad26.COV2.S (Janssen), BNT162b2 (Pfizer/BioNTech), and mRNA-1273 (Moderna) RCTs formally examined changes in vaccine efficacy over time.[30-34, 55] No decline in vaccine efficacy was identified up to 12 weeks after vaccination in the Ad26.COV2.S (Janssen) trial for moderate to severe-critical COVID-19 (66.1%%),[30] or up to six months for mRNA-1273 (Moderna) for symptomatic disease (93.2%).[55] While estimates in the BNT162b2 (Pfizer/BioNTech) trial suggest a possible decline in efficacy over time, there are concerns that the trial design may have led to biased measurement of the change in vaccine efficacy.[32-34] Vaccine efficacy still exceeded 83% for symptomatic disease up to six months after the second dose. After the review was conducted, another trial of ChAdOx1 (AstraZeneca) was identified, but the median follow-up was between six and eleven weeks.[112] Overall estimated vaccine efficacy for symptomatic disease was 74.0% (95% CI 65.3 to 80.5) and estimated vaccine efficacy was 83.5% (95% CI 54.2 to 94.1) in participants 65 years of age or older.

In contrast to the RCT results, evidence of vaccine waning for symptomatic and any infection was noted in the observational studies. For example, vaccine effectiveness estimates based on data from the Kaiser Permanente Healthcare System are not consistent with these results.[64]

Waning effectiveness over time was also observed in two UK studies. The study by Public Health England observed waning effectiveness for symptomatic disease for both BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca).[56] No waning was observed for mRNA-1273 (Moderna), but follow-up was shorter (10-14 weeks), and confidence intervals were wide (VE 90.3% 95% CI 67% to 97% at 10 -14 weeks after dose two). Vaccine effectiveness for ChAdOx1 (AstraZeneca) declined from 66.7% (95% CI 66.3 to 67.0) to 47.3% (95% CI 45.0 to 49.6) over the period from two to nine weeks to more than 20 weeks after the second dose while vaccine effectiveness for BNT162b2 (Pfizer/BioNTech) declined from 80.1% (95% CI 77.5 to 82.4) to 55.3% (95% CI 50.2 to 60.0) over the same periods.[56] Another UK study found evidence of differences by vaccine when considering those with any infection with a Ct<30; waning was observed for BNT162b2 (Pfizer/BioNTech), but not for ChAdOx1 (AstraZeneca).[39]

Data from four Israeli studies for any infection comparing early and late vaccinees suggested waning effectiveness over time with conflicting results regarding the association of waning with age.[42, 70, 80, 104]

Data from a large UK-based longitudinal survey of over 750,000 people compared the BNT162b2 (Pfizer/BioNTech) and ChAdOX1 (AstraZeneca) vaccines during periods when the Alpha and Delta variants of concern dominated.[39] While the effectiveness of ChAdOx1 (AstraZeneca) was similar to BNT162b2 (Pfizer/BioNTech) against symptomatic infection and in those with a Ct<30 in the Alpha dominant phase, its effectiveness was significantly lower than the equivalent Delta phase data for BNT162b2 (Pfizer/BioNTech). Lower estimates of effectiveness were also observed for ChAdOx1 (AstraZeneca) against any infection during the Alpha and Delta dominant phases, with these estimates noted to be significantly lower than those observed for BNT162b2 (Pfizer/BioNTech) in the Delta phase. These trends were also observed in a UK study by Public Health England,[56] but no formal tests were conducted to detect differences in effect.

In the US, evidence was identified that compared the mRNA vaccines to Ad26.COV2.S (Janssen), for both BNT162b2 (Pfizer/BioNTech) and mRNA-1273(Moderna) there was a lower occurrence of documented SARS-CoV-2 infection (aHR 0.54, 95% CI 0.51 to 0.58; aHR 0.36; 95% CI 0.33 to 0.38; for BNT162b (Pfizer BioNTtech) and mRNA-1273 (Moderna) respectively).[79] Another study reported no evidence of waning effectiveness over a mean follow-up of 15 weeks for Ad26.COV2.S (Janssen) with an estimated vaccine effectiveness of 69% (95% CI 67% to 71%), but the study was considered of poor quality.[62]

It is unclear if the inconsistency between efficacy and effectiveness for symptomatic and any infection is due to differences in populations between trials, unmeasured confounding or differences in the prevalence of variants of concern. While no firm conclusions can be drawn due to differences in the groups who received different vaccines, it is possible that the vaccines differ in their initial effect, their effect against the different variants, and the extent to which waning occurs. The potential impact of these findings is that some groups in the population with a suboptimal initial response to vaccination (for example, due to immunosenescence or an immunocompromising condition) may, over time, no longer have sufficient protection against COVID-19.

4.1.2 Individuals over 65 years

Primary Outcome: COVID-19 related mortality

Two large observational studies from the UK and Portugal, investigated effectiveness in older adults, the first in inidividuals aged over 65 and the second in those over 80. While a decrease over time was noted, both studies report effectiveness in excess of 74%, with maximum follow-up times of 20 weeks and 14 weeks after dose two for the UK and Portugeese study respectively.

Primary Outcome: Severe Disease

In all studies, point estimates for vaccine effectiveness for severe disease fell over time, but the change was not statistically significant in any study. Overall vaccine effectiveness remained over 74% across all these studies.

A number of the included studies found no difference in vaccine effectiveness for severe disease over time when stratified by age. For example, similar vaccine effectiveness over time was observed for those aged less than 60 and those aged 60 years and older up to 24 weeks after vaccination in a Qatar study,[35] and for those aged less than 65 years compared with those aged 65 years and older up to six months after vaccination in two US observational studies.[64] In a Portuguese study, no difference was observed in vaccine effectiveness for those age 80 and older, up to approximately 14 weeks post-dose two.[61]

In contrast, a number of studies reported differences in vaccine effectiveness for severe disease when stratified by age. For example, Thompson et al. (b) examined vaccine effectiveness in those over 50 years of age.[69] Subgroup analysis over a median follow-up of 12 weeks showed no difference in VE for hospitalisation in patients 85 years of age or older (VE 84%). However, in an updated analysis for the same data source during the Delta period (median time since final dose: 16 weeks), Grannis et al. reported a significantly lower vaccine effectiveness (76% vs. 89%) for adults aged 75 years or older compared with those aged less than 75 years. Polinski et al. estimated that vaccine effectiveness for COVID-19 related hospitalisation over a mean follow-up of 15 weeks 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) versus 79% (95% CI 74 to 84), respectively.[62] However, these age-stratified data from Grannis et al.,[66] and Polinski et al., [62] do not tell us whether vaccine effectiveness is waning over time, effectiveness may initially be lower in older adults.

In the Netherlands, vaccine effectiveness for those aged 70 years or older for hospitalisation was 92% (95% CI 90 to 93), 64% (95% CI 47 to 76), 78% (95% CI

63 to 86) for BNT162b2 (Pfizer BioNTech), mRNA-1273 (Moderna), and ChAdOx1 (AstraZeneca) respectively. No data for those aged 70 years or older was available for Ad26.COV2-2 (Janssen) from this study.[59]

The relationship between vaccine effectiveness and age for severe disease is inconsistent for adults aged over 65 across studies. Imprecision, and possible confounding due to the correlation between increasing age and increasing prevalence of co-morbidities may be responsible for some of this inconsistency.

Only the study by Public Health England provided data for adults aged 65 year or older who were not identified as having risk conditions.[56] The authors note sustained high levels of protection against hospitalisation in these individuals, with an estimated vaccine effectiveness of almost 95% for BNT162b2 (Pfizer/BioNTech) and almost 80% for ChAdOx1 (AstraZeneca) over 20 weeks after dose two.[56]

Secondary Outcomes: Symptomatic Disease.

The Public Health England study reported vaccine effectiveness for those aged 65 years or over for symptomatic disease.[56] There was evidence of waning effectiveness between two to nine weeks to 20+ weeks, with estimates declining from 80.1% to 55.3% for BNT162b2 (Pfizer BioNTech) and from 88.9% to 36.6% for ChAdOx1 (AstraZeneca). Waning in those aged over 65 appeared to be greater than for those aged 40 to 64 years. However, subgroup analysis by clinical risk group status was not reported, so it is not possible to ascertain the role that co-morbidities may have in understanding this change.

In those aged 65 years or older, a study based on the Kaiser Permanente Healthcare system in California, estimated vaccine effectiveness for any infection was 75% (95% CI 65 to 83) at two to three months and 43% (95% CI 30 to 54) five or more months after vaccination.[64] A second study from the Kaiser Permanente Healthcare system found similar waning of effectiveness for those aged 18-64 years compared to those aged 65 years or older, but 95% confidence intervals for the latter were very wide.[57] However, across the total follow-up period, vaccine effectiveness for any Delta infection was lower among individuals aged 65 years or older (75.2%) than those aged 18-64 years (87.9%).

Limited evidence for Ad26.COV2-2 (Janssen) vaccine for symptomatic disease was found in this age cohort. Polisnki et al. observed lower effectiveness for those aged older than 60 years compared to those less than 60 years. Sharma et al. observed lower effectiveness for Ad26.COV2-2 (Janssen) compared to mRNA vaccines in a US veteran cohort where the median age was 70 years.

4.1.3 Patients with co-morbidities and immunocompromising conditions

Individuals with co-morbidities and immuncomprising conditions are at a greater risk of severe disease outcomes following infection with SARS-CoV-2 and they constitute a larger proportion of the critical and hospitalised cases. For example, in the Scottish study outlined by McKeigue et al., those who have designated risk conditions or are in a clinically extremely vulnerable group account for 88% of critical cases and 77% of hospitalised cases.[103] Therefore, examining the duration of protective immunity for this group is particularly important.

Primary Outcome: COVID-19 related mortality and severe disease

No evidence was identified for COVID-19-related mortality in those with co-morbidities or immunocompromising conditions.

No efficacy data for severe disease was identified for those with an immunocompromising condition. Two studies of fair quality were identified that examined vaccine effectiveness over time in patients with immunocompromising conditions with inconsistent results.[54, 102] While both included the BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines, differing estimates of vaccine effectiveness against severe disease were reported. As noted previously, caution should be taken in comparing estimates across studies given differences in the populations and duration of follow-up as well as potential differences in the outcome assessed (for example, what constitutes severe disease).

The analysis of a CDC case-control study of hospitalised patients[107] found that vaccination (BNT162b2 (Pfizer/BioNTech) / mRNA-1273 (Moderna)) was significantly less effective in preventing COVID-19 related hospitalisations in those with immunocompromising conditions compared to those without, (63% (95% CI 44 to 76) versus 90% (95% CI 87 to 92)).[41] No evidence of waning effectiveness was observed up to 24 weeks, but confidence intervals were wide at all time points, thus the potential for waning over time cannot be excluded based on the data presented. Given the data from this study suggests that those with an immunocompromising condition start off with a lower level of vaccine effectiveness than those without, further reductions in effectiveness in this group could be of concern. While lower than for the general population, the study suggests that vaccination still confers protection from hospitalisations in individuals with immunocompromising conditions with an estimated vaccine effectiveness of 53.6% (95% CI 12.8 to 77.8) 13-24 weeks after the second dose. This study found no statistically significant difference or change in vaccine effectiveness for hospitalisation over time for those with multiple morbidities.

In a study limited to individuals who had previously received a kidney transplant,[54] vaccination was found to be effective in preventing severe disease, with numerical increases in vaccine effectiveness observed when comparing estimates at ≥ 2 weeks (VE 72.3%; 95% CI 0.0 to 90.9) versus ≥ 8 weeks (VE 83.8%; 95% CI 31.3 to 96.2) after the second dose. A study with a mean follow-up of 15 weeks presented estimates for the immunocompromised population.[62] Compared to the study in kidney transplant patients, the estimated vaccine effectiveness for Ad26.COV2.S (Janssen) vaccine were lower for those with immunocompromising conditions with estimates of 54% (95% CI 35 to 67) and 52% (95% CI 42 to 60%) for COVID-related hospitalisation and infection respectively.

No further evidence was found regarding people with immunocompromising conditions specifically, but the clinically extremely vulnerable group defined in the UK study by Public Health England, [56] and in the REACT-SCOT study in Scotland included some individuals with severe immunocompromising conditions.[56]

Data from Public Health England for those aged 65 years and older who were categorised as being in a clinically extremely vulnerable group estimated vaccine effectiveness for hospitalisation for BNT162b2 (Pfizer/BioNTech) which fell from 94.6% to 71.4% and for ChAdOx1 (AstraZeneca) and from 79.3% to 59.4% between the periods 2-9 weeks and 20+ weeks after dose two, respectively.[56]

Vaccine effectiveness across all ages in the clinically extremely vulnerable groups is presented in the REACT-SCOT study.[103] Vaccine effectiveness is lower in the clinically extremely vulnerable (CEV) category compared to those without risk conditions (66%). Stratified analysis by vaccines showed that consistent with the Public Health England data, vaccine effectiveness is numerically lower for those who received the AstraZeneca vaccine compared to those who received mRNA vaccines, but differences were not statistically significant. CEV group comprise a heterogeneous group of conditions, but insufficient data were identified to inform comparisons of effectiveness within the group.[113]

Public Health England data also showed evidence of waning in those aged 40 to 64 years defined as being in a clinically extremely vulnerable risk or clinical risk group. Vaccine effectiveness for hospitalisation for ChAdOx1 (AstraZeneca) fell from 93.7% (95% CI 92.3% to 94.8) to 69.7% (95% CI 29.7 to 86.9) between the periods 2-9 weeks and 20 + weeks after dose two, respectively. However, confidence intervals are very wide and formal statistical tests for a change over time are not reported. Given the high effectiveness observed in the clinical risk group in REACT-SCOT Scottish study (89% 95% CI 85 to 92), the reduction in those aged 40-64 years in the Public Health England study may be driven by those with most severe disease in the CEV group rather than the clinical risk group whose conditions are milder. This

conclusion is supported by the results of other studies which have not observed waning effectiveness in those with co-morbidities.[102] Comparisons are difficult, as results were not reported for all groups. The clinical risk group includes those with a wide range chronic conditions, for example those with cardiovascular disease, respiratory disease, neurological disease and some patients on immunosuppressants.[114] Clinically extremely vulnerable groups include those with severe respiratory conditions and those receiving specific immunosuppressing treatments.

Secondary outcome: symptomatic and any infection

A study using data from the UK Office for National Statistics reported that vaccine effectiveness estimates were lower for those with a self-reported long-term health condition compared with those without (range 81-92% versus 86-94% and 58-65% versus 69-73% for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca), respectively), but differences were not statistically significant.[39] As the interaction effect between long-term health conditions and age was not accounted for, these results should be interpreted with caution. Graphs for the odds of any infection over time would appear to suggest greater vaccine waning in those with long term conditions.[39] However, it is not possible to interpret this as evidence of an effect.

4.1.4 Healthcare workers

Primary Outcome: COVID-19 related mortality and severe disease

No evidence (efficacy or effectiveness) for the primary review outcomes of mortality and severe disease was identified for HCWs.

Secondary outcome: symptomatic and any infection

RCT data for the secondary review outcomes were limited to the mRNA-1273 (Moderna) vaccine based on six months follow-up data. No significant difference was observed for symptomatic disease in HCWs compared to the rest of the trial population, with efficacy exceeding 94% in both groups.[55]

Of the observational studies examining vaccine effectiveness in HCWs, the quality of the studies identified was generally considered poor due to the limited adjustment for confounders. For vaccine effectiveness for any infection, the longest follow-up was available from two US-based studies (HEROES-RECOVER and Pilishvili et al.) with maximum follow-up of approximately five months.[47, 48, 72] While the point estimates for both studies suggested a decline in vaccine effectiveness over time, confidence intervals were wide and overlapping and as such the data are insufficient

to support a conclusion of waning immunity.[48, 72] Furthermore, the observed decline in vaccine effectiveness corresponded with the modestly reduced effectiveness seen for the Delta versus Alpha variant observed in other studies, contributing to further uncertainty as to the cause of the declining effectiveness.[115]

4.1.5 Residents and staff of long term care facilities

Despite being one of the earliest groups prioritised for vaccinations, limited data were identified on the change in vaccine effectiveness over time in residents or staff of LTC facilities. This may be because of the rapid rollout and uptake of vaccination in these cohorts which diminished the size of the unvaccinated cohort available for the comparison. Across the outcomes considered, the maximum duration of follow-up was 11 weeks.

Primary Outcome: COVID-19 related mortality

The strongest evidence for vaccine effectiveness for mortality in LTC residents comes from the Public Health England Study.[74] No evidence of waning was observed for either BNT162b2 (Pfizer/BioNTech) or ChAdOx1 (AstraZeneca) for ≥61 days after the second dose, although it is noted that point estimates were lower for ChAdOx1 (AstraZeneca).

No evidence (efficacy or effectiveness) was identified for staff of LTC facilities.

Primary Outcome: Severe Disease

No long term data were identified for severe disease outcomes in LTC residents. The observed vaccine effectiveness is initially high with one study,[51] reporting estimates of 75% (95% CI 46 to 89), over a median follow-up of ten weeks and another study reporting 86% (95% CI 67 to 94) for severe disease after nine weeks follow-up.[52]

No evidence (efficacy or effectiveness) was identified for staff of LTC facilities.

Secondary outcome: symptomatic and any infection

For residents of LTC facilities, vaccine effectiveness estimates for any infection observed in two studies (53% and 49%) after ten and nine weeks follow-up, respectively, were lower than that observed in studies of the general population.[51, 52] Only one study considered vaccine effectiveness over time,[74] with no evidence of waning for BNT162b2 (Pfizer/BioNTech) two months after the second dose. Point estimates were numerically lower for ChAdOx1 (AstraZeneca) compared to BNT162b2 (Pfizer/BioNTech) and fell over time (>61 days, maximum not reported), but confidence intervals were wide and overlapping at all time points.

One study examined vaccine effectiveness in staff of LTC facilities, with a mean time since vaccination of 11 weeks, the vaccine effectiveness for any infection was considered high at 89%.[53]

A frequently cited CDC study, by Nanduri et al. was identified that examined vaccine effectiveness of the BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines overtime in nursing home residents.[116] The study did not meet the inclusion criteria for this review as the time since vaccination was not reported. While a reduction in vaccine effectiveness against any infection was seen between the periods March to May 2021 compared with June to July 2021, the reduction coincided with an increased prevalence of the Delta variant. Given a lack of data, the study was unable to adjust for many confounders including age and co-morbidities.

4.2 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.[117] 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 a number of 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.

Over half of the papers identified (30/57) are only published as preprints,[35, 36, 38-40, 42, 44, 45, 49, 51-54, 56-60, 62, 70, 73-76, 78-82, 104] and thus have not yet been formally peer-reviewed, raising additional concerns about the 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.[117]

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.[118] 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 Andrews et al.[56] and Thompson et al.,[69] 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.[117]

Estimating changes in effectiveness over time in real-world observational studies is difficult for a number of 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.

5 Conclusion

The aim of this evidence summary was to assess the duration of vaccine efficacy and effectiveness against COVID-19, and to identify any evidence of waning in particular populations.

The RCTs identified in this review were not designed or powered to examine efficacy against COVID-19 related mortality. Limited evidence from observational studies suggests no waning of vaccine effectiveness for mortality for up to 20 weeks after vaccination with observed rates of protection remaining high.

In terms of severe disease, overall vaccine efficacy exceeded 95% in the general population for both BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) vaccines, in the two RCTs presenting this outcome, up to six months post-vaccination. Conclusions regarding potential waning of effectiveness in observational studies differed across studies and by vaccine type. For the general population, vaccine effectiveness for severe disease for mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNTech), and ChAdOx1 (AstraZeneca) vaccines were considered high with estimates of at least 77% at every time point examined across all studies with up to six months of follow-up data. Evidence of effectiveness was more limited and inconsistent for Ad26.COV.2S (Janssen), ranging from 60% (median 16 weeks) to 91% (up to 20 weeks).

Three RCTs examined vaccine efficacy for symptomatic infection over time. No decline in efficacy was identified up to 12 weeks after vaccination with Ad26.COV2.S (Janssen) for moderate to severe-critical COVID-19, or up to six-months for mRNA-1273 (Moderna) for symptomatic disease. While estimates for the BNT162b2 (Pfizer/BioNTech) suggest a possible decline in efficacy over time, there are concerns that the trial design may have led to biased measurement of the change in vaccine efficacy; nonetheless, vaccine efficacy exceeded 83% for symptomatic disease up to six months after vaccination. In observational studies, effectiveness estimates for symptomatic infection for BNT162b2 (Pfizer/BioNTech) vaccine and ChAdOx1 (AstraZeneca) were as low as 47% at six-months.

For those aged 65 years or older without co-morbidities, overall point estimates for effectiveness for severe disease tended to be lower for older adults (particularly those aged over 65 years) compared with younger adults, but this was not consistent across all studies. There was also a trend for estimates to be lower when comparing longer with shorter durations of follow-up. Vaccine effectiveness for severe disease remained over 74% up to six-months after the second dose. Lower point estimates were reported for individual vaccines or limited subgroups, in a number of studies that did not report changes in effect over time. Similar to the

general population, there was evidence of waning for symptomatic disease with vaccine effectiveness as low as 36% after six-months for ChAdOx1 (AstraZeneca).

There is some evidence that vaccine effectiveness for severe disease may be lower for those with an immunocompromising condition or for vulnerable groups compared with the general population. There was also some evidence to suggest waning in those aged over 65 years in a clinically extremely vulnerable group compared to the general population. For those with other co-morbidities, the evidence of waning effectiveness was inconsistent.

No efficacy or effectiveness evidence specific to HCWs was identified for mortality or severe disease. However, evidence was identified to suggest that vaccine efficacy for symptomatic disease did not differ for HCWs compared to the general population. For any infection, all studies reported effectiveness in HCWs exceeding 80% up to five months after vaccination. One study reported effectiveness beyond five months with a small decline in vaccine effectiveness observed.

The change in effectiveness for mortality and infection over time for residents of LTC facilities was reported on in one study. Data were limited to follow-up for ≥61 days after the second dose with no evidence of waning of effectiveness over time observed for either BNT162b2 (Pfizer/BioNTech) or ChAdOx1 (AstraZeneca); however, point estimates were lower for the latter.

Overall, the evidence suggests that vaccination against COVID-19 continues to provide protection for at least six months post-vaccination. However, there are limited data to suggest potential waning of vaccine effectiveness for severe disease and mortality in individuals at higher risk of poor disease outcomes. Given the noted lower initial vaccine efficacy and effectiveness in these populations, any reduction 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.A1

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 Health Care 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%29001 69-1	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%29303 92-1	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/10.2174/092986732866210902094254	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 health care 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 health care 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;
Núñez López 2021	Untitled	10.1016/j.eimc.2021.06.021	Exclusion reason: Duplicate;

Núñez López 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 Health Care 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 health care 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 Health Care 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 Health Care 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 health care 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 health care 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 health care 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 healthy adults: a randomized, double-blind, placebo-controlled, Phase I trial	http://dx.doi.org/10.1080/22221751.2021.1951126	Exclusion reason: Wrong outcomes;

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 cross sectional studies from the general population.

	General Population									
Quality appraisal criteria	**Bruxvoort (2021) a[57]**	**De Gier (2021)[59]**	**Nunes (2021)[61]**	**Pawlowski (2021) [37]**	**Puranik (2021)a [38]**	**Polinski (2021)[62]**	**Pouwels (2021) [86]**	**Saciuk (2021)[40]**	**Sharma (2021)[79]**	**Tartof (2021)[64]**
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	✓	✓	✓	✓	✓	CD	✓	✓	✓
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	General Population									
Quality appraisal criteria	**Bruxvoort (2021) a[57]**	**De Gier (2021)[59]**	**Nunes (2021)[61]**	**Pawlowski (2021) [37]**	**Puranik (2021)a [38]**	**Polinski (2021)[62]**	**Pouwels (2021) [86]**	**Saciuk (2021)[40]**	**Sharma (2021)[79]**	**Tartof (2021)[64]**
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?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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	✓	✓	✓	✓	✓	X	✓	X	X	✓

	General Population									
Quality appraisal criteria	**Bruxvoort (2021) a[57]**	**De Gier (2021)[59]**	**Nunes (2021)[61]**	**Pawlowski (2021) [37]**	**Puranik (2021)a [38]**	**Polinski (2021)[62]**	**Pouwels (2021) [86]**	**Saciuk (2021)[40]**	**Sharma (2021)[79]**	**Tartof (2021)[64]**
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	✓	✓	✓	✓
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	CD	✓	✓	CD	CD	CD
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD

	General Population									
Quality appraisal criteria	**Bruxvoort (2021) a[57]**	**De Gier (2021)[59]**	**Nunes (2021)[61]**	**Pawlowski (2021) [37]**	**Puranik (2021)a [38]**	**Polinski (2021)[62]**	**Pouwels (2021) [86]**	**Saciuk (2021)[40]**	**Sharma (2021)[79]**	**Tartof (2021)[64]**
13. Was loss to follow-up after baseline 20% or less?	CD But likely to be low in large health insurer.	✓	✓	✓	✓	✓	CD	✓	NR	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	✓	✓	✓	✓	✓
Quality Rating†	Good	Fair	Good	Fair	Fair	Poor	Good	Fair	Fair	Good
Comment	Some concern regarding outcome ascertainment bias but primary review otucoems are reported.	Underlying conditions or other cofounders not taken into account.		Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level	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	Concern regarding outcome ascertainment bias, only secondary review outcomes are reported.	

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

Table App.B2: Quality appraisal of observational cross sectional studies studies with hospitalised patients, examined early versus late vaccination or natural or vaccine derived immunity.

	Hospitalised Patients	General population (Early vs. late vaccinaton)				General Population (SARS-CoV2 infection derived versus Vaccine Derived immunity			
Quality appraisal criteria	**Griffin (2021)[67]**	**Goldberg (2021) [70]**	**Israel (2021)[42]**	**Kertes (2021)[80]**	**Mizrahi (2021)[104]**	**Gazit (2021)[36]**	**Kojima (2021)[76]**	**Shrestha (2021)[81]**	**YoungXu(2021) [78]**
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	X	✓	✓	✓	✓
3. Was the participation rate of eligible persons at least 50%?	X	✓	✓	✓	✓	✓	✓	✓	✓
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	X	X	X	X	X	✓	X	✓	CD

	Hospitalised Patients	General population (Early vs. late vaccinaton)				General Population (SARS-CoV2 infection derived versus Vaccine Derived immunity			
Quality appraisal criteria	**Griffin (2021)[67]**	**Goldberg (2021) [70]**	**Israel (2021)[42]**	**Kertes (2021)[80]**	**Mizrahi (2021)[104]**	**Gazit (2021)[36]**	**Kojima (2021)[76]**	**Shrestha (2021)[81]**	**YoungXu(2021) [78]**
study pre-specified and applied uniformly to all participants?									
5. Was a sample size justification, power description, or variance and effect estimates provided?	X	✓	✓	✓	✓	✓	✓	✓	✓
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	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Hospitalised Patients	General population (Early vs. late vaccinaton)				General Population (SARS-CoV2 infection derived versus Vaccine Derived immunity			
Quality appraisal criteria	**Griffin (2021)[67]**	**Goldberg (2021) [70]**	**Israel (2021)[42]**	**Kertes (2021)[80]**	**Mizrahi (2021)[104]**	**Gazit (2021)[36]**	**Kojima (2021)[76]**	**Shrestha (2021)[81]**	**YoungXu(2021) [78]**
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	X	✓	X	X	X
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓
10. Was the exposure(s) assessed more	CD	X	X	X	X	✓	✓	✓	X

	Hospitalised Patients	General population (Early vs. late vaccinaton)				General Population (SARS-CoV2 infection derived versus Vaccine Derived immunity			
Quality appraisal criteria	**Griffin (2021)[67]**	**Goldberg (2021) [70]**	**Israel (2021)[42]**	**Kertes (2021)[80]**	**Mizrahi (2021)[104]**	**Gazit (2021)[36]**	**Kojima (2021)[76]**	**Shrestha (2021)[81]**	**YoungXu(2021) [78]**
than once over time?									
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	CD	CD	X	CD
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	CD	✓	✓	CD	✓	✓	✓	✓	CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on	X	X	X	✓	✓	CD	X	X	CD

	Hospitalised Patients	General population (Early vs. late vaccinaton)				General Population (SARS-CoV2 infection derived versus Vaccine Derived immunity			
Quality appraisal criteria	**Griffin (2021)[67]**	**Goldberg (2021) [70]**	**Israel (2021)[42]**	**Kertes (2021)[80]**	**Mizrahi (2021)[104]**	**Gazit (2021)[36]**	**Kojima (2021)[76]**	**Shrestha (2021)[81]**	**YoungXu(2021) [78]**
the relationship between exposure(s) and outcome(s)?									
Quality Rating†	Poor	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Poor
Comment	Insufficient adjustment for potential confounders, no confidence intervals presented.	Insufficient adjustment for confounders.	Insufficient adjustment potential for confounders.	Insufficient adjustment for potential confounders.	Population characteristic not given.	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level	Inconsistent assessment over time, confounding variables collected but not specified if included in analysis.

Table App.B3: Quality appraisal of cross sectional studies in healthcare and frontline workers.

	Healthcare and Frontline Workers							
Quality appraisal criteria	**Alali (2021)[44]**	**Bianchi (2021) [45]**	**Ghosh (2021)[46]**	**Giansante (2021)[71]**	**Fowlkes (2021) [105]– updated analysis of Thompson (2021)[119]**	**Issac (2021)[49]**	**Katz (2021)[73]**	**Yassi (2021) [50]**
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	X	X	✓	✓	✓	✓	X
3. Was the participation rate of eligible persons at least 50%?	✓	CD	NR	✓	✓	✓	✓	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?	✓	CD	✓	✓	✓	✓	✓	✓
5. Was a sample size justification, power description, or variance and effect estimates provided?	X	✓	X	✓	✓	✓	✓	✓

	Healthcare and Frontline Workers							
Quality appraisal criteria	**Alali (2021)[44]**	**Bianchi (2021) [45]**	**Ghosh (2021)[46]**	**Giansante (2021)[71]**	**Fowlkes (2021) [105]– updated analysis of Thompson (2021)[119]**	**Issac (2021)[49]**	**Katz (2021)[73]**	**Yassi (2021) [50]**
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	✓
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	X	✓	✓	✓	✓	✓	✓	✓

	Healthcare and Frontline Workers							
Quality appraisal criteria	**Alali (2021)[44]**	**Bianchi (2021) [45]**	**Ghosh (2021)[46]**	**Giansante (2021)[71]**	**Fowlkes (2021) [105]– updated analysis of Thompson (2021)[119]**	**Issac (2021)[49]**	**Katz (2021)[73]**	**Yassi (2021) [50]**
10. Was the exposure(s) assessed more than once over time?	✓	✓	✓	✓	✓	✓	X	✓
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	CD	✓	CD	CD	✓	CD	✓	CD
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	✓	✓	✓	✓	X	✓	✓	✓
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	X	✓	X	X	X
Quality Rating†	**Poor**	**Poor**	**Poor**	**Poor**	**Fair**	**Poor**	**Fair**	**Poor**
Comment	No adjustment for	No adjustment for any potential confounders.	Limited adjustment for confounder	Limited adjustment for confounders. Potential for	Insufficient information given regarding loss to follow-up since	No adjustment for confounders.	Some concerns regarding confounding.	Very limited adjustment for confounders. Insufficient

	Healthcare and Frontline Workers							
Quality appraisal criteria	**Alali (2021)[44]**	**Bianchi (2021) [45]**	**Ghosh (2021)[46]**	**Giansante (2021)[71]**	**Fowlkes (2021) [105]– updated analysis of Thompson (2021)[119]**	**Issac (2021)[49]**	**Katz (2021)[73]**	**Yassi (2021) [50]**
	confounders.	Insufficient descriptions of population.	s. Limited description of population provided. Potential for outcome ascertainment bias.	outcome ascertaintment bias.	original report by Thompson.			information given on whether testing differed by vaccination status.

Table App.B4: Quality appraisal of observational cross sectional studies if LTC facilities and individuals with immunocompromising conditions.

	HCW/LTC Facilities/ Homecare				Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Emborg (2021)[51]**	**Lefèvre (2021)[52]**	**Muhsen (2021)[53]**	**Subbaro (2021)[74]**	**Chemaitelly (2021)(a)[54]**
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	✓

	HCW/LTC Facilities/ Homecare				Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Emborg (2021)[51]**	**Lefèvre (2021)[52]**	**Muhsen (2021)[53]**	**Subbaro (2021)[74]**	**Chemaitelly (2021)(a)[54]**
3. Was the participation rate of eligible persons at least 50%?	✓	CD	X	✓	✓
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?	✓	CD	✓	✓	✓
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?	✓	✓	✓	✓	✓
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	✓	✓	X	✓	✓

	HCW/LTC Facilities/ Homecare				Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Emborg (2021)[51]**	**Lefèvre (2021)[52]**	**Muhsen (2021)[53]**	**Subbaro (2021)[74]**	**Chemaitelly (2021)(a)[54]**
the 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?	✓	✓	✓	✓	✓
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
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	✓	X	X	X	X

	HCW/LTC Facilities/ Homecare				Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Emborg (2021)[51]**	**Lefèvre (2021)[52]**	**Muhsen (2021)[53]**	**Subbaro (2021)[74]**	**Chemaitelly (2021)(a)[54]**
on the relationship between exposure(s) and outcome(s)?					
Quality Rating†	**Good**	**Fair**	**Fair**	**Fair**	**Fair**
Comment	Primary review outcomes are less susceptive to outcome ascertainment bias.	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level.	Some concern regarding confounding.	Some concern regarding confounding.	Some concern over confounding and outcome ascertainment bias from testing behaviour. Sufficient to warrant downgrading one level

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

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.B5: Quality appraisal of case control studies

	General Population				Hospitalised Patients					General population (Early vs. late vaccination)	Healthcare and Frontline Workers	Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Andrews (2021)[56]**	**Bruxvoort (2021) B [58]**	**Chemaitelly (2021)(b) [35]**	**McKeigue (2021) (a)[60]**	**Bajema (2021) [65]**	**Grannis (2021) [66]**	**Self (2021) [68]**	**Tenforde (2021) [102]**	**Thompson b (2021) [69]**	**Puranik (2021) b [38]**	**Pilishvili (2021) [72]**	**McKeigue (2021) b [103]**
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	✓	X	X	X	✓	X	X	✓	X	✓	X
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓

	General Population				Hospitalised Patients					General population (Early vs. late vaccination)	Healthcare and Frontline Workers	Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Andrews (2021)[56]**	**Bruxvoort (2021) B [58]**	**Chemaitelly (2021)(b) [35]**	**McKeigue (2021) (a)[60]**	**Bajema (2021) [65]**	**Grannis (2021) [66]**	**Self (2021) [68]**	**Tenforde (2021) [102]**	**Thompson b (2021) [69]**	**Puranik (2021) b [38]**	**Pilishvili (2021) [72]**	**McKeigue (2021) b [103]**
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	✓	✓	✓	CD	CD	✓	✓	✓	✓
6. Were the cases clearly defined and differentiated from controls?	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	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?	✓	✓	CD	CD	N/A	NA	NA	CD	✓	X	N/A	N/A
8. Was there use of concurrent controls?	✓	✓	✓	✓	CD	CD	CD	CD	✓	CD	✓	✓

	General Population				Hospitalised Patients					General population (Early vs. late vaccination)	Healthcare and Frontline Workers	Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Andrews (2021)[56]**	**Bruxvoort (2021) B [58]**	**Chemaitelly (2021)(b) [35]**	**McKeigue (2021) (a)[60]**	**Bajema (2021) [65]**	**Grannis (2021) [66]**	**Self (2021) [68]**	**Tenforde (2021) [102]**	**Thompson b (2021) [69]**	**Puranik (2021) b [38]**	**Pilishvili (2021) [72]**	**McKeigue (2021) b [103]**
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	CD	CD	CD	CD	CD	CD	CD

	General Population				Hospitalised Patients					General population (Early vs. late vaccination)	Healthcare and Frontline Workers	Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Andrews (2021)[56]**	**Bruxvoort (2021) B [58]**	**Chemaitelly (2021)(b) [35]**	**McKeigue (2021) (a)[60]**	**Bajema (2021) [65]**	**Grannis (2021) [66]**	**Self (2021) [68]**	**Tenforde (2021) [102]**	**Thompson b (2021) [69]**	**Puranik (2021) b [38]**	**Pilishvili (2021) [72]**	**McKeigue (2021) b [103]**
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?	✓	✓	X	✓	X	✓	✓	✓	✓	✓	✓	✓
Quality Rating†	Good	Good	Poor	Good	Fair	Fair	Fair	Fair	Good	Poor	Good	Good
Comment			Incomplete presentation of methods. Results lack face validity.			Insuffuicient information raegarding the characteristics of the study population	Incomplete information on matching process. Most key confounding variables adjusted	Incomplete information on matching process. Most key confounding variables adjusted				

	General Population				Hospitalised Patients					General population (Early vs. late vaccination)	Healthcare and Frontline Workers	Individuals with co-Morbidities and immunocompromising conditions
Quality appraisal criteria	**Andrews (2021)[56]**	**Bruxvoort (2021) B [58]**	**Chemaitelly (2021)(b) [35]**	**McKeigue (2021) (a)[60]**	**Bajema (2021) [65]**	**Grannis (2021) [66]**	**Self (2021) [68]**	**Tenforde (2021) [102]**	**Thompson b (2021) [69]**	**Puranik (2021) b [38]**	**Pilishvili (2021) [72]**	**McKeigue (2021) b [103]**
							for no adjustment for socioeconomic status.	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

Randomised Control Trials

AstraZeneca

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Madhi (2021) [27] Title: Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant DOI: 10.1056/NEJMoa2102214 NCT: NCT04444674 Study Design: RCT Country: South Africa	**Intervention**: ChAdOx1 nCoV-19 (AstraZeneca) **Control:** Placebo (Saline) **Time since final vaccination dose:** Mean 17.98 weeks Median 17.42 weeks (IQR 16.29 to 20.43)	**Description:** Adults aged ≥18 to ≤65 years of age with no or well-controlled chronic medical conditions. Only patients who were seronegative at randomisation were included in the efficacy analysis Results are also presented separately for participants who were previously seropositive (n=135). **N:** 1,467 [£] Intervention – 750[£] Control - 717[£] **Age:** Median age – 31 years (IQR 24-41) [£] **Male** = 57.1%[£] **Co-morbidities:** Chronic respiratory condition – 3.6%[£] Healthcare Worker – 9.8%[£]	**Severe Disease:** **≥14 days after second dose** *Severe Disease*[@] There were no cases of severe disease in either group. *Hospitalisation* There were no hospitalisations in either group. **Adjustments:** N/A **Mortality:** Two deaths occurred in the safety analysis cohort. Both were in the placebo arm. **Variants of Concern:** NR **Subgroups**: NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥ 14 days after second dose** <u>Previously seronegative</u> *Any NAAT confirmed infection* [$] VE = 26.1% (95% CI -28.7 to 58) *Mild - Moderate illness* [#,$] VE = 21.9 (95% CI -49.9 to 59.8) *Moderate COVID-19 clinical disease* [#,$] VE = 37% (95% CI -165.8 to 86.9)

Time Period: 24 June 2020 and 15 January 2021 (Interim analysis) Variants of Concern: 95.1% of sequenced cases were caused by the Beta variant. Publication status: Peer-reviewed			**Efficacy/effectiveness over time:** NR	Previously seropositive *Any NAAT confirmed infection* [$] VE = -14.2% (95% CI -752.9 to 84.7) **Adjustments:** N/A **Variants of Concern:** *B.1.351* [£, &] VE = 10.4 (95% CI -76.8 to 54.8) **Subgroups:** NR **Efficacy/effectiveness over time.** A Kaplan-Meyer Plot of incidence of symptomatic COVID-19 illness after two doses is presented. There is little data after 135 days of follow-up. A crossover of lines occurs at this point, however wide overlapping confidence intervals are evident.

£ Based on the primary efficacy analysis (previously seronegative) population only.

@ Definition of severe disease used in study - ≥ 1 of: 1.Tachypnea: ≥ 30 breaths per minute at rest, 2. SpO2: < 92% on room air or PAO2/FiO2 < 300, 3. High flow oxygen therapy, CPAP, or NIV (e.g., CPAP/BiPAP, 4. Mechanical ventilation or ECMO, 5. One or more major organ system failure (e.g., cardiac/circulatory, 6.pulmonary, renal, hepatic to

Definition of mild used in study - Any one of: 1. Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications, 2. New onset cough, 3. ≥ 2 Covid-19 respiratory/non respiratory symptoms in (Supplementary Table S1) AND 4. Does not meet criteria for moderate or severe

Definition of moderate used in study - ≥ 1 of: 1. Fever (≥ 37.8°C) + any 2 Covid-19 symptoms in Supplementary Table S1 for ≥ 3 days (need not be contiguous days, 2. High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days, 3. Any evidence of significant LRTI, 4. Shortness of breath (or breathlessness or difficulty breathing) with or without

exertion (beyond baseline), 5.Tachypnea: 20 to 29 breaths per minute at rest, 6. SpO2: < 94% on room air, 5. Abnormal chest x-ray/CT consistent with pneumonia or LRTI, and 6. Adventitious sounds on lung auscultation. Because no participants in the trial had severe Covid-19, the term "mild to moderate" is used.

$ Results are also provided in the study for analysis using the Oxford definition, this refers to definition used in the United Kingdom and Brazil Pooled Efficacy Analysis.

& - VE against B.1.351 defined as: The prespecified primary end point was Covid-19 illness of any severity, which includes mild, moderate, and severe illness confirmed by nucleic acid amplification test. Because no participants in the trial had severe Covid-19, the term "mild to moderate" is used.

Key: CI – Confidence Interval; IQR – Interquartile Range; N/A – Not applicable; NAAT – Nucleic Acid Amplification Test; NCT – National Clinical Trial; NR – Not Reported; 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): Voysey a (2020)[28] and b (2021)[29] **Title(s):** a. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK b. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials	**Intervention:** ChAdOx1 nCoV-19 vaccine (Oxford / AstraZeneca) **Control:** <u>COV001 and COV002</u> Placebo (MenACWY) <u>COV003</u> Placebo (MenACWY (first dose) and Saline (second dose) <u>COV005</u> Placebo (Saline) **Time since final vaccination dose:** Mean – 12.5 weeks	**Description:** Population recruited across 4 different trials; COV001, COV002, COV003 and COV005. All patients were seronegative at baseline with no previous evidence of SARS-CoV-2 infection. COV001 and COV005 enrolled healthy adults. COV002 and COV003 enrolled health-care workers and others at increased exposure to SARS-CoV-2 infection. The adjudicated results are used for the pooled analyses. The trial primary efficacy analysis included (n= 2,741) participants in COV002 who received a low dose of vaccine for their first dose followed by a standard dose for their second vaccination. The results presented in this evidence summary include only those from the secondary analysis, which include participants who	**Severe Disease:** **≥14 days after second/final dose** *Severe disease* NR £ *Hospitalisation for COVID-19* ~ Intervention – 0 Control – 9 **Adjustments:** N/A **Mortality:** There were seven deaths considered unrelated to vaccination (two in the ChAdOx1 nCov-19 group and five in the control group), including one COVID-19-related death in one participant in the control group. **Variants of Concern**: NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥14 days after second dose** *Any NAAT positive* VE 49.5% (95% CI 37.7 to 59%) *Symptomatic* @ VE = 63.1% (95% CI 51.8 to 71.7) *Asymptomatic* & VE = 2.0% (95% CI -50.7 to 36.2) **Adjustments:** N/A **Variants of Concern:** NR **Subgroups:** NR

DOI: (a) doi.org/10.1016/S0140-6736(20)32661-1 (b) doi.org/10.1016/S0140-6736(21)00628-0 **NCT:** NCT04324606 (COV001), NCT04400838 (COV002), ISRCTN89951424 (COV003), And NCT04444674 (COV005) **Study Design***:* RCT **Country**: UK (COV001 and COV002) Brazil (COV003), and South Africa (COV004) **Time Period***:* April 28 2020 to December 07 2020 (Interim Analysis) **Variants of Concern:** NR **Publication status**: Peer-reviewed		received two standard doses only, unless otherwise stated. **N:** 14,330 Intervention: 7,201 Control: 7,179 **Age:** Median 40 years (IQR 30-52) ~ **Male** = 43.56 % ~,$ **Co-morbidities:** Respiratory disease – 10.12% ~,$ Health or social care worker – 62.75% ~,$	**Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Efficacy/effectiveness over time:** Two Kaplan-Meier curves (KMC) are presented. One KMC depicts the incidence of symptomatic infection separately for COV002 and COV003. There is limited follow up after day 70 in both trials. A second KMC provides the same for the entire pooled population, which has limited data after day 70.

~ Value provided from primary efficacy analysis, which includes both the two standard dose group and the low dose-standard dose group (n=17,178). The low dose-standard dose group includes (n=2,741) participants and accounts for approximately 16.5% of the primary efficacy analysis.

$ Based on calculation of the proportion of each group of interest reported for each study as presented in Table S1.., £ Results are provided for VE against severe COVID-19 from the first dose only in the Voysey b. VE for severe COVID-19 after two doses is provided in Voysey a, however this report had <8 weeks of follow-up.

@ Definition of symptomatic: PCR-confirmed SARS-CoV-2 and at least one of the following symptoms: objective fever (defined as ≥ 37.8 °C), cough, shortness of breath, anosmia, or ageusia. Confirmed by adjudication committee.

& Definition of asymptomatic: PCR-confirmed SARS-CoV-2 infection and no symptom recorded in data. Confirmed by adjudication committee. Only analysed in COV002 UK only.

Key: CI – Confidence Interval; IQR; Interquartile Range; KMC – Kaplan Meier Curve; N/A – Not applicable; NAAT – Nucleic Acid Amplification Test; NCT – National Clinical Trial; NR – Not Reported; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Janssen

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Sadoff (2021)[30] **Title:** Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19 **DOI:** 10.1056/NEJMoa2101544 **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 (some endpoints reported up to a data cut of February 5th from FDA report) **Variants of Concern:** NR **Publication status**: Peer-reviewed	**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) CF <0.1% CKD 0.5% COPD: 1% 0.9% (PP) ICP <0.3% Pulmonary fibrosis <0.1%	**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:** Three 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 22nd Jan Cut Off *≥ 14 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) **Adjustments:** N/A **Subgroups:** *Symptomatic Covid-19 (weighted by burden of disease) (EPAR)*

			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 February 5th, (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. Immunocompromised from blood transplant: 1 case in the Ad26.COV2.S arm in 35 person years of follow-up and 0 cases	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

			in the placebo arm with 32 person years follow up. 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. 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. 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. HIV: VE 47.5% (95% CI -266 to 95.3%) With comorbidities[@] VE = 58.6% (95% CI 40.6 to 71.6) Without comorbidities[@] *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:** No evidence of waning efficacy was noted among the approximately 1,421 participants who were followed for 11 weeks or among 1000 participants who were followed for 15 week for the moderate to severe/critical COVID-19 endpoint. In the analysis there were no events in either arm after day 91.	

*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)[31] **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) Based on the pharmacovigilance database which includes data from study start through 3 December	**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 0.886 to 0.965) **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 – VE = 86.4 (95% CI 61.4 to 95.2) ≥65 to ≤75

			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 = 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 (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) ≥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.

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): El Sahly (2021) [55] **Title:** Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase	**Intervention/Exposure**: mRNA-1273 **Comparator/Control:** Placebo (Saline) **Time since final vaccination dose:**	**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:**	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* % VE = 98.2% (95% CI 92.8 to 99.6)	**Confirmed RT-PCR infection (PP)** **≥14 days after second/final dose** $ *Symptomatic*

DOI: 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	Median – 21.08 weeks (Duration of follow up from 0 to 220 days for 113 participants).	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% Healthcare Providers – 25.2% Emergency Response – 2.0% Personal Care and In-Home Services – 3.1% Nursing home or assisted living facility – 0.2%	*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**: NR **Efficacy/effectiveness over time:** NR	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> *Chronic Lung Disease* VE = 87.2 (95% ci 63.8 TO 95.5 *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) **Efficacy/effectiveness over time**

				<u>To Prevent Symptomatic Confirmed RT-PCR infection Covid-19$(PP) over time</u> *≥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 17.09 weeks or 113 patients at 31.34 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 two 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 three 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)[32] **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] **Time Period:** 27 July 2020 -14 November 2020 (enrolment period) **Variants of Concern:** NR	**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 (100 participants who were 12 - 15 years contributed to person-time years but included no cases) **Male** = 50.6 %	**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 from 91.7% to ~100% for combinations of age (16-64

Publication status: Peer-reviewed		**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)		v. 65+) and at risk (yes/no) At risk is defined as having at least one of the Charlson Comorbidity Index categories or obesity **Efficacy/effectiveness over time**: NR

* 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).

#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

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): Frenck (2021)[33] **Title:** Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents **DOI:** 10.1056/NEJMoa2107456	**Intervention/Exposure**: Vaccination with BNT162b2 (Pfizer/BioNtech) **Comparator/Control:** Placebo (saline) **Time since final vaccination dose:** Mean: 8.99 weeks (Intervention)	**Description:** This report presents subgroup analysis of the main trial in healthy persons (or stable pre-existing disease) aged 12 to 15 years in the US only. VE evaluated on all eligible participants a) seronegative only b) Regardless of evidence of prior infection **N:** 2264 underwent randomisation	**Severe Disease:** **≥7 days after second/final dose** No cases of severe Covid-19# were observed in this age cohort in either arm. **Adjustments:** N/A **Mortality:** NR	**Confirmed RT-PCR SARS-CoV-2 infection** * **≥7 days after second/final dose** *Symptomatic* a) (seronegative) VE 100% (95% CI 75.3 to 100)

NCT: NCT04368728 **Study Design***:* RCT multinational, placebo-controlled, observer-blinded trial. **Country**: USA (29 sites) **Time Period***:* 15 October 2020 – 12 January 2021 **Variants of Concern:** NR **Publication status**: Peer-reviewed	8.77 weeks (Placebo)	2260 were injected with vaccine or placebo Received dose two: BNT162b2: 1124 Placebo: 1117 **Age:** Median = 14 years Mean (SD) = 13.6 (1.11) years **Male**: BNT162b2: 50.1% Placebo: 51.8% **Co-morbidities:** NR	**Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time**: NR	intervention: 0 cases, placebo: 16 cases b) Regardless of evidence of prior infection VE 100% (95% CI 78.1 to 100) **Adjustments:** NA **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time.** *Symptomatic (Regardless of evidence of prior infection):* ≥7 days after dose 2 to < 2months after dose 2: VE 100.0% (74.8, 100.0) ≥2 months after dose 2 to <4 months after dose 2: VE 100.0% (–399.9, 100.0)

* 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).

#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

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Thomas (2021)[34] **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) 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]	**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% **Co-morbidities:** 34% BMI ≥30 g/m2, 21% had ≥1 underlying comorbidity	**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-19) and 14 deaths in the placebo arm. (1 due to COVID-19) **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time**. NR	**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:** For beta variant (seronegative, South Africa site): Vaccine efficacy: 100% (95% CI 53.5 to 100.0 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,

Time Period*:* Between 27 July and 29 Oct 2020, participants were. Enrolment of 12-15year-old began 15 Oct 2020. Efficacy analysis conducted on cases accrued to 13 Mar 2021. **Variants of Concern:** B.1.351 (beta) **Publication status**: Peer-reviewed				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. **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.

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.

General Population studies

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Andrews (2021) [56] **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**	**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%	**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.	**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

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 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		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/ 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), 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**:	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

			Age and co-morbidities. Reported by vaccine type below **Efficacy/effectiveness over time.**	

Primary 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
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)

Secondary Outcome results

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

Age group	wk 1	2 to 9 weeks	10 to 14 weeks	15 to 19 weeks	20+ 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	80.1 (77.	69.1 (66.	62.1 (58.	55.3 (50.

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)			

Efficacy/effectiveness over time. See above

	(34.2 to 81.8)	5 to 82.4)	2 to 71.8)	6 to 65.4)	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

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

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

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)	

Efficacy/effectiveness over time. See above

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.

See above

Moderna (Spikevax)(mRNA-1273)

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

	Wk 1	2-9wks	10- 14 wks
16+	97.5 (82.3 to 99.7)	100.0 (0 cases, 6363 con)	

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

	Wk 1	2-9 wks	10-14 wks
16+	95.2 (94.4 to 95.9)	94.5 (94.1 to 95.0)	90.3 (67.2 to 97.1)

Subgroups

VE against Delta symptomatic disease

	Wk 1	2-9 wks	10-14 wks
40 to 64	94.0 (92.1 to 95.5)	93.7 (92.9 to 94.4)	96.1 (70.1 to 99.5)

	16 to 39	95.0 (94.1 to 95.8)	94.9 (94.2 to 95.5)

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Bruxvoort (a)(2021) [57] **Title:** Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study **DOI:** **https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3916094** **Study Design***: Matched* Prospective observational cohort study **Country**: USA (South California) **Setting***:* Members of the Kaiser Permanente Southern California (KPSC)* health care system **Time Period***:* 18 December 2020– 30 June 2021	**Intervention/Exposure**: Moderna (mRNA-1273) **Comparator/Control:** Unvaccinated individuals **Time since final vaccination dose:** Mean 15.44 weeks Max five months (22 weeks).	**Description:** The study included a large cohort of individuals eligible to receive mRNA-1273 for diverse reasons (health care workers, long term care residents, individuals aged ≥65 years, workers in education, childcare, emergency services, food and agriculture, and individuals aged 18-64 with underlying conditions) who were followed until June 2021. Individuals who received a COVID-19 vaccine other than mRNA-1273 prior to the index date, received 2 doses of mRNA-1273 <24 days apart, received any COVID-19 vaccine <14 days after the index date, had no health care utilization and no vaccination from the 2 years prior to the index date through the index date, or had a COVID-19 outcome <14 days after the index date were excluded. A COVID-19 diagnosis was considered an incident diagnosis if there was no history of a COVID-19 diagnosis code or SARS-CoV-2 positive molecular test in the 90 days prior. **N:** *recipients of 2 doses of (Moderna) mRNA-1273 vaccine* 352,878 *Unvaccinated individuals* 352,878 **Age:** Median age was 65 years (IQR 45–73 years)	**Severe Disease:** **≥14 days after second/final dose** *COVID-19 Hospitalisation* VE (95% CI): 95·8% (92·5 to 97·6%) **Adjustments:** Adjusted for covariates age, sex, race/ethnicity, frailty index (in quartiles), history of COVID-19 diagnosis, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, preventive care, Medicaid, neighbourhood median household income, KPSC physician/employee status, medical center area. **Mortality** *COVID-19 Hospital death* VE: 97·9% (84·5-99·7%). **Variants of Concern** NR **Subgroups**:	**Confirmed RT-PCR SARS-CoV-2 infection** **≥14 days after second/final dose** *COVID-19 diagnosis (Any infection)* VE (95% CI): 87·4% (85·6% to 89·1%). *Asymptomatic* VE (95% CI): 72·7% (57·6% to 82·4%) *Symptomatic* VE (95% CI): 88·3% (86·5% to 89·9%) *VE among individuals with history of COVID-19* ranged from 8·2% (0·0%-41.8%) to 33·6% (0·0%-61.5%), depending on reinfection definition. **Adjustments:** Adjusted for covariates age, sex, race/ethnicity, frailty

Variants of Concern: The study included a large cohort of individuals who were followed until June 2021, a period that overlapped with the emergence of Delta in the US. Among fully vaccinated individuals, the most prevalent variants were Delta (47·1%), Alpha (21·4%), Gamma (11·4%), Epsilon (4·3%), and Iota (4·3%) among fully vaccinated individuals and Alpha (41·2%), Epsilon (18·2%), Delta (11·0%) and Gamma (8·6%) among unvaccinated individuals. **Publication status**: Preprint		**Male** = 40.6% **Co-morbidities:** Vaccinated and unvaccinated individuals had similar baseline distributions (ASD <0·1) of BMI, smoking, Charlson comorbidity scores, frailty, chronic diseases, immunocompromised status, autoimmune conditions, pregnancy, and ED visits and hospitalizations in the year prior to index date.	**Efficacy/effectiveness over time**: NR	index (in quartiles), history of COVID-19 diagnosis, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, preventive care, Medicaid, neighborhood median household income, KPSC physician/employee status, medical center area. **Variants of Concern:** NR **Subgroups** Any infection by age in years VE (95% CI) 12-17: 87·2% (83·6-90·1%) 18-44: 88·7% (85·3-91·4%) 45-64: 89·4% (85·6-92·1%) 65-74: 89·4% (85·6-92·1%) ≥75: 83·0% (76·8-87·6%) **Efficacy/effectiveness over time.** Kaplan Meier presented for each outcome but these results are not adjusted for confounding factors.

* KPSC is an integrated health care system including more than 4.6 million members of diverse sociodemographic, racial, and ethnic backgrounds.

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Bruxvoort (b)(2021) [58] **Title:** Effectiveness of mRNA-1273 against Delta, Mu, and other emerging variants **DOI:** **https://www.medrxiv.org/content/10.1101/2021.09.29.21264199v1** **NCT:** NA **Study Design**: test-negative case-control study **Country**: California, US **Setting***:* General population **Time Period***:* 01 March 2021 to 27 July 2021 **Variants of Concern:** The study included 8,153 test-positive cases, with variants identified for 5,186 cases (63.6% overall, of which 39.4% were Delta, 27.7% Alpha, 11.4% Epsilon, 6.9% Gamma, 2.2% Iota, 1.4% Mu, and 11.1% Other).	**Intervention/Exposure**: mRNA-1273 (Moderna) **Comparator** Unvaccinated **Cases and controls:** Cases were selected from individuals with a positive SARS-CoV-2 test. Test-negative controls were selected from eligible individuals with a negative SARS-CoV-2 test. **Time since final vaccination:** Up to 26 weeks after dose two.	**Description:** Individuals who had a SARS-CoV-2 positive test sent for WGS or a negative test from March 1, 2021 to July 27, 2021 were eligible for inclusion in the study if they were age ≥18 years and had ≥12 months of KPSC membership as of the specimen collection date. Individuals were excluded if they received a COVID-19 vaccine other than mRNA-1273, received 2 doses of mRNA-1273 <24 days apart or <14 days prior to specimen collection date, received >2 doses of mRNA-1273 prior to the specimen collection date, or had a positive SARS-CoV-2 test or COVID-19 diagnosis code between 12/18/2020 and 2/28/2021 or ≤90 days prior to positive test date. **N:** Delta cases: 2,027 232 (11.4%) were fully vaccinated Controls: 10,135 4,588 (45.3%) were fully vaccinated ***Sequencing Success*** ***Vaccinated:*** 273 ***Unvaccinated:*** 4859 ***Sequencing Failure (Unidentified Variants)***	**Severe Disease:** **≥14 days after second/final dose** ***Variants of Concert*** *VE against COVID-19 hospitalization* *Delta variant* *VE: 97.6% (95% CI 92.8 to 99.2)* *Non-Delta variant* *n/e* *Non-identified variant* *VE: 96.6% (95% CI 89.4 to 98.9)* **Adjustments:** Test-positive cases were matched 1:5 to test-negative controls on age, sex, race/ethnicity, and specimen collection date.	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **Variants of Concern:** *Any infection (Delta)* *VE: 86.7% (95% CI: 84.3-88.7%)* *Any infection (Alpha)* *VE: (98.4% [95% CI: 96.9-99.1%])* *VE against other* identified non-Delta variants* *VE:95.5-97.6%* *unidentified variants* *VE: 79.9% (95% CI: 76.9-82.5%)* **Adjustments:**

Among fully vaccinated cases, 85.0% of identified variants were Delta. Approximately 36% of specimens failed WGS. Compared to successfully sequenced specimens, specimens that failed sequencing were more often from fully vaccinated cases (11.0% vs. 5.3%) **Publication status**: Preprint		***Vaccinated:*** 326 ***Unvaccinated:*** 2583 **Age:** ***Age of SARS-CoV-2 test-positive cases for Delta*** Age: % — 18-44: 66.2; 45-64: 27.8; 65-74: 3.9; ≥75: 2.1 **Male** = *44.1%* **Co-morbidities:** Immunocompromised^ *Test positive (Delta)* 2.4% *Test Negative* 3.9%	**Mortality** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	Test-positive cases were matched 1:5 to test-negative controls on age, sex, race/ethnicity, and specimen collection date. Model for Delta adjusted for covariates: smoking, Charlson comorbidity score, frailty index, liver disease, pregnancy, history of COVID-19 diagnosis, number of outpatient and virtual visits, preventive care, medical center area, month of specimen collection, specimen type. Model for Non-Delta variant adjusted for covariates: BMI, smoking, Charlson comorbidity score, frailty index, kidney disease, heart disease, lung disease, immunocompromised status, pregnancy, history of COVID-19 diagnosis, number of outpatient and virtual visits, number of ED visits, number of hospitalizations, preventive care, medical centre area, month of specimen collection, specimen type.

				Model for Unidentified variants adjusted for covariates: BMI, smoking, Charlson comorbidity score, frailty index, pregnancy, history of COVID-19 diagnosis, number of outpatient and virtual visits, number of ED visits, preventive care, medical centre area, month of specimen collection, specimen type. Model for Subgroups adjusted for: smoking, Charlson comorbidity score, frailty index, liver disease, pregnancy, history of COVID-19 diagnosis, number of outpatient and virtual visits, preventive care, medical center area, month of specimen collection, specimen type **Subgroups:** see below **Efficacy/effectiveness over time:** see below
	Secondary outcomes (Subgroups and Efficacy/Effectiveness over time)			
	Subgroups			

Vaccine effectiveness of 2 doses of mRNA-1273 against Delta infection by time since vaccination and age group

	Age 18-64	Age 65 years and older
Overall	87.9% (95% CI: 85.5 to 89.9)	75.2% (95% CI: 59.6 to 84.8)
14-60 days	95.1% (95% CI:91.8 to 97.1)	52.9% (95% CI: 0.0 to 86.6)
61-90 days	89.2% (95% CI: 85.4 to 92.0)	85.7% (95% CI: 57.9 to 95.1)
91-120	86.2% (95% CI: 80.9 to 90.1)	85.8% (95% CI: 68.9 to 93.5)
121-150	80.4% (95% CI: 71.7 to 86.4	62.3% (95% CI: 32.4 to 79.0)
151-180	79.4% (95% CI: 68.8 to 86.3)	90.8% (95% CI: 25.6 to 98.9)

Efficacy/effectiveness over time.

Vaccine effectiveness of 2 doses of mRNA-1273 against infection with SARS-CoV-2 variants by time since vaccination

Days	***Delta Variant***	***Non-Delta variant***	***Unidentified variant***
14-60	94.1% (90.5-96.3%)	98.6 (97.3, 99.3)	VE
61-90	88.7 (85.0, 91.5)	96.9 (93.9, 98.5)	83.6 (79.5, 86.9)
91-120	85.9 (81.1, 89.5)	91.4 (83.9, 95.4)	82.2 (77.0, 86.2)
121-150	77.0 (69.1, 82.9)	88.7 (73.2, 95.2)	77.7 (70.7, 83.0)

	151-180	80.0% (70.2-86.6%)	n/e (Not Estimable)	66.4 (53.6, 75.6)	
	>180 days	n/e (Not Estimable)	n/e (Not Estimable)	68.5 (51.3, 79.6)	
* Beta, Eta, Kappa, and other variants					

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Chemaitelly (2021b)[35] **Title:** Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar **DOI:** https://doi.org/10.1101/2021.08.25.21262584 **NCT:** N/A **Study Design***:* matched test-negative, case-control study **Country**: Qatar **Setting***:* National, federated SARS-Co-V2 databases.	**Intervention/Exposure**: BNT162b2 (Pfizer)# **Comparator/Control:** No vaccination **Time since final vaccination dose:** (See results by time) **Adjustments:** Cases (PCR-positive persons) and controls (PCR-negative persons) were matched one-to-one by sex, 10-year age group, nationality, reason for SARS-CoV-2 PCR testing, and calendar week of PCR test. Sensitivity Analysis. Sensitivity analysis was conducted by adjusting for prior infection and matching factors in logistic regression that is, by sex, age, nationality, reason for PCR testing, and calendar week of PCR test.	**Description:** National Population Study. 891,481 completed the two-dose regimen Patients with prior infection are included in the primary analysis but are adjusted for in sensitivity analysis. **N:** Cases: 173,496 Controls: 1,422,333 **Age:** Median years (IQR) Case: 32 (23-39) Control :31 (23-39) **Male:** Case: 70.6% Control: 70.6% **Co-morbidities:** NR	See below	See below

Time Period*:* January 1, 2021 to August 15, 2021. **Variants of Concern:** Predominately Beta. Alpha wave in early 2021 when number vaccinated was small. Delta steadily increased during Summer 2021. **Publication status**: Preprint						
	Primary Outcome Results			**Secondary Outcome Results**		
Effectiveness over time	**Severe Disease**			**Confirmed RT-PCR Infection**		
Weeks after 2nd dose	*Severe Critical and fatal COVID-19 infection**			*Any*		
0-4	95.4 (93.4-96.9)			72.1 (70.9-73.2)		
5-9	94.2 (91.0-96.5)			65.8 (63.8-67.7)		
10-14	91.8 (86.0-95.5)			55.5 (52.0-58.8)		
15-19	86.4 (69.9-94.8)			29.7 (21.7-36.9)		
20-24	95.3 (70.5-99.9)			0.0 (0.0-0.0)		
≥25	71.5 (9.2-93.2)			0.0 (0.0-0.4)		
Weeks after 2nd dose	*Severe*	*Critical*	**Mortality** *Fatal Covid-19*	*Asymptomatic*	*Symptomatic*	
0-4	94.4 (91.9-96.3)	98.7 (95.3-99.8)	93.9 (84.5-98.1)	63.7 (61.2-66.1)	79.6 (77.9-81.2)	
5-9	95.1 (91.7-97.4)	91.6 (80.6-97.1)	90.0 (74.0-97.0)	54.9 (50.5-58.9)	70.8 (67.8-73.6)	
10-14	92.4 (85.9-96.3)	89.2 (69.3-97.2)	93.4 (73.1-99.2)	38.5 (31.0-45.2)	60.6 (55.2-65.4)	
15-19	85.9 (66.5-95.1)	89.0 (20.3-99.8)	80.4 (0.0-99.6)	0.0 (0.0-13.3)	49.6 (39.1-58.4)	
20-24	81.9 (46.7-95.5)	66.8 (0.0-99.4)	Omitted	0.0 (0.0-0.0)	0.0 (0.0-19.1)	
≥25				0.0 (0.0-0.0)	0.0 (0.0-8.0)	
	Variants of Concern			**Variants of Concern**		
	*Severe, critical and fatal COVID-19 infection**			*Any RT-PCR infection*		
Weeks after 2nd dose	Alpha	Beta	Delta	Alpha	Beta	Delta
0-4	100.0 (0.0-100.0)	97.0 (80.9-99.9)	100.0 (0.0-100.0)	67.8 (57.1-76.1)	74.3 (68.5-79.2)	83.8 (73.6-90.5)
5-9	100.0 (0.0-100.0)	94.6 (63.5-99.9)	100.0 (74.3-100.0)	82.2 (72.1-89.0)	52.7 (40.3-62.7)	72.0 (60.5-80.5)
10-14	69.6 (0.0-99.4)	86.5 (0.0-99.7)	81.6 (0.0-99.6)	64.5 (43.8-78.1)	58.8 (43.2-70.5)	48.7 (28.4-63.6)

15-19	Omitted	100.0 (0.0-100.0)	100.0 (0.0-100.0)	11.9 (0.0-59.1)	47.7 (7.5-71.2)	13.0 (0.0-34.8)
20-24	Omitted	100.0 (0.0-100.0)	81.6 (0.0-99.6)	0.0 (0.0-48.9)	26.4 (0.0-65.9)	0.0 (0.0-1.3)
≥25	Omitted	100.0 (0.0-100.0)	67.9 (0.0-99.4)	0.0 (0.0-57.3)	71.5 (0.0-97.1)	0.0 (0.0-21.3)
	Subgroups			**Subgroups**		
	*Severe, critical and fatal COVID-19 infection**			*Any infection*		
Weeks after 2nd dose	<60 years	≥60 years		<60 years	≥60 years	
0-4	96.7 (94.8-98.1)	91.1 (84.1-95.4)		72.6 (71.5-73.8)	66.3 (59.7-71.8)	
5-9	96.0 (92.2-98.2)	92.9 (86.7-96.5)		66.9 (64.8-68.9)	63.9 (57.1-69.7)	
10-14	96.7 (90.1-99.3)	88.8 (78.9-94.5)		56.7 (53.0-60.1)	53.4 (42.9-61.9)	
15-19	86.8 (62.4-96.6)	86.4 (53.8-97.4)		27.8 (19.1-35.5)	46.6 (23.1-63.2)	
20-24	92.9 (53.2-99.8)	100.0 (46.0-100.0)		0.0 (0.0-0.0)	27.3 (0.0-55.3)	
≥25	85.7 (0.0-99.7)	57.6 (0.0-93.0)		0.0 (0.0-2.2)	0.0 (0.0-17.4)	

* Classification of COVID-19 case severity (acute-care hospitalizations), criticality (ICU hospitalizations), and fatality followed World Health Organization (WHO) guidelines

#Over 500,000 patients received mRNA-1273 but these patients are not included in this analysis.

Key: CI – Confidence Interval; IQR – Interquartile Range ; N/A – Not Applicable; CT – National Clinical Trial; N/A – Not Applicable; NR – Not Reported; 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): de Gier (2021) [59] **Title:** COVID-19 vaccine effectiveness against hospitalizations and ICU admissions in the Netherlands, April- August 2021 **DOI:** [10.1101/2021.09.15.21263613]	**Exposure**: ▪ All hospitalised COVID-19 patients. ▪ Vaccinated with BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna), ChAdOx1-S (AstraZeneca), or Ad26.COV2-S (Janssen).	**Description:** All hospitalised cases from June 2020 onwards included. **N:** Total, 15,571 Fully vaccinated, 887, Partially vaccinated, 1,111 Unvaccinated, 13,574 **Age:** mean/median age NR **Male/Female:** NR	**Severe Disease:** **≥14 days after second/final dose*** *Hospitalisation** VE in Alpha period: 94% (95%CI 93-95%). VE in Delta period: 95% (95%CI 94-95%). *adjusted for calendar date and age group. *ICU admissions**	**Confirmed RT-PCR SARS-CoV-2 infection** **≥14 days after second/final dose*** NR **Adjustments:** NA **Variants of Concern:** NR

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	**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.	**Co-morbidities:** NR	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.	**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)	
	Comirnaty® (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)	
	Spikevax® (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)	
	Vaxzevria® (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) Age 50-69: 92% (95% CI: 89-95) Overall: 91% (95% CI: 88-94)	**ICU admission (VE) – fully vaccinated***** 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	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): McKeigue (a) (2021) [60] **Title:** Efficacy of vaccination against severe COVID-19 in relation to Delta variant and time since second dose: the REACT-SCOT case-control study **DOI:** https://doi.org/10.1101/2021.09.12.21263448 **NCT:** N/A **Study Design***:* Case control **Country**: Scotland	**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 (ChAdOx1-SARS-COV-2) or mRNA vaccine Pfizer (BNT162b2) or Moderna(mRNA-1273).	**Description:** Cases of COVID-19 among community population in Scotland and then matched to controls from general population. **N*:** 226,678 (23,467 fully vaccinated). **Age:** NR **Male/Female:** NR **Co-morbidities:** 88,867 with moderate risk condition or eligible for shielding	**Severe Disease:** **≥14 days after second dose** *Severe Disease*** Alpha Dominant Before 19th May RR#0.04 (95% CI 0.01 to 0.18) Delta dominant : After 19th May: 0.10 (95% CI 0.08 to 0.14) *Hospitalisation or mortality**** Alpha Dominant Before 19th May RR 0.05 (95% CI 0.03 to 0.10) Delta dominant : After 19th May: 0.15 (95% CI 0.13 to 0.17)	**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

Setting*:* Community **Time Period***:* 1 December 2020 to 19 August 2021 **Variants of Concern:** Alpha and then Delta. Cases analysed before and after 19 May 2021 – date at which delta variant became the predominant variant in Scotland **Publication status**: Preprint	**Control:** For every incident case of COVID-19 in the Scottish population ten 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:** Median = 9.57 weeks. IQR = 6 – 12.71 weeks. Max ~26 weeks.		**Adjustments:** care home residence, risk category (no risk condition, moderate risk condition, clinically extremely vulnerable), number of non-cardiovascular drug classes dispensed in last 240 days and recent hospital stay. **Mortality** NR separately (see above). **Variants of Concern:** See above. **Subgroups:** NR by vaccination status **Efficacy/effectiveness over time:** *For severe disease:* Modelled waning effect half-life of 27 (95% CI 14 to 143) days, constant efficacy 82%***. *For hospitalised or fatal COVID-19:* Modelled waning effect half-life of 17 (95% CI 9 to 39) days, constant efficacy of 83%.	
	Primary outcomes (by Vaccine)			
	Astra Zeneca (ChAdOx1-SARS-COV-2)		**RR for severe disease:** 0.14 (95% CI 0.11 to 0.19).	

			RR for hospitalisation or mortality: 0.21 (95% CI 0.18 to 0.23). **42 day window:** *Efficacy against severe disease:* 91% (95% CI 86% to 95%). *Efficacy against hospitalised or fatal:* 88% (95% CI 85% to 90%)	
	Pfizer (BNT162b2) /Moderna (mRNA-1273).	**mRNA**	**RR for severe disease:** 0.09 (95% CI 0.06 to 0.13). **RR for hospitalisation or mortality:** 0.10 (95% CI 0.08 to 0.12). **42 day window:** *Efficacy against severe disease:* 92% (95% CI 85% to 95%) *Efficacy against hospitalised or fatal:* 91% (95% CI 88% to 93%)	
* Calculated from Tables S1 and S2 ** 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 *** – Weak evidence favouring this model over the best-fitting model with waning to zero efficacy.				

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Nunes (2021) [61] **Title:** mRNA vaccine effectiveness against COVID-19-related hospitalisations and deaths in older adults: a cohort study based on data linkage of national health registries in Portugal, Feb to Aug 2021 **DOI:** 10.2807/1560-7917.ES.2021.26.38.2100833 **NCT:** N/A **Study Design***:* Cohort Study with crossover **Country**: Portugal **Setting***:* community-dwelling individuals aged 65 years and older residing in mainland Portugal **Time Period***:* Feb – Aug 2021.	**Intervention/Exposure**: mRNA vaccine: Comirnaty (BNT162b2 Pfizer.BioNTech) Spikevax (mRNA-1273 **Comparator/Control:** unvaccinated **Time since final vaccination dose:** See below	**Description:** community-dwelling individuals aged 65 years and older residing in mainland Portugal. Excluded: Individuals a) 110+ years, b) institutionalised (e.g. long term care residents) c) previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection d) 65–79 years, without at least one contact with the primary health care unit in the previous 3 years of the National Health Service e) 80+ years and did not receive any influenza/pneumococcal vaccine in last five years See below for demographics by age-group (65-79 years) and 80+ years	**Severe Disease: ≥14 days after second/final dose** See results for primary outcomes below by age-group **Adjustments:** age group, sex, health region, municipality level European Deprivation quintiles, number of chronic diseases, number of SARS-CoV-2 tests performed in 2021, influenza or pneumococcal vaccine uptake in the past 3 years and time (7-day periods	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose:** NR

<table>
<tr><td>Variants of Concern:
Alpha and delta

Publication status:
peer reviewed</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Outcomes and Population demographics (by age group)</td></tr>
<tr><td>65-79 years</td><td>Intervention/Exposure:
mRNA vaccine: Comirnaty (BNT162b2 (641,119) Pfizer.BioNTech) Spikevax (mRNA-1273) (112,032)

Control:
Unvaccinated

Time since final vaccination dose:
(Weeks)<table><tr><th></th><th>median</th><th>IQR</th><th></th></tr><tr><td>65-79</td><td>11.1</td><td>10.1</td><td>13.4</td></tr></table></td><td>N:
65-79 years
n = 878,489

Age:<table><tr><td></td><td colspan="2">mRNA vaccination</td><td colspan="2">Unvaccinated</td></tr><tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td></tr><tr><td>65–69</td><td>294,438</td><td>39.1</td><td>47,515</td><td>37.9</td></tr><tr><td>70–74</td><td>255,355</td><td>33.9</td><td>42,898</td><td>34.2</td></tr><tr><td>75–79</td><td>203,358</td><td>27.0</td><td>34,925</td><td>27.9</td></tr></table>Male = 43.7% (vaccinated), 44.5% (unvaccinated)

Co-morbidities: number of chronic conditions<table><tr><td></td><td colspan="2">mRNA vaccination</td><td colspan="2">Unvaccinated</td></tr><tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td></tr><tr><td>0</td><td>172,920</td><td>23.0</td><td>59,424</td><td>47.4</td></tr><tr><td>1</td><td>199,357</td><td>26.5</td><td>27,649</td><td>22.1</td></tr><tr><td>2</td><td>185,810</td><td>24.7</td><td>19,616</td><td>15.7</td></tr><tr><td>3</td><td>118,451</td><td>15.7</td><td>11,153</td><td>8.9</td></tr><tr><td>4</td><td>52,233</td><td>6.9</td><td>5,008</td><td>4.0</td></tr></table></td><td>Severe Disease: ≥14 days after second/final dose

Hospitalisation^
VE: 94% (95%CI 88% to 97%)

Mortality$
VE: 96% (95%CI 92% to 98%)

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time :
NR</td><td>Confirmed RT-PCR or Antigen SARS-CoV-2 infection

≥14 days after second/final dose

NR</td></tr>
</table>

		≥ 5 | 24,380 | 3.2 | 2,488 | 2.0		
80+	**Intervention/Exposure**: mRNA vaccine: Comirnaty (BNT162b2 (378,312) Pfizer.BioNTech) Spikevax (mRNA-1273) (55,566) **Control:** unvaccinated **Time since final vaccination dose:** (Weeks) **80+**: median 17.9, IQR 16.0 – 20.9	**N:** 80+ years n = 460,820 **Age:** 80–84: mRNA vaccination N 222,087 (51.2%); Unvaccinated N 10,342 (38.4%) 85–89: mRNA vaccination N 144,989 (33.4%); Unvaccinated N 9,197 (34.1%) 90–94: mRNA vaccination N 54,046 (12.5%); Unvaccinated N 5,301 (19.7%) ≥ 95: mRNA vaccination N 12,756 (2.9%); Unvaccinated N 2,102 (7.8%) **Male** = 40.7% (vaccinated) 35.7% (unvaccinated) **Co-morbidities:** no of chronic conditions 0: mRNA vaccination N 45,350 (10.5%); Unvaccinated N 9,325 (34.6%) 1: mRNA vaccination N 84,118 (19.4%); Unvaccinated N 4,279 (15.9%) 2: mRNA vaccination N 112,888 (26.0%); Unvaccinated N 4,940 (18.3%) 3: mRNA vaccination N 96,043 (22.1%); Unvaccinated N 4,249 (15.8%) 4: mRNA vaccination N 56,889 (13.1%); Unvaccinated N 2,393 (8.9%)	**Severe Disease: ≥14 days after second/final dose** **Hospitalisation^** VE: 82% (95%CI 72% to 89%) **Mortality$** *COVID-19 related* VE: 81% (95%CI 74% to 87%) **Variants of Concern** NR **Subgroups**: NR **Vaccine Effectiveness over time** **Hospitalisation** 14-41 days VE: 82% (95%CI 64% to 91%) 42-69 days VE: 81% (95%CI 61% to91%) 70-97 days VE: 78% (95%CI 57% to 88%) 98+ days VE: 89% (95%CI 71% to 96%) **Mortality**	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose** NR

		≥ 5	38,590	8.9	1,756	6.5		14-41 days VE: 86% (95%CI 68% to 93%) 42-69 days VE: 84% (95%CI 70% to 91%) 70-97 days VE: 87% (95%CI 77% to 92%) 98+ days VE: 74% (95%CI 60% to 83%)	

^A COVID-19-related hospitalisation was defined as admission for at least 24 h with COVID-19 as the primary diagnosis (ICD10 code U07.1), and a previous positive reverse transcription PCR (RT-PCR) test.

$A COVID-related death was considered an all cause death accompanied by a positive RT-PCR test that occurred within 30 days prior

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Chemaitelly (2021b)[35] **Title:** Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar **DOI:** https://doi.org/10.1101/2021.08.25.21262584 **NCT:** N/A	**Intervention/Exposure:** BNT162b2 (Pfizer)# **Comparator/Control:** No vaccination **Time since final vaccination dose:** (See results by time) **Adjustments:** Cases (PCR-positive persons) and controls (PCR-negative persons) were matched one-to-one by sex, 10-year age	**Description:** National Population Study. 891,481 completed the two-dose regimen Patients with prior infection are included in the primary analysis but are adjusted for in sensitivity analysis. **N:** Cases: 173,496 Controls: 1,422,333	See below	See below

Study Design*:* matched test-negative, case-control study **Country**: Qatar **Setting***:* National, federated SARS-Co-V2 databases. **Time Period***:* January 1, 2021 to August 15, 2021. **Variants of Concern:** Predominately Beta. Alpha wave in early 2021 when number vaccinated was small. Delta steadily increased during Summer 2021. **Publication status**: Preprint	group, nationality, reason for SARS-CoV-2 PCR testing, and calendar week of PCR test. Sensitivity Analysis. Sensitivity analysis was conducted by adjusting for prior infection and matching factors in logistic regression that is, by sex, age, nationality, reason for PCR testing, and calendar week of PCR test. .	**Age:** Median years (IQR) Case: 32 (23-39) Control :31 (23-39) **Male:** Case: 70.6% Control: 70.6% **Co-morbidities:** NR		

	Primary Outcome Results		**Secondary Outcome Results**			
Effectiveness over time	**Severe Disease**		**Confirmed RT-PCR Infection**			
Weeks after 2nd dose	*Severe Critical and fatal COVID-19 infection**		*Any*			
0-4	95.4 (93.4-96.9)			72.1 (70.9-73.2)		
5-9	94.2 (91.0-96.5)			65.8 (63.8-67.7)		
10-14	91.8 (86.0-95.5)			55.5 (52.0-58.8)		
15-19	86.4 (69.9-94.8)			29.7 (21.7-36.9)		
20-24	95.3 (70.5-99.9)			0.0 (0.0-0.0)		
≥25	71.5 (9.2-93.2)			0.0 (0.0-0.4)		
Weeks after 2nd dose	*Severe*	*Critical*	**Mortality** *Fatal Covid-19*	*Asymptomatic*	*Symptomatic*	
0-4	94.4 (91.9-96.3)	98.7 (95.3-99.8)	93.9 (84.5-98.1)	63.7 (61.2-66.1)	79.6 (77.9-81.2)	

5-9	95.1 (91.7-97.4)	91.6 (80.6-97.1)	90.0 (74.0-97.0)	54.9 (50.5-58.9)	70.8 (67.8-73.6)	
10-14	92.4 (85.9-96.3)	89.2 (69.3-97.2)	93.4 (73.1-99.2)	38.5 (31.0-45.2)	60.6 (55.2-65.4)	
15-19	85.9 (66.5-95.1)	89.0 (20.3-99.8)	80.4 (0.0-99.6)	0.0 (0.0-13.3)	49.6 (39.1-58.4)	
20-24	81.9 (46.7-95.5)	66.8 (0.0-99.4)	Omitted	0.0 (0.0-0.0)	0.0 (0.0-19.1)	
≥25				0.0 (0.0-0.0)	0.0 (0.0-8.0)	
	Variants of Concern		**Variants of Concern**			
	*Severe, critical and fatal COVID-19 infection**		*Any RT-PCR infection*			
Weeks after 2nd dose	Alpha	Beta	Delta	Alpha	Beta	Delta
0-4	100.0 (0.0-100.0)	97.0 (80.9-99.9)	100.0 (0.0-100.0)	67.8 (57.1-76.1)	74.3 (68.5-79.2)	83.8 (73.6-90.5)
5-9	100.0 (0.0-100.0)	94.6 (63.5-99.9)	100.0 (74.3-100.0)	82.2 (72.1-89.0)	52.7 (40.3-62.7)	72.0 (60.5-80.5)
10-14	69.6 (0.0-99.4)	86.5 (0.0-99.7)	81.6 (0.0-99.6)	64.5 (43.8-78.1)	58.8 (43.2-70.5)	48.7 (28.4-63.6)
15-19	Omitted	100.0 (0.0-100.0)	100.0 (0.0-100.0)	11.9 (0.0-59.1)	47.7 (7.5-71.2)	13.0 (0.0-34.8)
20-24	Omitted	100.0 (0.0-100.0)	81.6 (0.0-99.6)	0.0 (0.0-48.9)	26.4 (0.0-65.9)	0.0 (0.0-1.3)
≥25	Omitted	100.0 (0.0-100.0)	67.9 (0.0-99.4)	0.0 (0.0-57.3)	71.5 (0.0-97.1)	0.0 (0.0-21.3)
	Subgroups			**Subgroups**		
	*Severe, critical and fatal COVID-19 infection**		*Any infection*			
Weeks after 2nd dose	<60 years	≥60 years		<60 years	≥60 years	
0-4	96.7 (94.8-98.1)	91.1 (84.1-95.4)		72.6 (71.5-73.8)	66.3 (59.7-71.8)	
5-9	96.0 (92.2-98.2)	92.9 (86.7-96.5)		66.9 (64.8-68.9)	63.9 (57.1-69.7)	
10-14	96.7 (90.1-99.3)	88.8 (78.9-94.5)		56.7 (53.0-60.1)	53.4 (42.9-61.9)	
15-19	86.8 (62.4-96.6)	86.4 (53.8-97.4)		27.8 (19.1-35.5)	46.6 (23.1-63.2)	
20-24	92.9 (53.2-99.8)	100.0 (46.0-100.0)		0.0 (0.0-0.0)	27.3 (0.0-55.3)	

≥25	85.7 (0.0-99.7)	57.6 (0.0-93.0)		0.0 (0.0-2.2)	0.0 (0.0-17.4)	

* Classification of COVID-19 case severity (acute-care hospitalizations), criticality (ICU hospitalizations), and fatality followed World Health Organization (WHO) guidelines

#Over 500,000 patients received mRNA-1273 but these patients are not included in this analysis.

Key: CI – Confidence Interval; IQR – Interquartile Range ; N/A – Not Applicable; CT – National Clinical Trial; N/A – Not Applicable; 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): Gazit (2021)*[36] **Title:** Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections **NCT:** N/A **DOI:** https://doi.org/10.1101/2021.08.24.21262415 **Study Design***:* Retrospective observational study **Country**: Israel **Setting***:* General population	**Model 1 -** examined natural immunity and vaccine-induced immunity by comparing the likelihood of SARS-CoV-2-related outcomes between previously infected individuals who have never been vaccinated and fully vaccinated SARS-CoV-2-naïve individuals.			
	Exposure: BioNTech/Pfizer mRNA BNT162b2 **Control:** Previously infected individuals with no vaccination **Time since final vaccination dose:** At least 12.86 weeks	**Description:** Adults aged 16 or older: Exposure Group: fully vaccinated and SARS-CoV-2-naïve individuals, namely members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021; Control Group unvaccinated previously infected individuals a positive SARS-CoV-2 PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period. **N:** *Fully vaccinated* 673,676 *Previously infected* 62,883	**Severe Disease:** **At least three months after second dose.** *Hospitalisation* *OR 8.06 (95% CI 1.01* to 64.55, p 0.049) increased risk for increased risk to be admitted for vaccinated individuals compared to unvaccinated individuals who previously recovered from SARS-CoV-2. **Adjustment**s~: These groups were matched in a 1:1 ratio by age, sex, location, and time of first event. First event (the preliminary exposure) was either the time of administration of the second dose of the vaccine or the time of documented infection with SARS-CoV-2 (a positive RT-PCR	**Confirmed RT-PCR SARS-CoV-2 infection** **≥At least three months after second dose.** **Any** aOR 13.06 (95% CI, 8.08 to 21.11) increased risk for breakthrough infection in vaccinated group as opposed to reinfection (P<0.001). **Adjustments:** These groups were matched in a 1:1 ratio by age, sex and residential location and socioeconomic

<table>
<tr>
<td>Time Period: 01 June to 14 August, 2021

Variants of Concern:
During the follow-up period the Delta variant was dominant in Israel.

Publication status:
Preprint</td>
<td></td>
<td>In Model 1:
16,215 persons in each group were matched

Age:
Previously infected
Mean 36.1 (SD:13.9)

Vaccinated individuals
Mean 36.1 (SD: 13.9)

Male =

Previously infected 54.2%

Vaccinated individuals 54.2%

Co-morbidities:
<table>
<tr><th></th><th>Previously infected</th><th>Vaccinated</th></tr>
<tr><td>Immunocompromised</td><td>1%</td><td>2.6%</td></tr>
<tr><td>COPD</td><td>0.4%</td><td>0.6%</td></tr>
<tr><td>Cancer</td><td>2%</td><td>3.9%</td></tr>
</table>
</td>
<td>test result), both occurring between January 1, 2021 and February 28, 2021.

Mortality
COVID-19
No COVID-19-related deaths were recorded.

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time: NR</td>
<td>status. Adjusted for co-morbidity using regression.

First event (the preliminary exposure) was either the time of administration of the second dose of the vaccine or the time of documented infection with SARS-CoV-2 (a positive RT-PCR test result), both occurring between January 1, 2021 and February 28, 2021.Results were also adjusted for the presence of co-morbidities.

Symptomatic SARS-COV-2 infections[#]

aOR 27.02 (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection in vaccinated individuals as opposed to symptomatic reinfection in previously infected unvaccinated individuals (P<0.001).

Subgroup: NR

Variants of Concern: NR

Efficacy/effectiveness over time: NR</td>
</tr>
<tr>
<td colspan="4">Model 2: In model 2, SARS-CoV-2 naïve vaccinees were compared to unvaccinated previously infected individuals while intentionally not matching the time of the first event (i.e., either vaccination or infection), in order to compare vaccine-induced immunity to natural immunity, regardless of time of infection.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Exposure: BioNTech/Pfizer mRNA BNT162b2

Control:
Unvaccinated previously infected individuals

Time since final vaccination dose:
At least 12.86 weeks</td>
<td>Description:
Exposure Group:
fully vaccinated and SARS-CoV-2-naïve individuals, namely MHS members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021;

Control Group unvaccinated previously infected individuals a positive SARS-CoV-2 PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period.

N:
Fully vaccinated
673,676
Previously infected
62,883
In Model 2:
46,035 persons in each group were matched

Age:
Previously infected
Mean 36.1 (SD:14.7)
Vaccinated individuals
Mean 36.1 (SD:14.7)

Male =
Previously infected 50.8%
Vaccinated individuals 50.8%

Co-morbidities:
<table>
<tr><th></th><th>Previously infected</th><th>Vaccinated</th></tr>
<tr><td>Immunocompromised</td><td>1.1%</td><td>1.8%</td></tr>
<tr><td>COPD</td><td>0.5%</td><td>0.6%</td></tr>
<tr><td>Cancer</td><td>2.3%</td><td>3.0%</td></tr>
</table>
</td>
<td>Severe Disease:
At least three months after second dose.
Hospitalisation
OR 6.7 (95% CI, 1.99 to 22.56) increased risk to be admitted for vaccinated individuals compared to unvaccinated individuals who previously recovered from SARS-CoV-2.

Adjustments: ~
These groups were matched in a 1:1 ratio by age, sex, and residential socioeconomic status. Adjusted for co-morbidity using regression.

Mortality
COVID-19
No COVID-19-related deaths were recorded in our cohorts.

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time: NR</td>
<td>Confirmed RT-PCR SARS-CoV-2 infection

At least three months after second dose.

Infection

aOR 5.96 (95% CI, 4.85 to 7.33) increased risk for breakthrough infection in vaccinated individuals as opposed to reinfection in unvaccinated previously infected (P<0.001).

Adjustments:

These groups were matched in a 1:1 ratio by age, sex and residential location and socioeconomic status... Adjusted for co-morbidity using regression.

Symptomatic SARS-COV-2 infections#

aOR 7.13 (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection in vaccinated individuals compared to symptomatic reinfection in unvaccinated previously infected individuals.

Variants of Concern: NR
Subgroups NR

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

*A third model was analysed by Gazit et al but as it included partially vaccinated individuals, it did not meet the inclusion criteria for this review.

defined as presence of fever, cough, breathing difficulties, diarrhoea, loss of taste or smell, myalgia, weakness, headache and sore throat

~The text states that results were adjusted for co-morbidities using regression. While co-morbidities are included in the regression output for the secondary review outcomes, they are not reported in the regression output for the primary outcomes. It is unclear if this is because they are not reported or because they were not included in the hospitalisation endpoint, potentially because of a smaller number of events to inform the analysis.

Key: BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disorder; CI – Confidence Interval; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; OR – Odds Ratio; RT-PCR – Reverse Transcription Polymerase Chain Reaction; SD – Standard Deviation; VE – Vaccine Efficacy.

Mayo Clinic (Pawloski and Puranik analyses are based on an overlapping patient cohort).

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Pawlowski, 2021[37] **Title:** FDA-authorized mRNA COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system **NCT:** N/A **DOI:** https://doi.org/10.1016/j.medj.2021.06.007 **Study Design**: Retrospective Cohort study	**Comparator/Control:** No Vaccination	**Description:** Adults aged ≥18 years and underwent testing at MAYO clinical and affiliated hospitals. Participants had no positive PCR test before Dec. 1, 2020, had not received Janssen COVID-19 vaccine and lived in a Zip code with 25+ vaccinated patients	**Severe Disease:** **Adjustments:** Stage 1: Propensity score model included age, sex race, ethnicity, previous SARS-CoV-2 PCR testing, previous diagnostic influenza testing, LTC facility resident. Stage 2: Matching based on sex, geography, LTC status, PCR testing history and propensity score. **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR	**Adjustments:** As for primary outcome. **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time:** NR

With propensity score matching) **Country**: USA (Arizona, Florida, Iowa, Minnesota and Wisconsin) **Setting***:* Tested at Mayo Clinic and Associated Hospitals. **Time Period***:* 01 Dec to 20 April, 2021 **Variants of Concern:** NR **Publication status**: Peer-reviewed			**Effectiveness over time:** NR	
	Exposure: BNT162b2 (Pfizer/BioNTech) **Time since final vaccination dose:** Median 10 weeks	**N (after matching) :** *BNT162b2 (Pfizer/BioNTech):* 51,795 *Unvaccinated cohort:* 51,795 **Age:** *BNT162b2 (Pfizer/BioNTech)* mean 53.83 (SD: 18.32) *Unvaccinated cohort* mean 53.5 (SD:18.02) **Male** = *BNT162b2 (Pfizer/BioNTech)* 40.0% *Unvaccinated* 40.0% **Co-morbidity and Special Populations**: 0.1%	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* VE: 88.3% (95% CI: 72.6% to 95.9%) *ICU admissions* 100.0% (95% CI: 18.7% to 100%)	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose** VE: 88.0% (95% CI: 84.2% to 91.0%)
	Exposure: mRNA-1273 (Moderna) **Time since final vaccination dose** Median 8.29 weeks	**N (after matching:** *mRNA-1273 (Moderna):* 16,471 *Unvaccinated cohort:* 16,471 **Age:** *mRNA-1273 (Moderna)* mean 63 years (SD: 16.14) *Unvaccinated cohort* mean 62.23 years (SD: 16.72)	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation* VE: 90.6% (95% CI: 76.5% to 97.1%) *ICU admissions* 100% (95% CI: 17.9% to 100%)	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14days after second/final dose** *Any* VE: 92.3% (95% CI: 82.4% to 97.3%)
Study characteristics	**Exposure and Controls**	**Population and Patient demographics**	**Primary outcome results**	**Secondary outcome results**
Author (Year): Puranik, 2021[38] **Title:** Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence	**Exposure**: mRNA-1273 (Moderna) **Control:** Unvaccinated **Time since final vaccination dose:** Mean 16.94 weeks	**Description:** Adults aged ≥18 years and underwent testing at Mayo clinical and affiliated hospitals. Participants did not have any positive SARS-CoV-2 PCR tests prior to their first vaccine dose **N** mRNA-1273 (Moderna): 21,179 Unvaccinated: 24,990	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation#* VE: 91.6%, (95% CI: 81 to 97%, p<0.001) *ICU admissions~* VE: 93.3%, (95% CI: 57 to 99.8%, p=<0.001)	**Confirmed RT-PCR infection** **≥14 days after second/final dose** VE: 86% (95% CI: 81 to 90.6%, p<0.001)

DOI: https://doi.org/10.1101/2021.08.06.21261707

NCT: N/A

Study Design*:* Retrospective matched cohort study

Country: USA

Setting*:* Tested at Mayo Clinic and Associated Hospitals.
Time Period*:* 01 December 2020 to 19 July 2021

Variants of Concern: Initially alpha was dominant. Delta variant became prominent in each state from July. (Graph presented of frequency of variant detection in each state over time).

Publication status: Preprint

Age:

	IRR mRNA-1273 (Moderna)	Unvaccinated
18-34	14.7%	15.8%
35-54	23.3%	23.6%
55-74	47.7%	46.6%
75-85+	14.3%	13.9%

Male:

mRNA-1273 (Moderna): 43.5%

Unvaccinated: 43.4%

Co-morbidities: NR

Adjustments: The following were matched: Sex, Race, Ethnicity State of residence), SARS-CoV-2 PCR testing history, Date of vaccination.

Mortality*
COVID-19 associated death
There were no deaths in 6,070 person years in the mRNA-12743 group. There were 4 COVID -19 associated deaths in 6951 person years in the unvaccinated group. VE not computed.

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time:

Longitudinal analysis measuring incidence rate ratio of hospitalizations associated with breakthrough infections in Minnesota, split by month.

Month	IRR / mRNA-1273 (Moderna) / Unvaccinated
March	0.12 (0.0028, 0.9)
April	0.057 (0.0014, 0.36)
May	0.046 (0.0011, 0.28)
June	0 (0, 0.8)
July	0.19 (0.037,

Adjustments: The following were matched: sex, race, ethnicity, state of residence, SARS-CoV-2 PCR testing history, date of vaccination.

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time.

Longitudinal analysis measuring incidence rate ratio of breakthrough infections in Minnesota, split by month.

Month	IRR (95% CI) mRNA-1273 (Moderna) / Unvaccinated
March	0.091 (0.018, 0.29)
April	0.085 (0.033, 0.18)
May	0.069 (0.022, 0.17)
June	0.38 (0.15, 0.88)
July	0.24 (0.13, 0.42)

			0.67)	
	Exposure: BNT162b2 (Pfizer/BioNTech) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Mean 17.10 weeks	**Description:** Participants did not have any positive SARS-CoV-2 PCR tests prior to their first vaccine dose **N** **Total:** BNT162b2 (Pfizer/BioNTech) : 22,064 Unvaccinated: 24,990 **Age:** BNT162b2 (Pfizer/BioNTech) / Unvaccinated 18-34: 14.9% / 15.8% 35-54: 22.6% / 23.6% 55-74: 47.3% / 46.6% 75-85+: 15.3% / 13.9% **Male**: BNT162b2 (Pfizer/BioNTech): 43.3% Unvaccinated: 43.4% **Co-morbidities:** NR	**Severe Disease:** **≥14 days after second dose** *Hospitalisation#* VE: 85%, (95% CI: 73 to 93%, p<0.001)) *ICU admissions~* VE: 87%, (95% CI: 46 to 98.6%, p=<0.001) **Mortality** **≥14 days after second/final dose** *COVID-19 associated death* There were no deaths in 6,394 person years in the **BNT162b2** group. There were 4 COVID -19 associated deaths in 6951 person years in the unvaccinated group. VE not computed. **Adjustments:** The following were matched: Sex (exact match), Race (exact match), Ethnicity (exact match), State of residence (exact match), and SARS-CoV-2 PCR testing history (bucketed match), Date of vaccination (bucketed).	**Confirmed RT-PCR infection** **≥14 days after second/final dose** VE: 76% (95% CI: 69 to 81%, p=<0.001)) **Adjustments:** The following were matched: Sex (exact match), Race (exact match), Ethnicity (exact match), State of residence (exact match), and SARS-CoV-2 PCR testing history (bucketed match), Date of vaccination (bucketed). **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time**. Longitudinal analysis measuring incidence rate ratio of breakthrough infections in Minnesota, split by month. Incidence Rate Ratio (IRR) (95% CI) BNT162b2 (Pfizer/BioNTech)

			Variants of Concern: NR **Subgroups**: NR **Efficacy/effectiveness over time:** Longitudinal analysis measuring incidence rate ratio of hospitalizations associated with breakthrough infections in Minnesota, split by month.	

	Incidence Rate Ratio (IRR) (95% CI) BNT162b2 (Pfizer/BioNTech) / Unvaccinated
March	0.11 (0.0026, 0.82)
April	0.1 (0.012, 0.43)
May	0.13 (0.025, 0.43)
June	0.16 (0.0035, 1.2)
July	0.25 (0.061, 0.76)

/ Unvaccinated	
March	0.11 (0.028, 0.31)
April	0.12 (0.059, 0.23)
May	0.17 (0.087, 0.31)
June	0.18 (0.046, 0.53)
July	0.58 (0.38, 0.87)

*death occurring within 28 days after SARS-CoV-2 infection

#: admission to the hospital occurring within 21 days after SARS-CoV-2 infection.

~ COVID-19 associated ICU admission: admission to the intensive care unit (ICU) occurring within 21 days after SARS-CoV-2 infection.

Key: CI – Confidence Interval; ICU – Intensive Care Unit; IQR – Interquartile Range ; IRR – Incidence Rate Ratio; 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	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Polinski 2021 [62] **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 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. **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%	**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**:	**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%)

		Unvaccinated COPD: 10.4% Organ transplant: 0.4% Malignancies: 4.5% Pulmonary fibrosis: 0.5% HIV: 0.4%	<u><50 years</u> VE = 79% (95% CI 70 to, 85) <u>≥50 years</u> VE = 71% (95% CI 66 to 74%) <u><60 years</u> 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 (see figure 3b in study)	<u>≥50 years</u> VE = 65% (95% CI 63 to, 68%) <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

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Pouwels (2021)[39] **Title:** Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK **DOI:** 10.1101/2021.08.18.21262237 **NCT:** N/A **Study Design***:* Prospective cohort study (with cross-over). **Country**: UK	**Exposure*** ▪ BNT162b2 ▪ ChAdOx1 **Control:** No vaccination no prior positive, >21 days before vaccination no prior positive. **Time since final vaccination dose:** Median (IQR) weeks ▪ BNT162b2: 8.43 (5 to 12.29) ▪ ChAdOx1:	**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. Dominant Phase: Alpha / Delta Individuals: 384,543 / 358,983 Households: 221,909 / 213,825 Visits: 2,580,021 / 811,624	**Severe Disease:** NR **Adjustments:** NA **Mortality:** NR **Variants of Concern:** NA **Subgroups:** NA **Effectiveness over time:** NR	See below

Setting: National longitudinal survey from UK National statistics agency. **Time Period***:* 1 December 2020 to 01 August 2021 **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**: Preprint	5.86 (3.86 to 8.14)	Visits per person - Median (IQR)	7 (6-8)		2 (2-3)			
		Characteristics of visits included in the analyses (All ≥18 years)[#]						
		Not vaccinated, no prior positive, >21 days before vaccination	1,561,154		27,135			
		≥ 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%		

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
18 to 64 years (Delta dominant phase)	VE Any infections	86% (80-90%)	81% (69-89%)	0.23	69% (62-74%)	58% (39-71%)	0.10
	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						
		Odds ratio of testing positive for fully vaccinated vs unvaccinated per 30 days longer after being fully vaccinated in the delta dominant period					
		BNT162b2 (Pfizer)	*ChAdOx1 (Astra Zeneca)*	*Heterogeneity p*			
VE 18 – 64 year	*Any infection*	OR 1.22 (95% CI 1.06-1.41) (p=0.007)	OR 1.07 (95% CI 0.98-1.18, p=0.15))	0.14			
	Ct<30	OR 1.52 (95% CI 1.26 to 1.84) (p<0.0001)	OR=1.09 (95% CI 0.0.97 to 1.22) (p=0.14)	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"			
	Reported symptoms	Graph only	Graph only Same direction of effect as for Any infection and Ct <30.	Same direction of effect as for PCR positive infection and Ct <30.			

		Same direction of effect as for Any infection and Ct <30.		" Extrapolating declines beyond the observed follow-up, both vaccines would be equally effective against…. after the second dose and 116 days (3.8 months) against PCR- positives with symptoms"
		Low Ct versus High Ct Population		
≥18 years (All periods)	"Independently of this effect of calendar time (Alpha versus Delta), new PCR-positives were less likely to be in the low Ct sub-population 14 days after two BNT162b2 than ChAdOx1 vaccinations (adjusted odds ratio (aOR) =0.33 (95% CI 0.16-0.67) p=0.002; Table S4, Figure S7A), but this likelihood increased significantly over time from second vaccination (aOR per month=1.43 (1.07-1.91) p=0.01; unadjusted in Figure 4A). In contrast, there was no evidence of changing likelihood over time for ChAdOx1 (aOR per month=0.97 (0.79- 1.19) p=0.78; heterogeneity p=0.02). Overall, therefore, by around 3 months post second vaccination the probability of being in the low Ct sub-population was similar for both BNT162b2 and ChAdOx1 (Figure S7A)" "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-positives 14 days 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 (Figure S7B). Calendar date was the only other factor strongly associated with Ct in both low and high Ct sub-populations (Figure S7C), with modest declines and increases within the low Ct sub-population consistent with increasing and decreasing positivity rates (Figure S1C) leading to new infections being identified slightly earlier/later."			
	Effectiveness over time by subgroup			
18 – 64 years Delta dominant period	Graphs showing the odds of testing positive versus unvaccinated 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. Previous analysis by the authors have concluded that the vaccine effectiveness declines with time (odds over time of testing positive increases) and that the modelled rate of decline is greater for BNT162b2. In the graphs, the steeper the line upwards, the greater the modelled rate of waning. A difference in the slopes between subgroups indicates a potential interaction effect between subgroups and the modelled rate of treatment waning (that is differences in the rate of waning between subgroups). However, numerical results are not provided. Confidence intervals are wide and formal statistical tests are not reported. Further, graphs by subgroup are not interpreted by the paper authors. **NB.** For these reasons, descriptions of the graphs 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 (Figure 2 in Pouwels). Age: The rate of increase in odds over time of testing positive (treatment effectiveness waning) for participants vaccinated with BNT162b2 (Pfizer) versus unvaccinated appears greater for those 35-64 years compared to those aged 18-34 years. A similar interaction between age and time also appears for AZ but the interaction effect appears to be much smaller.			

	Long term health condition: The graph suggests a very small interaction between the rate of treatment waning and evidence of a long term health condition with those with a long term health condition having a marginally large rate of treatment waning. Prior infection: The graph indicates the presence of interaction between evidence of prior infection and the modelled rate of treatment waning for both AZ and Pfizer with the rate of increase in odds over time of testing positive is much lower for those with evidence of prior infection. There was no graphical evidence that the rate of increase in the odds of testing positive for vaccinated participants versus unvaccinated (treatment waning) differed by dosing interval.
*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)[40] **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:** Follow up period: 98 days (maximum). Median: 10.14 weeks	**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 | | --- | --- | --- | --- |	**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	**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.

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	Median follow up for unvaccinated: 5.7 weeks	<table><tr><td>16-44</td><td>18%</td><td>71%</td><td>64%</td></tr><tr><td>45-59</td><td>33%</td><td>23%</td><td>20%</td></tr><tr><td>60-74</td><td>36%</td><td>5%</td><td>10%</td></tr><tr><td>75+</td><td>13%</td><td>1%</td><td>5%</td></tr></table> **Male** = 48% **Co-morbidities/Special populations:** No relevant groups reported.	geographical statistical area (proxy for population group and 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 **Efficacy/effectiveness over time:** NR	**Variants of Concern:** 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. **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): Sharma (2021) [79] **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 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	**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	**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:** NR

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. **Publication status**: Preprint		**Age:** median 70 (interquartile range [IQR]: 58-76) **Male** = 91.5% **Co-morbidities:** Solid Tumor, Leukemia, or Lymphoma: 484,311 (16.0%)	**Efficacy/effectiveness over time:** NR	
	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	Exposure and Controls	Population and Patient demographics	Primary outcome results*	Secondary outcome results*
Author (Year): Tartof, 2021 [64] **Title:** Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study **DOI:** **https://doi.org/10.1016/S0140-6736(21)02183-8** **NCT:** NCT04848584 **Study Design***:* Retrospective cohort study **Country**: United States **Setting***:* Kaiser Permanente Southern California Healthcare System **Time Period***:* Dec 14, 2020 – Aug 8, 2021	**Intervention/Exposure**: BNT162b2 (Pfizer-BioNTech) **Comparator/Control:** Unvaccinated [£] **Time since final vaccination dose:** Mean 14.72 weeks (Range 0 to 25.99 weeks post-vaccination) SD – 7.8 weeks	**Description:** All individuals' ≥12 years with ≥1 year of prior membership with KPSC. **N: 3 436 957** Unvaccinated, 2,290,189 Fully vaccinated (two doses plus ≥7 days), 1,043,289 **Age:** Unvaccinated, median (IQR) yrs, 45 (29-61) Fully vaccinated, median (IQR) yrs, 46 (29–62). **Male** Unvaccinated, 48.7% Fully vaccinated, 45.3% **Co-morbidities:** COPD Unvaccinated, 8.9% Fully vaccinated, 9.7%	**Severe Disease:** **≥7 days after second/final dose** *See below* **Mortality:** NR **Adjustments:** age, sex, race/ethnicity, BMI, cardiac disease, organ transplant, diabetes (by A1C), chronic obstructive pulmonary disease, renal disease, malignancy, hypertension, Charlson index, healthcare utilization in year prior to index date (outpatient, virtual, ED, inpatient), influenza and pneumococcal vaccinations in year prior, neighborhood deprivation index (NDI)3, and prior infection with SARS-CoV-2 as indicated by PCR or serology. **Variants of Concern** See below	**Confirmed RT-PCR infection ≥7 days after second/final dose** See below **Adjustments:** age, sex, race/ethnicity, BMI, cardiac disease, organ transplant, diabetes (by A1C), chronic obstructive pulmonary disease, renal disease, malignancy, hypertension, Charlson index, healthcare utilization in year prior to index date (outpatient, virtual, ED, inpatient), influenza and pneumococcal vaccinations in year prior, neighborhood deprivation index (NDI), and prior infection with SARS-CoV-2 as indicated by PCR or serology.

Variants of Concern: Over the study period, 28·4% of specimens for which a sequence could be determined were Delta. A graphic depicting the distribution of variants from January 2021 through July 2021 is provided also **Publication status**: Peer-reviewed						
	Primary and Secondary Outcomes					
		SARS-CoV-2 infection [$]		SARS-CoV-2 hospitalisation[&]		
	Age	**VE_{adj}** (95% CI)		**VE_{adj}** (95% CI)		
	12-15 years	91 (88-93)		81 (-55-98)		
	16-44 years	73 (71-74)		92 (88-95)		
	45-64 years	73 (71-74)		91 (88-93)		
	≥65 years	61 (57-65)		86 (82-88)		
	≥12 years	73 (72-74)		90 (89-92)		
	≥16 years	72 (71-73)		90 (89-92)		
	SARS-CoV-2 infection[$] by number of months since being fully vaccinated					
	Age	2 - < 3months	3 - <4months	4 - <5 months	>=5 months	
		VE_{adj} (95% CI)	**VE_{adj}** (95% CI)	**VE_{adj}** (95% CI)	**VE_{adj}** (95% CI)	
	12-15 years	88 (68-96)	84 (-14-98)	100 (100-100)	100 (100-100)	
	16-44 years	78 (75-80)	68 (65-71)	57 (51-62)	39 (32-45)	
	45-64 years	78 (74-81)	67 (63-70)	61 (55-66)	50 (43-57)	

	≥65 years	75 (65-83)	56 (45-65)	49 (41-57)	43 (30-54)
	≥12 years	78 (76-79)	68 (65-70)	61 (58-64)	47 (43-51)
	≥16 years	77 (76-79)	68 (65-70)	61 (58-64)	47 (43-51)
	SARS-CoV-2 hospitalisation[&] by number of months since being fully vaccinated[%]				
	Age	2 - < 3months	3 - <4months	4 - <5 months	>=5 months
		VE_{adj} (95% CI)	**VE_{adj}** (95% CI)	**VE_{adj}** (95% CI)	**VE_{adj}** (95% CI)
	12-15 years	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
	16-44 years	98 (90-99)	94 (85-98)	88 (67-95)	90 (69-97)
	45-64 years	91 (83-95)	94 (88-97)	95 (84-98)	90 (75-96)
	≥65 years	89 (78-94)	86 (77-92)	85 (77-90)	83 (69-90)
	≥12 years	92 (89-95)	93 (89-95)	91 (87-93)	88 (82-92)
	≥16 years	92 (89-95)	93 (89-95)	91 (87-93)	88 (82-92)
	SARS-CoV-2 infection[$] and hospitalisation[&] by variant				
	Variant	**Infection**		**Hospitalisation**	
		VE_{adj} (95% CI)		**VE_{adj}** (95% CI)	
	Delta Variant	75 (71-78)		93 (84-96)	

	Other Variant	91 (88-92)		95 (90-98)	
	SARS-CoV-2 infection$ by variant and month%				
	Variant	2 - < 3months	3 - <4months	4 - <5 months	
		VE_{adj} (95% CI)	**VE_{adj}** (95% CI)	**VE_{adj}** (95% CI)	
	Delta Variant	78 (70-83)	60 (48-69)	53 (39-65)	
	Other Variant	88 (81-92)	80 (69-87)	67 (45-80)	

£ - Unvaccinated group includes those not vaccinated with BNT162b2 as of Aug 8, and those vaccinated with COVID-19 vaccines· Those vaccinated with COVID-19 vaccines other than BNT162b2 are censored in the VE modelling at vaccination date·

*- VE was calculated as (1–HR) * 100%

$ - SARS-CoV2 infection defined as testing positive for SARS-CoV-2 via a polymerase chain reaction (PCR) test from any sample (i.e., bronchial lavage, nasopharyngeal or nasal swab, oropharyngeal swab, throat swab, saliva, sputum, or tracheal aspirate) in any clinical

setting regardless of the presence of symptoms

& - Hospitalization with a positive SARS-CoV-2 PCR test that was conducted between 14 days prior to 3 days after the date of hospital admission

% - Results are also presented for vaccine efficacy at <1 months and 1-<2 months

Hospitalised patients

Study characteristics	Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Bajema (2021) [65]	**Intervention/Exposure**: BNT162b2 - Pfizer-BioNTech (Cases^: 79.6%, Controls^ – 64.0%)	**Description:** Adults aged ≥18 years hospitalized at five VAMCs (in Atlanta, Georgia; Bronx, New York; Houston,	**Severe Disease: ≥14 days after second/final dose**	**Confirmed RT-PCR or Antigen SARS-CoV-2 injection**

Title: Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021 **DOI:** doi: 10.15585/mmwr.mm7037e3 **NCT:** N/A **Study Design***:* Test-negative case control **Country**: US **Setting***:* Hospital **Time Period***:* February 1–August 6, 2021 **Variants of Concern:** Delta became the predominant variant across all sites in July 2021 **Publication status**: Peer-reviewed	mRNA-1273 – Moderna (Cases^: 20.4% Controls^: 36.0%) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Median – 11.82 weeks (IQR = 6.98–18.38 weeks)	Texas; Los Angeles, California; and Palo Alto, California. **N:** Total – 1,175 Positive SARS-CoV-2 test – 388 (13.9% fully vaccinated) Negative SARS-CoV-2 test 787 (48% fully vaccinated) **Age (overall):** Median: 68 years (IQR 59 to 75 years) **Male (overall)** = 93.0% **Co-morbidities (overall):** Asthma – 7.3% COPD – 25.4% Immunocompromising condition or therapy% – 18.4%	*Severe Disease* *COVID-19 associated Hospitalisation* £ VE = 86.8% (95% CI 80.4 to 91.1%) **Adjustments:** VAMC site, admission date and age (with the use of cubic splines), sex, and race/ethnicity. Additional factors were included if they changed the aOR by ≥5% when added individually **Mortality** Positive SARS-CoV-2 test – 28 (7.7%) Negative SARS-CoV-2 – 33 (4.2%) **Variants of Concern** (Before delta variant predominance) February 1 – June 30 VE = 84.1% (95% CI 74.1 to 90.2) During delta variant predominance (July 1 to August 6) VE = 89.3% (95% CI 80.1 to 94.3) **Subgroups**:	**≥14 days after second/final dose** NR

			COVID-19 associated hospitalisation 18 – 64 years VE = 95.1% (95% CI 89.1 to 97.8) ≥65 years VE = 79.8% (95% CI 67.7 to 87.4%) BNT162b2 (Pfizer/BioNTech) VE = 83.4% (74.0 to 89.4) mRNA-1273 (Moderna) VE = 91.6% (83.5 to 95.7) **Efficacy/effectiveness over time.** ***COVID-19 associated hospitalisation*** Fully vaccinated (<90 days) VE = 86.1 (95% CI 76.5 to 91.8) Fully vaccinated (≥90 days) VE = 87.2% (95% CI 78.2 to 92.5)	

			No difference was found between persons who had completed the full vaccination series	

% Includes HIV/AIDS, malignancy, history of solid organ or stem cell transplant, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, and receipt of immunosuppressive therapy (systemic steroids, chemotherapy, or other immunosuppressive therapy) within 1 month of SARS-CoV-2 test.

£ Patients were eligible for inclusion if they had COVID-19–like illness (i.e., fever, new or worsened cough or shortness of breath, loss of taste or smell, oxygen saturation on room air <94%, requirement for noninvasive ventilation or endotracheal intubation with mechanical ventilation, or chest radiograph or computed tomography pulmonaryfindings consistent with pneumonia) (1) and a molecular test (reverse transcription–polymerase chain reaction [RT-PCR] or isothermal nucleic acid amplification test) for SARS-CoV-2 performed within 14 days before admission or during the first 72 hours of hospitalization.

^ Patients with COVID-19–like illness who received a positive SARS-CoV-2 test result were included as case-patients, and those with COVID-19–like illness with negative SARS-CoV-2 test results were included as controls.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Grannis (2021) [66] **Title:** Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19–Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2 (Janssen) **Comparator/Control:**	**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.	**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:**	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second/final dose:** NR

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 (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.	Unvaccinated [*] **Time since final vaccination dose: ~** To hospital admission or Emergency department /Urgent care (EC/UC) *Pfizer-BioNTech* – Hospitalisation – 17.66 weeks ED/UC – 15.25 weeks *Moderna* – Hospitalisation – 17.09 weeks ED/UC – 15.68 weeks *Janssen* – Hospitalisation – 15.39 weeks EC/UC – 15.39 weeks	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:** Median = 65 years (IQR: 48-77 years). *Admitted to ED/UC with COVID-19 like illness –* 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	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 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* 18-74 years VE = 89% (95% CI 85 to 92) ≥75 years	

			VE = 76% (95% CI 64 TO 84) Vaccine type **Vaccine** / **VE (95% CI)** Pfizer-BioNTech / 80% (73 to 85) Moderna / 95% (92 to 97) Janssen / 60% (31 to 77) *ED/UC encounter* Vaccine type **Vaccine** / **VE (95% CI)** Pfizer-BioNTech / 77% (74 to 80) Moderna / 92% (89 to 93) Janssen / 65 (56 to 72) **Efficacy/effectiveness over time.** NR	

@ No case or control definition provided

ED/UC- Emergency depart Urgent Care Encounter.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Griffin (2021) [67] **Title:** SARS-CoV-2 Infections and Hospitalizations Among Persons Aged ≥ 16 Years, by Vaccination Status — Los Angeles County, California, May 1–July 25, 2021 **DOI:** **10.15585/mmwr.mm7034e5** **Study Design***:* Cohort study **Country**: USA **Setting***:* Persons Aged ≥16 Years in Los Angeles County, Californnia **Time Period***:* 01 May 2021 – 25 July 2021	**Intervention/Exposure**: Individual were considered fully vaccinated ≥14 days after receipt of: ▪ 1-dose Janssen (Ad26.COV2.S); ▪ 2-dose series of Moderna (mRNA-1273) OR Pfizer-BioNTech vaccine (BNT162b2) **Comparator/Control:** Unvaccinated participants. Individuals were considered unvaccinated <14 days after receipt of the first dose of a 2-dose series or 1 dose of the single-dose vaccine or if no vaccination data were available.	**Description:** Persons Aged ≥16 Years **N:** *Janssen (Johnson & Johnson):* 1,830 (16.8%), *Moderna:* 3,047 (28%) Pfizer –BioNTech: 6,018 (55.2%) *Unvaccinated:* 30,801 (71.4%) **Age:** *Overall population Median age, yrs (IQR): 34 (26-46)* *Fully vaccinated Median age, yrs (IQR):* 37 (28-52) *Unvaccinated Median age, yrs (IQR): 32 (26-44)* **Male** *Fully vaccinated:* 48.2% *Unvaccinated:*47.1%	**Severe Disease:** **≥14 days after second/final dose** *Admitted to hospital ≤14 days after positive SARS-CoV-2 test date* A significantly lower percentage of fully vaccinated (1.2%) persons were admitted to a hospital after their SARS-CoV-2 positive test result date compared with unvaccinated persons (4.2%) (p<0.001). *Hospitalisation* [£] A significantly lower percentage of fully vaccinated persons were hospitalized (3.2%) compared with unvaccinated persons (7.6%) (p<0.001). *ICU admissions* A significantly lower percentage of fully vaccinated persons were admitted to an intensive care unit (0.5%), compared with unvaccinated persons (1.5%) (p<0.001). *Required mechanical ventilation*	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** [@] **≥14 days after second/final dose** NR **Adjustments:** NA **Variants of Concern:** See VOC outcomes in primary outcomes column **Subgroups:** NR **Efficacy/effectiveness over time:** NR

Variants of Concern: During May 1–July 25, the percentages of B.1.617.2 (Delta) variant infections estimated from 6,752 samples with lineage data increased among fully vaccinated persons (from 8.6% to 91.2%) and unvaccinated persons (from 8.2% to 87.1%). Gamma (P.1), Other and Alpha (B.1.1.7) were also in circulation during this study period. **Publication status**: Published	**Time since final vaccination dose:** Median (IQR) 14 (10.57-17.14) weeks	**Co-morbidities:** Co-morbidities not reported for overall population.	A significantly lower percentage of fully vaccinated persons-required mechanical ventilation (0.2%) compared with unvaccinated persons (0.5%) (p<0.001). **Adjustments:** **Vaccination status was ascertained by matching SARS-CoV-2 case surveillance and CAIR2 data on person-level identifiers using an algorithm with both deterministic and probabilistic passes. Age-adjusted rolling 7-day SARS-CoV-2 infection and hospitalization rates were estimated by vaccination status. **Mortality** *All Cause/COVID-19* $ A significantly lower percentage of deaths (0.2%) occurred among fully vaccinated persons than among partially vaccinated (0.5%) and unvaccinated (0.6%) persons (p<0.001). Death investigations determined that six of the 24 fully vaccinated persons who died had immunocompromising conditions, including HIV infection, cancer (i.e., prostate, pancreatic, lung, or leukemia), and liver transplantation. **Variants of Concern:** During May 1–July 25, the percentages of residents aged ≥16 years with SARS-CoV-2 Delta variant infections increased from 8.6% to 91.2% in fully vaccinated persons (1,667) and from 8.2% to	

			87.1% in unvaccinated persons (4,887). **Subgroups:** NR **Efficacy/effectiveness over time:** NR	

** Adjusted rates were calculated using 2018 population estimates and were standardized using the year 2000 U.S. standard population (https://www.cdc.gov/cancer/uscs/technical_notes/stat_methods/rates.htm). Rolling 7-day incidence was calculated by summing the total number of persons or hospitalizations during a 7-day period and dividing by the total population at the end of the 7-day period.

£ COVID-19–associated hospitalizations were defined as hospital admissions occurring ≤14 days after a first SARS-CoV-2 infection.

$ COVID-19 associated deaths defined as deaths occurring ≤60 days of SAES-COV-2 infection or deaths with COVID-19 listed as a cause of or contributing condition to death

@ A laboratory-confirmed SARS-CoV-2 infection was defined as a first detection§ of SARS-CoV-2 RNA or antigen in a respiratory specimen

CAIR2, COVID-19 surveillance and California Immunization Registry 2

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Self (2021) (68) Title: Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in	**Intervention/Exposure**: Vaccinated, 1,327 (36.0%) ▪ Moderna – 476 (12.9%) ▪ Pfizer-BioNTech – 738 (20.0%)	**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	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* NR *Hospitalisation* See below	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥14 days after second/final dose** NR

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. **Variants of Concern:** NR **Publication status**: On 17 September 2021, this report was posted online as an MMWR Early Release.	▪ 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	**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% 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%	*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 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	>28 days after full vaccination£	14-120 days after full vaccination	>120 days after full vaccination
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): Tenforde 2021[102]	**Exposure**: mRNA vaccine Pfizer-BioNTech: 59%	**Description:** Adults aged ≥18 years admitted to 21 hospitals in 18 US states.	**Severe Disease:** **≥14 days after second/final dose** *Hospitalisation*	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection:** NR

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 **Variants of Concern:** Of sequenced cases: 53.3% Alpha, 16.3% Delta. Delta became dominant in Mid-June. **Publication status**: Peer-reviewed.	Moderna: 41% **Comparator/Control:** No Vaccination **Time since final vaccination dose:** Median 9.29 weeks (IQR 5.84 to 13.25 weeks)	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% **Co-morbidities and Special Populations** ≥1 chronic condition: 82.1% Pulmonary Disease: 26% Immunocompromising condition: 21.1%* LTC Resident: 4.7%	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 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.

Group	2-12 weeks VE (95% CI)	13-24 weeks VE (95% CI)
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 (b) (2021) [69] **Title:** Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings **DOI:** 10.1056/NEJMoa2110362 **NCT:** N/A	**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*:**	**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)***	**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*	**Confirmed RT-PCR SARS-CoV-2 infection** N/R **Adjustments:** N/A **Variants of Concern:** NR

Study Design*:* Test negative (case-controll) **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**: Published	Hospitalisation – Median - 53 IQR (33 to 75) ICU admission – Median - 52 (IQR 34 to 73) ED/UC – Median 50 (IQR 31 to 73)	***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* **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*	*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 January 1, 2021, to the index date for each medical visit), and local virus circulation. **Mortality** *All Cause/COVID-19:* NR **Variants of Concern** NR **Subgroups**:	**Subgroups**: N/R **Efficacy/effectiveness over time:** N/R

			50–64 yr	5,532	1898	282	*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)	
			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					

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).

General Population (early v. late vaccinees)

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Goldberg 2021 [70] **Title:** Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel **DOI:** 10.1101/2021.08.24.21262423 **NCT:** N/A **Study Design***:* Retrospective Cohort study **Country**: Israel **Setting***:* Residents of Israel **Time Period***:* July 11-31, 2021 **Variants of Concern:** The Delta variant became dominant in Israel during June 2021 with more than 98% of positive cases in Israel are attributed to the Delta variant	**1.** **Intervention/Exposure**: Early vacinees (BNT162b2 (Pfizer/BioNTech) vaccination in Jan 16-31) **Comparator/Control:** Late vaccinees (BNT162b2 (Pfizer/BioNTech) in Feb,Mar,Apr and May. **2.** **Intervention / Exposure** BNT162b2 (Pfizer/BioNTech) **Comparator / Control** Unvaccinated **Estimated Time Since Vaccination** % Jan 16-31 – 27.92 weeks	**Description:** All residents of Israel excluding those under 16 years of age and those who returned from abroad during July. Participants were fully vaccinated before June 1st 2021 and not infected before the study period (11-31 July,2021). Confirmed cases before this period were excluded. Data on all PCR positive test results between July 11-31, 2021 of Israeli residents who became fully vaccinated before June 2021 were used in this analysis **N:** Total – 9,395,923 Vaccinated - 4,785,245 Positive PCR test n=12,927 Severe COVID 19 n=348	**Severe Disease: ≥7 days after second/final dose** See below **Adjustments** Age, week, past PCR tests prior to vaccination campaign, demographic group (general Jewish, Arab, ultra-Orthdox Jews), and gender **Mortality** NR **Variants of Concern:** NR **Subgroups**: NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥7 days after second/final dose** See below **Adjustments:** Age, week, past PCR tests prior to vaccination campaign, demographic group (general Jewish, Arab, ultra-Orthdox Jews), and gender **Variants of Concern:** NR

Publication status: Preprint	Feb 1-15 – 25.64 weeks Feb 16 – 28 – 23.5 weeks Mar 1 – 15 – 21.65 weeks Mar 16-31 – 19.52 weeks April – 17.24 weeks May – 12.96 weeks	Jan 16-31	**N:** 1,073,766 vaccinated **Age:** 16-39 years– 12% 40 -59 years– 23% 60+ years - 66% **Males:** 48%			
		Feb 1-15	**N:** 971,218 vaccinated **Age:** 16-39 years– 20% 40 -59 years– 43% 60+ years – 37% **Males:** 47%			
		Feb 16 - 28	**N:** 746,944 vaccinated **Age:** 16-39 years– 47% 40 -59 years– 44% 60+ years – 9% **Males:** 51%			
		Mar 1-15	**N:** 818,975 vaccinated **Age:** 16-39 years– 67% 40 -59 years– 25% 60+ years – 8% **Males:** 50%			
		Mar 16 - 31	**N:** 748,932 vaccinated **Age:**			

	16-39 years– 66% 40 -59 years– 25% 60+ years – 8% **Males:** 48%
April	**N:** 324,996 vaccinated **Age:** 16-39 years– 67% 40 -59 years– 24% 60+ years – 9% **Males:** 47%
May	**N:** 100,414 vaccinated **Age:** 16-39 years– 67% 40 -59 years– 22% 60+ years – 11% **Males:** 46%

Primary and Secondary outcomes

(Intervention/Comparator 1)

Incidence Rate ratio (IRR) of all Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥7 days after second/final dose denoting **protection** against documented SARS-CoV-2 infection and severe COVID-19 [95% CI] compared to the first period (January 16-31)

Severe Disease (VE:95% CI)

Age	Feb	Mar
40 – 59	2.2 (0.8 to 6.1)	2.8 (0.7 to 10.9)
60+	1.2 (0.9 to 1.5)	1.7 (1.0 to 2.7)

Positive SARS-CoV-2 PCR test (VE:95% CI)

Age	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	April	May
16-39	0.9 (0.8 to 1)	1.2 (1 to 1.3)	1.3 (1.1 to 1.4)	1.5 (1.4 to 1.7)	2 (1.7 to 2.3)	2 (1.6 to 2.5)
40 – 59	1.1 (1 to 1.1)	1.1 (1 to 1.2)	1.2 (1.1 to 1.4)	1.6 (1.4 to 1.8)	1.9 (1.6 to 2.4)	2.3 (1.6 to 3.3)
60+	1.1 (1.1 to 1.2)	1.3 (1.1 to 1.5)	1.6 (1.3 to 2)	1.6 (1.3 to 2)	2.1 (1.5 to 2.9)	2.1 (1.2 to 3.4)

(Intervention/Comparator 2)

Vaccine effectiveness (VE) against all documented SARS-CoV-2 infection and severe COVID-19 [95% CI] compared to the unvaccinated cohort

Severe Disease (VE: 95% CI)

Time period indicates time period of vaccination

All tests are from the period 11-31 July 2021

Age	Jan	Feb	Mar
40 – 59	94% (87 to 97)	98% (95 to 99)	98% (94 to 99)
60+	86% (82 to 90)	88% (84 to 91)	91% (85 to 95)

Documented SARS-CoV-2 infection (VE: 95% CI)

Age	Jan 16 -31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	April	May
16-39	50% (45 to 55)	47% (42 to 52)	58% (55 to 62)	62% (59 to 64)	68% (65 to 70)	74% (71 to 77)	73% (67 to 78)
40 – 59	58% (54 to 62)	61% (58 to 65)	63% (59 to 66)	67% (63 to 70)	74% (70 to 77)	78% (73 to 82)	80% (71 to 86)
60+	57% (52 to 62)	63% (57 to 67)	65% (57 to 71)	73% (66 to 78)	72% (64 to 77)	73% (63 to 81)	75% (58 to 85)

% Estimated from the earliest date to the 31st of July

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author: Israel, A[42] **Title:** Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort **DOI:** 10.1101/2021.08.03.21261496 **NCT:** N/A **Country**: Israel **Setting***:* A nationwide healthcare provider in Israel **Time Period***:* May 15, 2021 to July 26, 2021 **Study Design***:* Retrospective cohort study **Variants:** 93% of 113 isolates sent for sequencing were the delta variant. **Publication status**: Preprint	**Intervention**: Vaccination with Pfizer (BNT162b2) Group 1: those with ≥146 days since vaccination **Comparator:** Vaccination with Pfizer (BNT162b2) Group 2: Those with <146 days since vaccination **Time since final vaccination:** Median 146 days	**Description:** All healthcare provider members who have been fully vaccinated and underwent a SARS-CoV-2 PCR test between May 15, 2021 and July 26, 2021 Tests from individual who previously tested positive were excluded. **N:** 33,993 **Age:** 18-39: 39% 40-59: 34% >=60: 27% mean (sd): 46.8 (17.4) years **Male** = 51% **Comorbidities:** Asthma 9% COPD 5% Solid Tumour 6%	**Severe Disease:** NR **Mortality:** NR	**Confirmed RT-PCR Infection** **≥14 days since final dose** Adj OR for infection (any) >=146 days v. <146 days since second dose. Adj OR (95% CI) 18-39: 1.67 (1.21,2.29) 40-59: 2.22 (1.62,3.08) >=60: 2.76 (1.62-3.08) Pooled: 2.06 (1.69,2.51) **Adjustments** Adjusted for sex, SES, ethnic group, hypertension, asthma, COPD, IHD, malignancy, CKD. Pooled results were also adjusted for age category **Subgroups** Subgroup results for those with Asthma, COPD or a solid tumour are presented by age. No significant difference in VE was observed between groups. **Variants:** NR. **Effectiveness over time** See above.

Key: Adj – Adjusted; CI – Confidence Interval; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction; SD – Standard Deviation; VE – Vaccine Efficacy.

<table>
<tr><th>Study characteristics</th><th>Intervention and Comparators
Or
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): Kertes (2021) [80]

Title: Effectiveness of the mRNA BNT162b2 vaccine six months after vaccination: findings from a large Israeli HMO

DOI:10.1101/2021.09.01.21262957

NCT: NA

Study Design: retrospective cohort analyses

Country: Israel

Setting: Maccabi HealthCare Services, Israel

Time Period: 11 January – 18 July 2021

Variants of Concern: This study was carried out during a period where the Delta</td>
<td>Intervention/Exposure: Participants vaccinated between January -February

Comparator/Control: Participants vaccinated between March - May

Time since final vaccination: Maximum follow up period 21.57 weeks</td>
<td>Description: All data were extracted from the Maccabi HealthCare Services database. PCR testing is carried out free of charge for any HMO member presenting with symptoms or reporting exposure to a confirmed case. All HMO members who, as of the 9.6.2021, were at least seven days post- second vaccination dose with no prior positive PCR result were included in this component of the study. Members having received three doses or with an appointment to receive the third dose (N=320) in the follow-up period were excluded from analysis.

N: 1,432,098

Participants vaccinated between January – February:
821,231

Participants vaccinated between March – May:
601,867

Age:
<table>
<tr><td></td><td>Jan-Feb N=821,231</td><td>Mar-May N=601,867</td></tr>
<tr><td>< 18</td><td>2.6%</td><td>10.4%</td></tr>
<tr><td>18-44</td><td>25.7%</td><td>68.9%</td></tr>
<tr><td>45-59</td><td>35.3%</td><td>14.3%</td></tr>
</table>
</td>
<td>Severe Disease: NR

Adjustments: NA

Mortality
NR

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time: NR</td>
<td>Confirmed RT-PCR SARS-CoV-2 infection ≥7 days after second dose

Any infection

(OR) 1.61 (95% CI: 1.45 - 1.79)

Adjustments:

Age group, socio-economic status and presence of chronic illness (heart disease, HTN, diabetes, CKD, and immunosuppressive disorder) were controlled for. Study findings were not adjusted for serology test accuracy

Variants of Concern:

NR

Subgroups: NR

Efficacy/effectiveness over time: see any infection outcome above</td>
</tr>
</table>

variant was in circulation. Conclusions are made on the assumption that the majority of those infected in the third component of the study (by time of vaccination) were infected with the Delta variant, given its prevalence in Israel. **Publication status**: Preprint		<table><tr><td>60-74</td><td>26.7%</td><td>4.8%</td></tr><tr><td>75+</td><td>9.7%</td><td>1.6%</td></tr></table> **Male** = % Participants vaccinated between January – February: 48% males Participants vaccinated between March – May: 47.6% males **Co-morbidities:** Immunosuppressive disorder Participants vaccinated between January – February: 1.6% males Participants vaccinated between March – May: 0.6% males		

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Mizrahi 2021)[104] **Title:** Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study **DOI:** https://doi.org/10.1101/2021.07.29.21261317 **NCT:** N/A	**Exposure**: Early vaccinees (individuals who received second dose of BNT162b2 in January/ February 2021) **Comparator/Control:** Late vaccinees (individuals who received second dose of BNT162b2 in March/April 2021)	**Description:** All members aged 16 and above who received the second vaccine dose between January and April 2021. Individuals who had a previously had a positive PCR test were excluded. **N:** 1,352,444 in the MHS who received dose 2 of vaccine of which 329,177 were matched in each group (early/late vaccinees) **Age:** NR	**Severe Disease:** NR **Mortality** NR	**Confirmed RT-PCR SARS-CoV-2 infection** **≥14 days after second/final dose** *Any* OR 1.53 (95% CI 1.40 to 1.68) of breakthrough infection in early vaccinees versus late vaccinees. **Adjustments:**

Study Design*:* retrospective cohort study comparing the incidence rates of breakthrough infections between early and late vaccinees **Country**: Israel **Setting***:* Health Maintenance Organization – Maccabi Healthcare Services (Health insurance) **Time Period***:* Outcome assessment from 01 June 2021 to 27 July 2021. **Variants of Concern:** Delta **Publication status**: Preprint	**Time since final vaccination:** At least three months for early vaccines.	**Male**: NR **Co-morbidities:** Patients with chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD) cancer and immune-compromising conditions were included but the exact proportions are not reported.		Matched each early vaccinee to a late vaccinee individual in a 1:1 ratio, based on age group (18-39, 40-59 and 60 and over), sex, city of residence, socioeconomic status. Adjusted for comorbidities **Variants of Concern:** NR **Subgroups:** *Age* odds ratio 16-39 years: 1.53 (95% CI 1.37 to 1.71) 40-59 years: 1.49 (95% CI 1.24 to 1.79) ≥60 years: 1.54 (95% CI 1.03 to 2.32) *Comparing vaccinees by month of vaccination.* OR (95% CI) Jan/Feb: 1.33 (1.21 to 1.46) Jan/Mar 1.65 (1.44 to 1.89) Jan/Apr 2.26 (1.70 to 3.01) Feb/Mar 1.40 (1.27 to 1.55) Feb/Apr 2.00 (1.51 to 2.64) Mar/Apr 1.37 (1.02 to 1.84) **Efficacy/effectiveness over time**: See above

Key: COPD – Chronic Obstructive Pulmonary Disease; CI – Confidence Interval; IBD - Inflammatory Bowel Disease; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; OR – Odds Ratio; 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): Puranik (b) (2021) [75] **Title:** Durability analysis of the highly effective BNT162b2 vaccine against COVID-19 **DOI:** https://www.medrxiv.org/content/10.1101/2021.09.04.21263115v1 **NCT:** NA **Study Design***:* test-negative case-control study **Country**: US **Setting***:* Tested at Mayo Clinic **Time Period***:* February 1, 2021 and August 22, 2021 **Variants of Concern:** This study was carried out during a period where Alpha and Delta variants were in circulation.	**Exposure** Later Vaccination **Comparator.** Early Vaccination (BioNTech, Pfizer vaccine (BNT162b2)) **Time since final vaccination:** Median time since vaccination for cases: 17.8 weeks max follow up, 23.71 Median follow up for controls: 17 weeks max follow up, 23.86 weeks	**Description:** The underlying population corresponds to the set of individuals who received their first BNT162b2 dose on or after February 1, 2021 and were fully vaccinated per protocol (i.e. with two doses administered 18-28 days apart and with no prior positive SARS-CoV-2 PCR tests before the date of full vaccination). **N:** **Cases:** 652 1+ positive symptomatic test after full vaccination (BioNTech, Pfizer vaccine (BNT162b2)) **Controls:** 5,946 (analysable data for primary analysis) *1+ negative symptomatic test after full vaccination* (BioNTech, Pfizer vaccine (BNT162b2))*, subsampled* **Age:** Cases: 57.5 (17.4) Controls: 56.5 (18.6) **Male** = % Case: 44.8% Control: 41.8%	**Severe Disease:** **≥14 days after second dose** NR **Adjustments:** NA **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time.** NR	See below

Publication status: Preprint		**Co-morbidities:** NR		

Secondary outcomes

Confirmed RT-PCR SARS-CoV-2 Symptomatic infection

Efficacy/effectiveness over time.

Adjusted Odds Ratio of symptomatic infection after full vaccination			
Time relative to full vaccination	**aOR (95% CI)**	**Age**	**aOR (95% CI)**
30 days	1.81, (0.68-4.82)	**18**	1 (Reference)
60 days	2.32, (0.97-5.52)	**25**	0.67 (0.27, 1.66)
90 days	3.5, (1.47-8.35)	**35**	0.9 (0.45, 1.79)
120 days	3.21, (1.33-7.74)	**45**	1.16 (0.57, 2.35)
		55	1.18 (0.59, 2.34)
		65	0.95 (0.47, 1.91)
		75	1.14 (0.55, 2.34)
		85	0.92 (0.42, 2.04)

Adjusted odds ratios of symptomatic SARS-CoV-2 infection split by age group			
	18-44 years	*45-64 years*	*65+ years*

Time relative to first dose	**aOR (95% CI)**		
Day 21 (Expected second dose)	0.48 (0.18, 1.24)	0.31 (0.13, 0.73)	0.68 (0.25, 1.86)
Day 35 (Expected full vaccination)	0.06 (0.02, 0.25)	0.26 (0.1, 0.69)	0.21 (0.07, 0.63)
Day 60	0.1 (0.03, 0.34)	0.14 (0.05, 0.42)	0.14 (0.04, 0.49)
Day 90	0.43 (0.18, 1.06)	0.25 (0.1, 0.64)	0.05 (0.01, 0.19)
Day 120	0.21 (0.1, 0.47)	0.34 (0.17, 0.7)	0.22 (0.07, 0.71)
Day 150	0.37 (0.17, 0.81)	0.27 (0.13, 0.54)	0.18 (0.06, 0.5)

Adjustments: Adjusted for age, sex, race, ethnicity, county, and the calendar date of testing

Variants of Concern: NR

Subgroups: NR

General Population (SARS-CoV2 infection derived versus Vaccine Derived immunity)

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Gazit (2021)*[36] **Title:** Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections **NCT:** N/A **DOI:** https://doi.org/10.1101/2021.08.24.21262415 **Study Design***:* Retrospective observational study **Country**: Israel **Setting***:* General population **Time Period***:* 01 June to 14 August, 2021 **Variants of Concern:** During the follow-up period the Delta variant was dominant in Israel.	**Model 1 -** examined natural immunity and vaccine-induced immunity by comparing the likelihood of SARS-CoV-2-related outcomes between previously infected individuals who have never been vaccinated and fully vaccinated SARS-CoV-2-naïve individuals.			
	Exposure: BioNTech/Pfizer mRNA BNT162b2 **Control:** Previously infected individuals with no vaccination **Time since final vaccination dose:** At least 12.86 weeks	**Description:** Adults aged 16 or older: Exposure Group: fully vaccinated and SARS-CoV-2-naïve individuals, namely members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021; Control Group unvaccinated previously infected individuals a positive SARS-CoV-2 PCR test recorded by February 28, 2021 and who had not been vaccinated by the end of the study period. **N:** *Fully vaccinated* 673,676 *Previously infected* 62,883 **In Model 1:** 16,215 persons in each group were matched **Age:** *Previously infected* Mean 36.1 (SD:13.9)	**Severe Disease:** **At least three months after second dose.** *Hospitalisation* *OR 8.06 (95% CI 1.01* to 64.55, p 0.049) increased risk for increased risk to be admitted for vaccinated individuals compared to unvaccinated individuals who previously recovered from SARS-CoV-2. **Adjustment**s~: These groups were matched in a 1:1 ratio by age, sex, location, and time of first event. First event (the preliminary exposure) was either the time of administration of the second dose of the vaccine or the time of documented infection with SARS-CoV-2 (a positive RT-PCR test result), both occurring between January 1, 2021 and February 28, 2021. **Mortality** *COVID-19*	**Confirmed RT-PCR SARS-CoV-2 infection** **≥At least three months after second dose.** **Any** OR 13.06 (95% CI, 8.08 to 21.11) increased risk for breakthrough infection in vaccinated group as opposed to reinfection (P<0.001). **Adjustments:** These groups were matched in a 1:1 ratio by age, sex and residential location and socioeconomic status. Adjusted for co-morbidity using regression. First event (the preliminary exposure) was either the time of administration of the second dose of the vaccine or the time of documented infection with

<table>
<tr>
<td rowspan="2">Publication status:
Preprint</td>
<td></td>
<td>Vaccinated individuals
Mean 36.1 (SD: 13.9)

Male =

Previously infected 54.2%

Vaccinated individuals 54.2%

Co-morbidities:
<table>
<tr><th></th><th>Previously infected</th><th>Vaccinated</th></tr>
<tr><td>Immunocompromised</td><td>1%</td><td>2.6%</td></tr>
<tr><td>COPD</td><td>0.4%</td><td>0.6%</td></tr>
<tr><td>Cancer</td><td>2%</td><td>3.9%</td></tr>
</table>
</td>
<td>No COVID-19-related deaths were recorded.

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time: NR</td>
<td>SARS-CoV-2 (a positive RT-PCR test result), both occurring between January 1, 2021 and February 28, 2021.Results were also adjusted for the presence of co-morbidities.

Symptomatic SARS-COV-2 infections#

OR 27.02 (95% CI, 12.7 to 57.5) for symptomatic breakthrough infection in vaccinated individuals as opposed to symptomatic reinfection in previously infected unvaccinated individuals (P<0.001).

Subgroup: NR

Variants of Concern: NR

Efficacy/effectiveness over time: NR</td>
</tr>
<tr>
<td colspan="4">Model 2: In model 2, SARS-CoV-2 naïve vaccinees were compared to unvaccinated previously infected individuals while intentionally not matching the time of the first event (i.e., either vaccination or infection), in order to compare vaccine-induced immunity to natural immunity, regardless of time of infection.</td>
</tr>
<tr>
<td></td>
<td>Exposure: BioNTech/Pfizer mRNA BNT162b2

Control:
Unvaccinated previously infected individuals

Time since final vaccination dose:
At least 12.86 weeks</td>
<td>Description:
Exposure Group:
fully vaccinated and SARS-CoV-2-naïve individuals, namely MHS members who received two doses of the BioNTech/Pfizer mRNA BNT162b2 vaccine by February 28, 2021, did not receive the third dose by the end of the study period and did not have a positive PCR test result by June 1, 2021;

Control Group unvaccinated previously infected individuals a positive SARS-CoV-2 PCR test</td>
<td>Severe Disease:
At least three months after second dose.
Hospitalisation
OR 6.7 (95% CI, 1.99 to 22.56) increased risk to be admitted for vaccinated individuals compared to unvaccinated individuals who previously recovered from SARS-CoV-2.

Adjustments: ~</td>
<td>Confirmed RT-PCR SARS-CoV-2 infection

At least three months after second dose.

Infection

OR 5.96 (95% CI, 4.85 to 7.33) increased risk for breakthrough infection in vaccinated individuals as</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>recorded by February 28, 2021 and who had not been vaccinated by the end of the study period.

N:
Fully vaccinated
673,676
Previously infected
62,883
In Model 2:
46,035 persons in each group were matched

Age:
Previously infected
Mean 36.1 (SD:14.7)
Vaccinated individuals
Mean 36.1 (SD:14.7)

Male =
Previously infected 50.8%
Vaccinated individuals 50.8%

Co-morbidities:
<table>
<tr><th></th><th>Previously infected</th><th>Vaccinated</th></tr>
<tr><td>Immunocompromised</td><td>1.1%</td><td>1.8%</td></tr>
<tr><td>COPD</td><td>0.5%</td><td>0.6%</td></tr>
<tr><td>Cancer</td><td>2.3%</td><td>3.0%</td></tr>
</table>
</td>
<td>These groups were matched in a 1:1 ratio by age, sex, and residential socioeconomic status. Adjusted for co-morbidity using regression.

Mortality
COVID-19
No COVID-19-related deaths were recorded in our cohorts.

Variants of Concern: NR

Subgroups: NR

Efficacy/effectiveness over time: NR</td>
<td>opposed to reinfection in unvaccinated previously infected (P<0.001).

Adjustments:

These groups were matched in a 1:1 ratio by age, sex and residential location and socioeconomic status... Adjusted for co-morbidity using regression.

Symptomatic SARS-COV-2 infections#

OR 7.13 (95% CI, 5.51 to 9.21) increased risk for symptomatic breakthrough infection in vaccinated individuals compared to symptomatic reinfection in unvaccinated previously infected individuals.

Variants of Concern: NR
Subgroups: NR

Effectiveness over time:
NR</td>
</tr>
<tr>
<td colspan="5">*A third model was analysed by Gazit et al but as it included partially vaccinated individuals, it did not meet the inclusion criteria for this review.

defined as presence of fever, cough, breathing difficulties, diarrhoea, loss of taste or smell, myalgia, weakness, headache and sore throat</td>
</tr>
</table>

~The text states that results were adjusted for co-morbidities using regression. While co-morbidities are included in the regression output for the secondary review outcomes, they are not reported in the regression output for the primary outcomes. It is unclear if this is because they are not reported or because they were not included in the hospitalisation endpoint, potentially because of a smaller number of events to inform the analysis.

Key: BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disorder; CI – Confidence Interval; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; OR – Odds Ratio; RT-PCR – Reverse Transcription Polymerase Chain Reaction; SD – Standard Deviation; VE – Vaccine Efficacy.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Shrestha (2021) [81] **Title:** Necessity of COVID-19 vaccination in previously infected individuals **DOI:** https://doi.org/10.1101/2021.06.01.21258176 **Title:** Necessity of COVID-19 vaccination in previously infected individuals **NCT:** NA **Study Design**: Retrospective cohort study **Country**: US	**Intervention/Exposure**: Previously infected and vaccinated Vaccination occurred using either the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) or Johnson & Johnson vaccines/Janssen (**Ad26.COV2-S)**. A person was considered vaccinated 14 days after receipt of the second dose of the vaccine. It is unclear what % of participants received type of vaccine **Comparator/Control:** Previously infected and unvaccinated	**Description:** Employees of the Cleveland Clinic Health System working in Ohio. Those employed on Dec 16,2020 were included. A person was considered vaccinated 14 days after receipt of the second dose of the vaccine. **N:** Previously infected : 2,579 Vaccinated 1,220 of 2,579 (47%) Unvaccinated 1,359 of 2,579 (53%) **Age:** mean ± SD, 39 years ±13 **Male** = NR **Co-morbidities:**	**Severe Disease:** NR **Adjustments:** NA **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Confirmed SARS-CoV-2 infection ≥14 days after second/final dose*** *Any infection* 0 reinfections occurred in those previously infected (0/2,579; 0%). In a Cox proportional hazards regression model vaccinated was not associated with a significantly lower risk of SARS-CoV-2 infection among those previously infected (HR 0.313, 95% CI 0 to Infinity). **Adjustments:** adjusted the analyses for the phase of the epidemic at all time points **Variants of Concern:** NR

Setting*:* Employees of the Cleveland Clinic Health System working in Ohio **Time Period***:* 16 December 2020 until 15 May 2021 **Variants of Concern:** NR **Publication status**: Preprint	**Time since final vaccination:** Median follow up 8.77-11.43 weeks			**Subgroups:** NR **Efficacy/effectiveness over time**: NR
	Intervention/Exposure: Not previously infected and vaccinated Vaccination occurred using either the Pfizer-BioNTech, Moderna or Johnson & Johnson vaccines/Janssen (**Ad26.COV2-S)**. A person was considered vaccinated 14 days after receipt of the second dose of the vaccine. It is unclear what % of participants received type of vaccine **Comparator/Control:** Not previously infected and unvaccinated **Time since final vaccination:** See above	**Description:** A person was considered vaccinated 14 days after receipt of the second dose of the vaccine. <u>Not previously infected</u> (49,659) Vaccinated 28,855 of 49,659 (58%) Unvaccinated 20,804 of 49,659 (42%) **Age:** mean ± SD, 42 years ±13 **Male** = NR **Co-morbidities:** NR	**Severe Disease:** NR **Adjustments:** NA **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Confirmed RT-PCR SARS-CoV-2 infection ≥14 days after second/final dose** *Any infection* 2,139 infections occurred in those not previously infected and who remained unvaccinated (2,139/20,804; 10.28%). Of 2154 SARS-CoV-2 infections 2139 (99.3%) occurred among those not previously infected who remained unvaccinated. 15 breakthrough infections occurred in those not previously infected, but fully vaccinated (15/28,855; 0.05%). In a cox proportional hazards regression model, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI: 0.015 to 0.061)

				Adjustments: adjusted the analyses for the phase of the epidemic at all time points **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time**: NR
* SARS-CoV-2 infection was defined as a positive nucleic acid amplification test on or after 16th December 2020.				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Young-Xu (2021) [78] **Title:** SARS-Cov-2 Infection versus Vaccine-Induced Immunity among Veterans **DOI:** 10.1101/2021.09.27.21264194] **NCT: N/A** **Study Design***:* Retrospective cohort study **Country**: USA	**Compared two groups whose incident vaccination or infection occurred within the first two months of 2021, that is before 1 March 2021.** **Exposure**: ▪ SARS-CoV-2-naïve individuals who received a full mRNA vaccination - 2 doses of either Pfizer or Moderna vaccine before 1 March 2021. **Control:**	**Description:** Patients were SARS-CoV-2-naïve prior to January 1, 2021, and then were either fully vaccinated or had a documented, laboratory-confirmed, SARSCoV-2 infection prior to March 1, 2021. **N:** 47,102 total. ▪ 9,539 unvaccinated, previously infected ▪ 14,458 fully vaccinated with Moderna ▪ 23,105 fully vaccinated with Pfizer. **Age:** Mean yrs (±SD): Overall: 62.87 yrs (±14.10) ▪ Unvaccinated, previously infected: 61.72 yrs (±14.83) ▪ Moderna: 64.46 yrs (±14.35) ▪ Pfizer: 62.34 yrs (±13.54)	**Severe Disease:** **(days after second/final dose NR)** *Hospitalisation (incidence rate)* Unvaccinated previously infected: ▪ Age 65+: 3.2 per 100,000 person-days ▪ Age <65: 0.9 per 100,000 person-days Pfizer vaccinated: ▪ Age 65+: 2.5 per 100,000 person-days	**Confirmed RT-PCR SARS-CoV-2 infection** **(days after second/final dose NR)** *Any* Unvaccinated previously infected: ▪ 2.7 per 100,000 patient-days. ▪ Age 65+: 4.8 per 100,000 person-days ▪ Age <65: 1.4 per 100,000 person-days

Setting*:* Electronic health record data from the Veterans Health Administration Corporate Data Warehouse **Time Period***:* June to 18 August 2021 **Variants of Concern:** Delta predominant period **Publication status**: Preprint	▪ Newly infected individuals who were subdivided into those have not been vaccinated and those have been vaccinated after their infection.[$] ▪ Previously infected individuals were matched with up to four vaccinated individuals for state and index event dates (within +/-2 weeks), race/ethnicity, age groups, sex, rural/urban, CCI, and VHA priority (proxy for socioeconomic burden). **Time since final vaccination dose:** At least three months	**Male** = 91.37% **Co-morbidities:** Asthma (10.66%) Cancer (8.75%) Cancer (metastatic) (1.31%) Chronic obstructive pulmonary disease (11.53%)	▪ Age <65: 2.9 per 100,000 person-days Moderna vaccinated: ▪ Age 65+: 2.2 per 100,000 person-days ▪ Age <65: 2.3 per 100,000 person-days **Adjustments:** NR *Mortality (incidence rate)* Unvaccinated previously infected: ▪ Age 65+: 0.5 per 100,000 person-days ▪ Age <65: 0 per 100,000 person-days Pfizer vaccinated: ▪ Age 65+: 0.2 per 100,000 person-days ▪ Age <65: 0.09 per 100,000 person-days Moderna vaccinated: ▪ Age 65+: 0.1 per 100,000 person-days ▪ Age <65: 0.08 per 100,000 person-days **Variants of Concern** Delta predominant period.	Pfizer vaccinated: • 1.3 per 100,000 person-days ▪ Age 65+: 1.5 per 100,000 person-days ▪ Age <65: 1.2 per 100,000 person-days Moderna vaccinated: • 0.9 per 100,000 person-days ▪ Age 65+: 1.2 per 100,000 person-days ▪ Age <65: 0.7 per 100,000 person-days **Adjustments:** NR **Subgroups** Vaccine and age group as above and by table below. **Efficacy/effectiveness over time.** NR

			Subgroups: Vaccine and age group as above and by table below. **Efficacy/effectiveness over time.** NR	
	Pfizer:		**Hospitalisation (HR*€)** Age 65+: 0.82 (95% CI: 0.36-1.88) Age <65: 2.33 (95% CI: 0.92-5.93) **Death (HR*)** N/A	**Any infection (HR*€)** Age 65+: 0.32 (95% CI: 0.14,0.70) Age <65: 0.64 (95% CI: 0.24, 1.69)
	Moderna:		**Hospitalisation (HR*€)** Age 65+: 0.76 (95% CI: 0.31-1.83) Age <65: 1.46 (95% CI: 0.55-3.88) **Death (HR*€)** Age 65+: 0.70 (95% CI: 0.04-11.79) Age <65: N/A	**Any infection (HR*€)** Age 65+: 0.34 (95% CI: 0.14,0.78) Age <65: 0.35 (95% CI: 0.11, 1.13)

*** Reference Group are those previously infected**

€ Multivariable cox model – variables include in model not reported.

$ This paper only describes those who were not vaccinated after their infection with SARS-CoV-2

CCI, Charlson Comorbidity Index

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Kojima (2021) [76] **Title:** Incidence of Severe Acute Respiratory Syndrome Coronavirus-2 infection among previously infected or vaccinated employees **DOI:** https://doi.org/10.1101/2021.07.03.21259976 **NCT:** NA **Study Design***:* Retrospective cohort study **Country**: *US* **Setting***:* SARS-CoV-2 testing company (workplace) **Time Period***:* December 2020 – July 2021 **Variants of Concern:** There was at least three SARS-CoV-2 variants	**Comparator/Control:** ▪ (Group 1) SARS-CoV-2 naïve and unvaccinated# ▪ (Group 2) previous SARS-CoV-2 infection, unvaccinated~ **Intervention/Exposure:** ▪ (Group 3) fully vaccinated (either the BNT162b2 (Pfizer/BioNTech) or mRNA-1273 vaccines (Moderna)) & **Time since final vaccination:** Median follow up: NR Maximum follow up: Group 1 and 2: 31.57 weeks Group 3: 59.85 weeks	**Description:** In March 2020, Curative, a SARS-CoV-2 testing company, began routinely screening its workforce with an Food and Drug Administration-authorized SARS-CoV-2 polymerase chain reaction (PCR)-based test. The workforce was screened daily. A standardized employee testing database was implemented on 8 May 2020. On December 15, 2020, vaccination with either the BNT162b2 or mRNA-1273 vaccines became available. Routine screening has continued through July 2021. Individuals with fewer than 14 days of follow up were excluded **N:** ▪ (1) SARS-CoV-2 naïve and unvaccinated# (n=4,313) ▪ (2) previous SARS-CoV-2 infection, unvaccinated~ (n=254) ▪ (3) fully vaccinated (either the BNT162b2 or mRNA-1273 vaccines) & (n=739) **Age:** Median age 29 years (IQR, 23.6-39.9 years); **Male** = NR **Co-morbidities:** NR	**Severe Disease:** NR **Adjustments:** NA **Mortality** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time**: NR	**Confirmed RT-PCR or SARS-CoV-2 infection*** *Any Infection* Group 1 (SARS-CoV-2 naïve and unvaccinated) had an incidence of 25.9 per 100 person years (95% CI: 22.8 to 29.3). A total of 254 infections occurred among 4,313 individuals (5.9%). Group 2 (previous SARS-CoV-2 infection and unvaccinated) had an incidence of 0 per 100 person-years (95% CI: 0 to 5.0). No reinfections occurred (0%). Group 3 (fully vaccinated) had an incidence of 1.6 per 100 person-years (95% CI: 0.04 to 4.2). A total of 4 breakthrough infections occurred among 739 individuals. *Relative risk of reinfection*

(B.1.1.7 [U.K.], B.1.351 [South Africa], 122 and B.1.1.248 [Brazil]) in circulation at the time of this study **Publication status**: Preprint				The IRR of those vaccinated compared to SARS-CoV-2 naïve (unvaccinated) was 0.06 (95% CI: 0.02 to 0.16). The IRR of those vaccinated compared to prior SARS-CoV-2 (unvaccinated) was 0 (95% CI: 0 to 4.98) **Adjustments:** NR **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time**: NR

*SARS-CoV-2 infection was defined as two positive SARS-CoV-2 PCR tests in a 30-day period

#any employee without previous infection that tested from 8 May up to 15 December 2020 (when vaccination became available)

~any employee with documented previous SARS-CoV-2 infection (at least 2 positive PCR tests) between 8 May to 15 December 2020.

& employee with documented completion of vaccination through 1 July 2021

Healthcare and frontline workers

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Alali (2021)[44] **Title:** Effectiveness of BNT162b2 and ChAdOx1 vaccines against symptomatic COVID-19 among Healthcare Workers in Kuwait: A retrospective cohort study **NCT**: N/A **DOI:** https://doi.org/10.1101/2021.07.25.21261083 **Country**: Kuwait **Setting***:* Single 900-bed Public Hospital **Time Period***:* 24 December 2020 to 15 June 2021 **Study Design***:* Retrospective Cohort Study (with crossover) **Publication status**: Preprint	**Exposure**: BNT162b2 (Pfizer)~ **Control:** No vaccination **Time since final vaccination:** Mean 15 weeks	**Description:** 3,246 HCWs [%] HCWs with PCR confirmed infection before the start of the study were excluded. **N:** 3,246 28.3% were fully vaccinated by the end of the study. 17.9% remained unvaccinated by the end of the study ≥ **Age:** Median 38 years (IQR = 33-44) **Male**: 36.6% **Special populations**: HCWs: 100%	**Severe Disease:** NR **Mortality:** NR **Adjustments**: N/A **Subgroups:** N/A **Variants:** NR **Effectiveness over Time:** N/A	**RT-PCR or antigen Confirmed SARS-CoV-2 infection** *Symptomatic* ≥ 7 days after BNT162b2 second dose [#] VE 94.5% (95% CI 89.4% to 97.2%). **Adjustments** Age group, Sex, Nationality* **Subgroups:** NR **Variants:** NR **Effectiveness over Time**: NR

% Population contains a group receiving one dose of ChAdOx1 but they are not censored at time of vaccination.

*Staff group and Occupation Setting were considered but were not included. All variables including sociodemographic variables were not statistically significant in the adjusted analysis.

Reported as ≥ 7 days after second dose in Table of Results but ≥14 days in text.

~ 50.4% of patients received one dose of ChAdOx1 (AstraZeneca) but as they are only partially vaccinated VE is not presented for this cohort.

Key: CI – Confidence Interval; IQR – Interquartile Range; 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): Bianchi (2021)[45] **Title:** BNT162B2 mRNA Covid-19 Vaccine Effectiveness in the Prevention of SARS-CoV-2 Infection and Symptomatic Disease in the Medium - to Long-Term: A Retrospective Cohort Study **DOI:** https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3894959 **NCT:** N/A	**Exposure**: BNT162b2 (Pfizer) **Comparator/Control:** No vaccine **Time since final vaccination dose:** Median 19.86 weeks	**Description:** HCWs in University Hospital who completed both doses matched with HCWs who refused vaccination. HCWs with a documented history of SARS-CoV-2 infection before enrolment were excluded from participation in the study **N:** 6,136 HCWs Vaccinated group, 5,351 (87.2%) Unvaccinated group, 787 (12.8%) **Age:** *mRNA-1273 (Moderna)* mean 44·9 (SD:12.7),range (22–70) *Unvaccinated* mean 43·1(SD:12.8),range (21–70)	**Severe Disease:** Nine hospitalizations were reported, including 8 (1·0%) HCWs in the unvaccinated group and 1 (0·02%) HCW in the vaccinated group (p<0·0001). **Adjustments:** NA **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Confirmed RT-PCR infection** **days after second/final dose** **Efficacy/effectiveness over time.** *Documented infection* 14–41 days VE: 94.8% (95% CI 87·0 to 97·8%) 42–69 days VE: 83·0% (95% CI 65·0 to 92·0%), >69 days

Study Design*:* Matched cohort study[#] **Country**: Italy **Setting***:* Bari Policlinico General University-Hospital **Time Period***:* December 27, 2020 and March 31, 2021 **Variants of Concern:** NR **Publication status**: Preprint		**Male** = *mRNA-1273 (Moderna)* 40.5% *Unvaccinated* 37.7% **Co-morbidities:** NR		VE: 81·0% (95% CI 42·0 to 94·0%) *Symptomatic disease** 14–41 days VE: 97·2% (95% CI 90·3 to 99·2%), 42–69 days VE: 85·0% (63·0 to 94·2%) >69 days VE: 88·0% (42·0 to 97·6%) **Adjustments:** NR **Variants of Concern:** NR **Subgroups:** NR
***** COVID-19, defined as a SARS-COV-2 infection with the development of typical symptoms (fever, cough, etc.). **#**The study states that the two cohorts were matched, but no matching factors are described.				

Key: CI – Confidence Interval; HCW – Healthcare worker; HCWs – Healthcare workers; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RCT – Randomised Controlled Trial; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy.

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Ghosh (2021)[46] **Title:** COVISHIELD (AZD1222) Vaccine effectiveness among healthcare and frontline	**Exposure**: ChAdOx1 (Covishield®) **Control:** No vaccination	**Description:** Health care workers and frontline workers of the Indian Armed forces (regardless of previous serological or previous COVID positive status) **N:** 1.6 million.	**Severe Disease:** NR **Mortality:** *All cause*	**RT-PCR or antigen Confirmed SARS-CoV-2 infection >14 days after second dose.** *Any*

Workers of Indian Armed Forces: Interim results of VIN-WIN cohort study **NCT**: N/A **DOI:** https://doi.org/10.1016/j.mjafi.2021.06.032 **Country**: India **Setting***:* Indian Armed forces **Time Period***:* 16 January 2021 to 30 May 2021 (Interim Analysis) **Study Design***:* Cohort Study with Cross over **Variants of Concern:** NR **Publication status**: Peer-reviewed.	**Time since final vaccination:** Mean 8.38 weeks	At the end of the study time period 30 May 21, 95.4% and 82.2% were partially and fully vaccinated. **Age:** Mean 27.6 years (SD 6.16) **Male**:99% **Comorbidities:** "Minimal" **Special populations**: NR	VE: 98.53% (95% CI: 0.00 to 99.99) **Adjustments**: None **Subgroups:** NR **Effectiveness over Time:** NR	**Method#1** VE **:** 94.93% (95% CI 92.49 to 96.58) **Method#2** (Time dependent Cox analysis) VE : 91.81% (95% CI 88.79 to 94.02) **Adjustments** Changing risk of infection over time. **Variants:** NR **Effectiveness over Time**: NR

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

…

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Giansante (2021) [71]	**Exposure**: mRNA vaccine **Control:** unvaccinated	**Description:** All the staff of the Bologna health trust (not only health care workers)	**Severe Disease:** **≥7 days after second/final dose**	**Confirmed RT-PCR SARS-CoV-2 infection**

Title: COVID-19 vaccine effectiveness among the staff of the Bologna Health Trust, Italy, December 2020 – April 2021 **DOI:** 10.23750/abm.v92i4.11896 **NCT:** N/A **Study Design***:* Retrospective cohort study **Country**: Italy **Setting***:* staff at a health trust in Bologna, Italy **Time Period***:* Surveillance data from 27 Dec 2020 to 30 April 2021 **Variants of Concern:** In March covid-19 incidence "reached 630 cases per 100.000 inhabitants per week and a very high prevalence of the UK (93.3%) and the Brazilian (6.8%) variants" **Publication status**: peer-reviewed	**Time since final vaccination dose:** Mean 11.67 weeks (sd NR)	Excluded: Subjects with a previously documented SARS-CoV-2 infection and subjects vaccinated with non-mRNA vaccines. Individuals with zero follow-up days after vaccination **N:** 9839 subjects **Age:** 18-34 1859 (18.9%) 35-44 1839 (18.7%) 45-54 3075 (31.3%) 55+ 3066 (31.2%) **Male** = 30% **Co-morbidities: NR**	*Hospitalisation* 15 cases in unvaccinated, 0 cases in fully vaccinated. Note: "multivariate analyses was not run because of the few numbers" *ICU admissions* 4 cases in unvaccinated and 0 in vaccinated **Adjustments:** sex, age group, role, working context and starting week of exposure **Mortality:** NR **Variants of Concern:** NR **Subgroups**:*In healthcare workers only:* *Hospitalisation* *8* cases in unvaccinated, 0 cases in fully vaccinated. *ICU admissions* 2 cases in unvaccinated and 0 in vaccinated **Efficacy/effectiveness over time:** NR	**≥7 days after second/final dose** *Any* VE: 84.8%(95%CI: 73.2-91.4) *Symptomatic* VE: 87.1% (95%CI: 69.3-94.6 **Adjustments:** sex, age group, role, working context and starting week of exposure **Variants of Concern:** NR **Subgroups:** It is stated that: Similar VE estimates were found when considering only health care workers. In Health care workers: VE any infection 84.4 (69.7-92.0) VE symptomatic infection 86.5 (62.9-95.1) **Efficacy/effectiveness over time**: NR

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Pilishvili (2021) [72] **Title:** Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel **DOI:** 10.1056/NEJMoa2106599 **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	**Intervention/Exposure**: ▪ BNT162b2 (Pfizer/BioNTech) (Cases: 78%, Controls 79%) ▪ mRNA-1273 (Moderna) (Cases: 21%, Controls 20%) **Comparator/Control:** Unvaccinated individuals.^ **Time since final vaccination dose:** Median – 5.98 weeks (range 1 to 23.5 weeks	**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:** 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%	**Severe Disease:** **≥7 days after second/final dose** *Hospitalisation in cases by vaccination status* [&] Completely vaccinated – 4 (2%) Partially vaccinated 1 (1%) 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	**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 VE: 88.8% (95%CI 84.6% to 91.8%) mRNA-1273 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**

Publication status: Peer reviewed.		*Controls* Asthma – 18% Immunocompromising condition [%] – 4% COPD – 1%		≥1Underlying condition or risk factor[#] VE: 90.3% (95%CI 86.4% to 93.0%) ≥2Underlying conditions or risk factors[#] VE: 88.5% (95%CI 83.2% to 92.2%) ≥3Underlying conditions or risk factors[#] VE: 89.4% (95%CI 83.1% to 93.4%) No underlying risk factor[#] VE: 91.1% (95%CI 85.5% to 94.6%) Asthma VE: 90.5% (95%CI 81.9% to 95.0%) Any immunocompromising condition, (assessed for partial and complete vaccination)[€] VE: 39.1% (95%CI −45.0% to 74.4%) <50 years

				VE: 90.3% (95%CI 86.5% to 93.0%) <u>≥50 yr</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 Health Care 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

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Thompson (a) (2021)[47] **Title:** Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines	**Intervention/Exposure*** BNT162b2 vaccine (Pfizer-BioNTech) : 67% mRNA-1273 vaccine (Moderna): 33%	**Description:** Healthcare workers, first responders, frontline and essential workers. Swabbed weekly regardless of symptoms. previously seropositive status is considered a confounder	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* 3 unvaccinated participants were hospitalized (no further analysis reported)	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second dose** *Any*

DOI: 10.1056/NEJMoa2107058 **NCT:** N/A **Study Design***:* prospective cohort study (crossover) **Country**: USA (Arizona, Florida, Minnesota, Oregon, Texas, and Utah) **Setting***:* HEROES-RECOVER network: Healthcare, Emergency Response, and Other Essential Workers **Time Period***:* December 14, 2020, to April 10, 2021 **Variants of Concern:** One of 81 sequenced cases was Alpha (B.1.1.7) **Publication status**: Peer-reviewed	**Comparator/Control:** unvaccinated **Time since final vaccination dose:** Fully Vaccinated: Median 11.86 weeks Unvaccinated: median 2.71 weeks	**N:** Total Eligible and Consented Participants: 5021 *Vaccine Effectiveness Analytic* Population: 3975 *unvaccinated* 3964 contributed days : 127,971 *Fully vaccinated* 2510 contributed 161,613 days **Age:** 18-49 year: 72% 50+ years: 28% **Male** = 38% **Co-morbidities:** ≥1 chronic conditions: 31%	*Hospitalisation* NR *ICU admissions* NR **Adjustments:**NR **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time.** NR	VE 91% (95% CI 76 to 97) **Adjustments:** Adjusted vaccine effectiveness was inversely weighted for the propensity to be vaccinated (baseline sociodemographic and health characteristics and the most recent reports of potential virus exposure and PPE use), with doubly robust adjustment for local viral circulation, site, and occupation. **Variants of Concern:** NR **Subgroups** <50 years 90% (95%CI 69–97) ≥50 years 94% (95%CI 51–99) **Efficacy/effectiveness over time.** NR
	Exposure BNT162b2 vaccine (Pfizer-BioNTech) **Control** Unvaccinated			**≥14 days after second dose** *Any* VE 93% (95% CI 78 to 98)

	Exposure mRNA-1273 vaccine (Moderna) **Control** Unvaccinated			**≥14 days after second dose** *Any* VE 82% (95%CI 20 to 96)
Author (Year): Fowlkes (2021)[105] **Title:** Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021 **DOI:** http://dx.doi.org/10.15585/mmwr.mm7034e4 **NCT:** N/A **Study Design**: prospective cohort study **Country**: USA (Arizona, Florida, Minnesota, Oregon, Texas, and Utah) **Setting**: HEROES-RECOVER network:	**HEROES RECOVER Study – Fowlkes et al. is an update of the original analysis of Thompson.**			
	Intervention/Exposure: ▪ 65% BNT162b2 vaccine (Pfizer-BioNTech) ▪ 33% mRNA-1273 vaccine (Moderna) ▪ 2% Janssen (Johnson and Johnson **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Median 27 weeks (fully vaccinated) IQR (18.4 to 29.9 weeks)	**Description:** Healthcare workers, first responders, frontline and essential workers. Swabbed weekly regardless of symptoms. No previous laboratory -documented SARS-CoV-2 infection **N:** Unvaccinated 4135 (181,357 person days) Vaccinated 2976 (455,175 person days) **Age:** NR **Male** = NR **Co-morbidities:** NR	**Severe Disease:** **≥14 days after second/final dose:** NR **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time :** NR	**Confirmed RT-PCR SARS-CoV-2 infection** *Any* *Vaccine Effectiveness* Overall: 80% (95% CI 69 to 98) *Symptomatic* 89.7% of infections in unvaccinated were symptomatic v. 80.6% of infections in vaccinated **Adjustments:** Adjusted for occupation, site, and local viral circulation, and weighted for inverse probability of vaccination using socio-demographic characteristics, health information, frequency of close social contact, and mask use. **Variants of Concern:** Pre-Delta variant predominance*

Healthcare, emergency response, and other essential workers (This report updates vaccine effectiveness estimates) **Time Period***:* 14 December 2020 -14 August 2021 **Variants of Concern:** Before and during delta dominance. **Publication status**: Published report (CDC)				VE: 91% (95% CI 81 to 96) Delta Variant Dominant* VE: 66% (95% CI 26 to 84) **Subgroups:** NR **Effectiveness over time:** 14–119 days after full vaccination: 85% (95% CI 68 to 93) 120–149 days after full vaccination: 81% (95% CI 34 to 95) 150+ days after full vaccination: 73% (95% CI 49 to 86) "The VE 95% CI were overlapping, indicating the difference was not statistically significant"

Key: CDC – Centres for Disease Control and Prevention; CI – Confidence Interval; 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): Issac (2021)[49]	**Exposure:** ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca)	**Description** HCWs in secondary care hospital. No information is given regarding previous infection.	**Severe Disease:** **≥14 days after second:** NR **Adjustments:** N/A	**Confirmed RT-PCR or Antigen SARS-CoV-2**

Title: SARS-CoV-2 Breakthrough Infections among the Healthcare Workers Post-Vaccination with ChAdOx1 nCoV-19 Vaccine in the South Indian State of Kerala **DOI:** https://www.medrxiv.org/content/10.1101/2021.08.07.21261587v1.full.pdf **NCT:** N/A **Study Design***:* Prospective cohort study **Country**: India **Setting***:* Secondary care hospital in South Indian state of Kerala **Time Period***:* April 01 to 15 July **Variants of Concern:** NR **Publication status**: Preprint	**Comparator/Control:** No vaccine **Time since final vaccination dose:** At least 15 weeks	**N:** 324 healthcare workers *Vaccinated* 243 *Unvaccinated* 80 **Age:** *Vaccinated* mean 35.28 (SD ± 10.02) *Unvaccinated* mean 30.26 (SD ± 6.26) **Male** = *Vaccinated* 20.16% Unvaccinated 3.75% **Co-morbidities:** NR	**Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**infection ≥14 days after second/final dose** *Any* VE: 84.95% (95% CI NR p<0.05). **Adjustments:** N/A. **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time:** NR

Key: CI – Confidence Interval; HCWs – Healthcare Workers; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction, SD – Standard Deviation; VE – Vaccine Efficacy.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Katz (2021)[73] **Title:** Covid-19 Vaccine Effectiveness in Healthcare Personnel in six Israeli Hospitals (CoVEHPI) **DOI:** doi.org/10.1101/2021.08.30.21262465; **NCT:** N/A **Study Design***:* Prospective Cohort Study **Country**: Israel **Setting***:* Six hospitals **Time Period***:* 27 December 2020 to 15 February 2021 **Variants of Concern:** Alpha variant dominant during study period.	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** **Vaccinated:** Median – 11.11 weeks (10.54 to 10.82 weeks)	**Description:** HCWs from six CHS hospitals who were insured by the CHS, eligible to receive the COVID-19 vaccine. HCWs who had received their first dose of the vaccine more than 21 days prior to the enrolment date were excluded. Participants with non-negative enrollment serology or non-negative 30-day serology results those who were vaccinated after enrollment, and those who received only one dose of vaccine, were excluded from the analysis. We also excluded fully vaccinated participants who had PCR-confirmed SARS-CoV-2 infection prior to seven days after their second vaccine dose. **N:** Total – 1,250 Vaccinated – 998 (79.8%) Unvaccinated – 252 (20.2%) **Age:** Overall, Median – 45 (IQR - 36 to 55) **Male (overall)** = 20.1 % Clinical worker with direct patient contact – Yes – 58% No – 39.4% **Co-morbidities (overall):** COPD – 0.5% Asthma – 6.2% Other Respiratory Disease – 0.1%	**Severe Disease:** **≥7 days after second/final dose[Delete** *Severe Disease* NR *Hospitalisation* none of the symptomatic participants required hospitalization *ICU admissions* NR **Adjustments:** NA **Mortality:** NR **Variants of Concern** NR **Subgroups** NR **Efficacy/effectiveness over time.** NR	**Confirmed RT-PCR SARS-CoV-2 infection** %, ^ **≥7 days after second/final dose**] *Any* VE= 94.5% (95% CI 82.6 – 98.2%) *Asymptomatic* * Among the 13 PCR-positive events, 11 were symptomatic and 2 were asymptomatic. VE against asymptomatic infection could not be estimated due to the low number of events during the follow-up period. *Symptomatic* VE = 97.0% (95% CI: 72.0% to 99.7%). Two-dose VE against any infection (14 days after second dose) VE: 94.5% (95%CI 82.5%-98.2%) **Adjustments:**

Publication status: Pre-print		Immunosuppression – 3%		Age, sex, socioeconomic status, population sector (Arab/Jewish) and occupation (physician/nurse or administrative/support staff). Hospital of employment was included as a random effect. In all analyses, two methods were used to account for fluctuations in the weekly Covid-19 infection rates in Israel. First, calendar time was used as the time scale of the Cox model. Second, as a sensitivity analysis, time from start of follow-up was used as the time scale of the Cox model, and a time-varying covariate with the weekly incidence of new COVID-19 cases in Israel was added to the model. **Variants of Concern:** Three samples from infections identified in the primary analysis, and two samples from infections identified among vaccinated participants in the period between the first and the second dose, underwent genetic sequencing and were determined to be alpha variant (B.1.1.7). **Subgroups**

				NR **Efficacy/effectiveness over time.** NR
% Covid-19): fever; a new or worsening cough; new or worsening shortness of breath; chills; new or worsening muscle aches; new loss of taste; new loss of smell; sore throat; vomiting; diarrhea; nausea; fatigue; headache; nasal congestion or runny nose; *. asymptomatic infection as one in which the participant was PCR-positive and denied symptoms in the seven days before and five days after specimen collection change in mental state. ^ there are results for a secondary analysis which is regardless of serostatus at baseline				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Yassi (2021)[50] **Title:** Infection control, occupational and public health measures including mRNA-based vaccination against SARS-CoV-2 infections to protect healthcare workers from variants of concern: A 14-month observational study using surveillance data **DOI:**	**Intervention/Exposure**: Pfizer-BioNTech (BNT162b2) (93.3%) OR Moderna (6.6%) (mRNA-1273) **Comparator:** Unvaccinated cohort **Time since final vaccination dose:** Median 54 days (IQR 44–62) Mean 53.1 days (95% CI 43.2–62.9) are reported	**Description:** All active healthcare employees who worked for Healthcare provider. HCWs who tested positive prior to December 15, 2020 were excluded from the analysis **N:** 25,116 HCWs, of which 7,328 were fully vaccinated by the end of the study period. **Age:** Range (20–69)	**Severe Disease:** NR **Mortality**: NR	**Confirmed RT-PCR SARS-CoV-2 infection** **≥7 days after second dose** VE: 79.2% (95% CI: 64.6 to 87.8%) **Adjustments:** Cox regression modelling

10.1371/journal.pone.0254920 **NCT:** N/A **Study Design***:* Cohort study with crossover. **Country**: Vancouver, Canada **Setting***:* Healthcare provider. **Time Period***:* December 15, 2020 to May 13, 2021 **Variants of Concern:** During this period, the dominant variants changed from <1% VOC to >92%, with the Alpha and Gamma variants dominating; Vancouver was documented at that time as having the highest rate of Gamma variant outside of Brazil. **Publication status**: Peer-reviewed		**Male** = NR **Co-morbidities:** NR		adjusted for age and calendar-time **Variants of Concern:** NR **Subgroups:** NR **Efficacy/effectiveness over time:** Graph presented of VE over time. No decline observed but confidence intervals are very wide.

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

HCWs/LTC/Homecare

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Emborg (2021)[51] **Title:** Vaccine effectiveness of the BNT162b2 mRNA COVID-19 vaccine against RT-PCR confirmed SARS-CoV-2 infections, hospitalisations and mortality in prioritised risk groups **DOI:** https://www.medrxiv.org/content/10.1101/2021.05.27.21257583v1 **NCT:** N/A **Study Design**: Retrospective cohort study **Country**: Denmark **Setting***:* National Registry Study (LTCF and HCWs, people require **Time Period***:* 27 December 2020 to 11 April 2021	**Intervention/Exposure**: BNT162b2 mRNA (Pfizer/BioNTech) **Comparator/Control:** No vaccination **Time since final vaccination dose:** LTCF Resident Median 10.23 (IQR 10;11) At least 65 years old at home requiring practical help and personal care (65PHC) Median 8.57 (IQR 4.29;9.29) HCWs Median 9.57 (IQR 8.28;10.29)	**Description*:** Individuals registered with Danish Civil registration system who belong to one of the follow three groups: LTC resident 65 years old but requiring practical help and personal care (65PHC) HCWs Individuals with an RT-PCR confirmed SARS-CoV-2 infection before December 27, 2020 were excluded. **N:** Total number of individuals included in the analysis (Total number of vaccinated individuals included in the analysis) LTC residents 46,101 (40,061) 65PHC 61,805 (45,924) HCWs 425,799 (112,824) **Median age (IQR):** LTC residents	**Severe Disease:** **≥7 days after second/final dose[Delete** *VE against hospital admission related to COVID-19#* LTC residents VE: 75% (95% CI: 46% to 89%) 65PHC VE: 87% (95% CI: 70% to 95%) HCWs There was no events of COVID-19 related admissions among vaccinated HCW in 16,339 person years. The incidence rate of COVID-19 related admissions among unvaccinated HCW was 0.002 for 78,907 person years. **Mortality** *VE against all-cause death* LTC residents VE: 26% (95% CI: 17% to 34%) 65PHC VE: 62% (95% CI: 57% to 66%) HCWs	**Confirmed RT-PCR SARS-CoV-2 infection** **≥7 days after second dose** *confirmed SARS-CoV-2 infection* LTC residents VE: 53% (95% CI: 29% to 69%) 65PHC 86% (95% CI: 78% to 91%) HCWs 80% (95% CI: 77% to 83%) **Adjustments:** Adjusted for calendar time, age, sex, co-morbidities and hospital admission

Variants of Concern: NR **Publication status**: Preprint		84 (77; 90) 65PHC 83 (76; 89) HCWs 49 (37; 58) **Male** (%) LTC residents (37.4%) 65PHC (34.2%) HCWs (20%) **Co-morbidities:** Comorbidity (yes/no) in the previous five years (from 2016 to 2020) was defined by diagnose codes registered for all hospital admissions. Comorbidities were not reported in this study.	VE: 23% (95% CI: -54% to 62%) *VE against death related to COVID-19~* LTC residents VE: 89% (95% CI: 81 – 93%) 65PHC VE: 97% (95% CI: 88% - 99) HCWs There were no cases of COVID-19 related death among vaccinated HCWs. The incidence rate of COVID-19 related death among unvaccinated HCWs was 0.004 for 78,972 person years. **Adjustments:** VE against hospital admission related to COVID-19 was adjusted for calendar time, age, sex and co-morbidity. VE against all-cause death and VE against death related to COVID-19 was adjusted for calendar time, age, sex, co-morbidities and hospital admission **Variants of Concern:** NR **Subgroups**: results presented above **Efficacy/effectiveness over time**. NR	**Variants of Concern:** NR **Subgroups** Results presented above **Efficacy/effectiveness over time**. NR
* A subgroup of participants who (1) were 85 years and older and (2) Individuals with high risk of severe COVID-19 disease were also included in the study. However the follow up of these groups did not meet our inclusion criteria so the information relevant to these groups were not extracted.				

~ COVID-19 related death defined as death within 30 days after confirmed SARS-CoV-2 infection

COVID-19 related admission to hospital defined as an admission within 14 days after a confirmed SARS-CoV-2 infection

Key: CI – Confidence Interval; HCWs – Healthcare Workers; IQR – Interquartile Range; LTCF – Long term care facility; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction, VE – Vaccine Efficacy; 65PHC - 65 years old but requiring practical help and personal care.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Lefèvre (2021)[52] **Title:** Impact of B.1.351 (beta) SARS-CoV-2 variant on BNT162b2 mRNA vaccine effectiveness in long-term care facilities of eastern France: a retrospective cohort study **DOI:**https://doi.org/10.1101/2021.07.28.21261285 **NCT:** N/A **Study Design***:* Retrospective cohort study **Country**: France **Setting***:* long-term care facility (LCTF)	**Exposure**: BNT162b2 mRNA vaccine (Pfizer/BioNTech) **Comparator/Control:** No vaccine **Time since final vaccination dose:** mean 8.68 weeks	**Description:** Residents in LTCF in eastern France in which any outbreak that implicated beta had been documented during the study period. Patients with prior infection were included in the analysis but were adjusted for when calculating VE estimates. The proportion with past infection was not different between those who had received at least one vaccine dose and those who had not received any vaccine dose (5.3% and 5.0%, respectively). **N** = 378, Fully vaccinated = 279 (73.8%) Unvaccinated= 40 (10.6%) **Age:** Median (IQR) 89 (83-92) years **Male:** 24%	**Severe Disease:** **≥7 days after second/final dose** *Severe Disease** VE 86% (95% CI: 67 to 94) **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Confirmed RT-PCR** **≥7 days after second/final dose** *Any infection* *VE 49*% (95% CI: 14% to 69%) **Adjustments:** centre, Age, sex, calendar time, history of Past SARS-CoV-2 infection. **Variants of Concern:** Beta variant was dominant. **Subgroups:** No infections were observed in residents who previously tested positive for SARS-CoV-2 infection.

Time Period*:* 29 March and 19 May 2021 **Variants of Concern:** Nationwide surveillance of variants indicated that the P.1 (Gamma) lineage was not circulating in eastern France at the time of the study, all targets identifying B.1.351/P.1 lineages (K417N, E484K) were considered to be B.1.351 (Beta) **Publication status**: Preprint				**Efficacy/ effectiveness over time.** NR
**categorized as severe if the resident had symptoms that required oxygen support and/or the resident was transferred to a hospital, or the resident died*				

Key: CI – Confidence Interval; IQR – Interquartile Range; LTCF – Long term care facility; 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): Muhsen (2021)[53] **Title:** Effectiveness of BNT162b2 mRNA COVID-19 Vaccine Against Acquisitions of SARS-CoV-2 Among Health Care Workers in Long-Term Care Facilities: A Prospective Cohort Study	**Intervention/Exposure**: BNT162b2 vaccine (Pfizer/BioNtech) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Median	**Description:** HCWs working at LTC facilities *Inclusion criteria* 1. HCWs adhering to routine testing. 2. Working in LCT facilities that vaccinated ≥75% of employees over three consecutive days 3. Being RT-PCR negative for SARS-CoV-2 infection by the date of immunization with dose 2.	**Severe Disease:** **≥14 days after second/final dose** NR **Mortality:** NR	**Confirmed RT-PCR SARS-CoV-2 infection** **≥14 days after second/final dose** *Any*

DOI: http://dx.doi.org/10.2139/ssrn.3885633 **NCT:** N/A **Study Design***:* Prospective Cohort Study (No Crossover) **Country**: Israel **Setting***:* healthcare workers (HCWs) of LTC facilities **Time Period***:* December 2020 – 11 April 2021 **Variants of Concern:** Alpha Dominant **Publication status**: Preprint	fully vaccinated: 11.4 weeks Unvaccinated: 6.1 weeks	*Exclusion* 1. Those who had a RT-PCR-confirmed SARS-CoV-2 infection before immunization, or between immunization with the second dose until day seven or 14 days post immunization. **N:** Fully vaccinated: 6,960 Unvaccinated: 2,202 **Age:** 46.2 years (SD = 11.8) **Male** = 20.5% **Co-morbidities:** NR		VE: 89% (95% CI 83% to 93%) **Adjustments:** Age (years), gender, population group (general Jewish, ultraorthodox Jewish or Arab), residential area incidence rates of RT-PCR-confirmed infection and residential socioeconomic status. **Variants of Concern:** NR **Subgroups:** NR, **Efficacy/effectiveness over time**. NR

Key: CI – Confidence Interval; HCWs – Healthcare Workers; LTC – Long term care; N/A – Not Applicable; NCT – National Clinical Trial; NR – Not Reported; RT-PCR – Reverse Transcription Polymerase Chain Reaction, SD – Standard Deviation; VE – Vaccine Efficacy

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Subbarao (2021)[74] **Title:** Vaccine effectiveness against infection and death	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) ChAdOx-1 (AstraZeneca)	**Description:** The study population were residents greater than 65 years in LTCFs in England with at least two recorded tests for SARS CoV-2 and at least one test during the study period.	**Severe Disease:** **≥15 days after second/final dose** (results are presented from 0 days after final dose, but not shown here) *Severe Disease* NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection**

<table>
<tr>
<td>due to SARS-CoV-2, following one and two
doses of the BNT162b2 and ChAdOx-1 in residents of long-term care facilities in England, using a
time-varying proportional hazards model

DOI:
http://dx.doi.org/10.2139/ssrn.3922678
NCT: N/A

Study Design: observational population study (cohort study with crossover)

Country: England

Setting: Long term care facilities (LTCF)

Time Period: This observational study uses testing, immunisation and mortality data from 8 December 2020 to 01July 2021

Variants of Concern:
The start of the study period coincided with the emergence of the Alpha (B.1.17) variant, which remained dominant until mid-May 2021. However, by the end of the study period in July 2021, the Delta variant</td>
<td>Comparator/Control:
Unvaccinated and those with only one dose of vaccine
Time since final vaccination dose:
Mean 11.0 weeks, no measure of spread</td>
<td>Excluded:
- staff at LTCF
- Individuals who were
resident in more than one LTCF during the study period,
- Residents with a positive result in the 90 days prior to 8 December 2020 were excluded.

N: 219,733
Note: Among these, 19,056 (8.7%) remained unvaccinated, 22,074 (10%) received only one dose of vaccine and the rest
178,603 (81.2%) received two doses of vaccine

Tests: 41828 (19.0%) had a laboratory confirmed SARS-CoV-2

Age:
<table>
<tr><td>Age-group</td><td>N (%)</td></tr>
<tr><td>65-69</td><td>8290 (3.8)</td></tr>
<tr><td>70-74</td><td>16762 (7.6)</td></tr>
<tr><td>75-79</td><td>24976 (11.4)</td></tr>
<tr><td>80-84</td><td>38357 (17.5)</td></tr>
<tr><td>85-89</td><td>52449 (23.9)</td></tr>
<tr><td>90+</td><td>78899 (35.9)</td></tr>
</table>
Male = 29.5%

Co-morbidities: None (“were unable to adjust for comorbidities at the
individual level as data were not available”)</td>
<td>Hospitalisation NR
ICU admissions NR

Mortality
Death within 28 days of positive SARS-CoV-2 test result

Both vaccines combined (results by vaccine presented below)

VE
<u>1-14 days</u>
87% (95%CI 68-95%)
<u>15+ days</u>
78% (95%CI 36 – 92)

Adjustments

Sex, age group, IMD (index of multiple deprivation) and case rate in local authority

Variants of Concern

NR

Subgroups: NR

Efficacy/effectiveness over time. See main results</td>
<td>≥15 days after second/final dose
(results are presented from 0 days after final dose, but not shown here)

<u>Any infection</u>

Both vaccines combined (results by vaccine presented below)

VE
<u>15-28 days</u>
70% (95% CI 56 – 80)
<u>29-60 days</u>
73% (95% CI 62-80%)
<u>61+ days</u>

65% (95% CI 50 – 76)

Adjustments:

Sex, age group (in five-year age bands, starting from 65 years), previous infection, index of multiple deprivation (IMD), and incidence rate at local authority level.

Variants of Concern:

By restricting data to the time when Alpha was the dominant strain, VE against infection was 87% (95%CI 74-93%) and</td>
</tr>
</table>

accounted for ~ 99% of sequenced and 97% genotyped cases **Publication status**: pre-print				82% (95%CI 70-90%) 15-28 days after the second dose ChAdOx-1 and BNT162b2 respectively. There were too few cases among LTCF residents in May-June 2021 to be able to undertake a specific VE analysis against Delta variant. **Subgroups:**NR **Efficacy/effectiveness over time.** See main results
	BNT162b2 (Pfizer/BioNTech)		*Death within 28 days of positive SARS-CoV-2 test result* *VE* 15+ days 72% (95%CI 23 – 90)	*Any infection* VE 15-28 days 71% (95% CI 53 – 82) 29-60 days 78% (95% CI 65 - 86) 61+ days 72% (95% CI 52 – 83)
	ChAdOx-1 (AstraZeneca)		*Death within 28 days of positive SARS-CoV-2 test result* *VE* 15+ days 89% (95%CI 47 - 98)	*Any infection* VE 15-28 days 71% (95% CI 53 – 83) 29-60 days 69% (95% CI 53 - 79) 61+ days 58% (95% CI 35 – 73)

Individuals with co-morbidities and immunocompromised conditions

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Chemaitelly (2021a)[54] **Title:** SARS-CoV-2 vaccine effectiveness in immunosuppressed kidney transplant recipients **NCT**: N/A **DOI:** 10.1101/2021.08.07.21261578 **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	**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) Vaccinated: Median 52 years (IQR 40-61) **Male**: Vaccinated : 63.1% Unvaccinated: 70.4% **Comorbidities:** NR **Special populations**: 100% Kidney transplant recipients.	**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%) ≥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	**Confirmed RT-PCR or SARS-CoV-2 infection** *Any infection symptomatic or asymptomatic* Days after the second dose: ≥14 days 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.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): McKeigue (2021)[82] **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:** [https://doi.org/10.1101/2021.09.13.21262360] **NCT:** N/A **Study Design***:* Case control	**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	**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*:** 226,678 (23,467 fully vaccinated). **Age:** NR **Male/Female:** NR **Co-morbidities##:** Moderate risk condition: 71511	**Severe Disease:** **≥14 days after second dose** *Severe Disease*** No risk condition RR# 0.07 (95% CI 0.05 to 0.10) VE 93% (95 % CI 90% to 95%) Moderate risk condition RR 0.11 (95% CI 0.08 to 0.15) VE= 89% (95% CI 85% to 92%) Condition eligible for shielding RR 0.34 (95% CI 0.24 to 0.48) VE = 66% (95% CI 52% to 76%) *Hospitalisation or mortality**** No risk condition RR# 0.13 (95% CI 0.11 to 0.15) VE = 87% (85 to 89)	**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

Country: Scotland **Setting***:* Community **Time Period***:* 1 December 2020 to 19 August 2021 **Variants of Concern:** Delta. **Publication status**: Preprint	○ Moderate risk condition ○ Eligible for shielding **Control:** For every incident case of COVID-19 in the Scottish population ten 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:** Median = 9.57 weeks. IQR = 6 – 12.71 weeks.Max 26 weeks. (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.)	Solid organ transplant: 412 Specific cancers: 2330 Severe respiratory: 7863 Rare diseases: 777 On immunosuppressants: 1864 Additional conditions: 4109	Moderate risk condition RR 0.15 (95% CI 0.13 to 0.17) Condition eligible for shielding RR 0.33 (95% CI 0.28 to 0.39) VE = 67% (95 percent CI 61% to 72%) **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:	40.6 (95% CI:10.5 to 156.6) 0.39 (95% CI: 0.11 to 1.33)~ VE = 98 (95% CI 29 to 332)	13.2 (95% CI: 6.2 to 27.8) 0.68 (95% CI:0.36 to 1.29) ~ 40.8 (95% CI 21.0 to 79.5)	0.87
	Specific cancers:	12.2 (95% CI:5.8 to 25.5) 0.44 (95% CI: 0.22 to 0.89) ~	3.42 (95% CI:2.32 to 5.06) 0.27 (95% CI:0.18 to 0.40) ~	0.38
	Severe respiratory:	4.66 (95% CI:2.63 to 8.25) 0.20 (95% CI: 0.13 to 0.32) ~	2.82 (95% CI:2.16 to 3.68) 0.28 (95% CI:0.22 to 0.36) ~	0.22
	Rare diseases:	9.1 (95% CI:1.9 to 44.6) 0.23 (95% CI: 0.05 to 1.03) ~	4.57 (95% CI:2.41 to 8.66) 0.29 (95% CI:0.15 to 0.56) ~	0.22 (combined with additional conditions)
	On immunosuppressants:	26.7 (95% CI:9.9 to 72.0) 1.09 (95% CI: 0.48 to 2.49) ~	4.35 (95% CI:2.80 to 6.77) 0.48 (95% CI:0.31 to 0.73) ~	0.24
	Additional conditions:	8.9 (95% CI:4.4 to 18.1) 0.37 (95% CI: 0.20 to 0.69) ~	3.77 (95% CI:2.73 to 5.20) 0.31 (95% CI:0.23 to 0.43) ~	
	Astra Zeneca		**RR for severe disease:** No risk condition RR# 0.06 (0.04, 0.10) Moderate risk condition RR 0.14 (0.10, 0.19) Condition eligible for shielding RR 0.37 (0.25, 0.54) VE = (63% (95 percent CI 46% to 75%)) **RR for hospitalisation or mortality:** No risk condition RR# 0.16 (0.14, 0.19) Moderate risk condition RR 0.20 (0.17, 0.24) Condition eligible for shielding RR 0.37 (0.31, 0.45)	
	Pfizer/Moderna	**mRNA**	**RR for severe disease:** No risk condition RR# 0.08 (0.04, 0.15) Moderate risk condition RR 0.06 (0.04, 0.10) Condition eligible for shielding RR 0.28 (0.16, 0.49)	

			VE= 72% (95% CI 51% to 84%)). **RR for hospitalisation or mortality:** No risk condition RR# 0.09 (0.07, 0.11) Moderate risk condition RR 0.08 (0.07, 0.11) Condition eligible for shielding RR 0.28 (0.20, 0.38)	

* 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

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