Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Duration of protective immunity following COVID-19 vaccination of healthcare workers (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

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Key points

- The duration of protective immunity from COVID-19 following vaccination is an important consideration for Ireland's vaccination strategy, particularly for groups who may be at a higher risk of exposure (such as healthcare workers), those who 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 92% of those aged 18 years and older in Ireland are fully vaccinated.
- This review aimed to assess the duration of vaccine efficacy and effectiveness against COVID-19 and to identify any evidence of waning of effect among healthcare workers (HCWs).
- 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.
- Sixteen relevant papers reporting on 14 unique studies were identified: one randomised controlled trial (RCT) and 13 observational studies, of which 12 were cohort studies and one was a case-control study. Median duration of follow-up ranged from six to 26 weeks.
- Of the four licensed vaccines against COVID -19 in Ireland, BNT162b2 (Pfizer/BioNTech) was the most frequently included vaccine in studies (in 11 studies) and Ad26.COV2.S (Janssen) was the least frequently included (in two studies).
- There was very limited evidence (efficacy or effectiveness) related to the primary review outcomes of mortality and severe disease for vaccinated HCWs.

- The one included RCT reported no deaths among fully vaccinated participants and reported a vaccine efficacy of 98.2% for prevention of severe illness with a median follow-up of 26 weeks.
- Only one observational study reported COVID-19 associated deaths and reported a vaccine effectiveness for prevention of COVID-19 related mortality of 98.5% over a period of 19.3 weeks. Two observational studies reported a small number of hospitalisations of vaccinated staff.

- The RCT data on mRNA-1273 (Moderna) estimated overall vaccine efficacy for the prevention of symptomatic infection was 94.4% (95% CI 90.3 to 96.8%) for healthcare workers with a median follow-up of 26 weeks. For any infection, all observational studies reported effectiveness exceeding 70% up to six months after vaccination. Estimates for vaccine effectiveness were higher against symptomatic infection, with the lowest estimate reported at 80.9% effectiveness at 13-14 weeks.
- There was evidence to suggest that overall vaccine efficacy and effectiveness for symptomatic disease for HCWs is similar to that of the general population. The included RCT reported a vaccine efficacy of 94.4% (95% CI 90.3 to 96.8%) for HCWs and 93.2% (95% CI 90.9 to 94.8%) for the general population. The observational study that reported results separately for HCWs and the general population reported effectiveness estimates of 86.5% and 87.1%, respectively.
- Changes in vaccine effectiveness over time were presented in five studies. Data from three studies provided trends in vaccine effectiveness up to 21.4 weeks since complete vaccination. Point estimates for vaccine effectiveness against symptomatic or any infection decreased over time for all three studies. However, the confidence intervals at each time point were wide and overlapped. Consequently, it is not possible to conclude waning immunity from these data. Additionally, the decline in vaccine effectiveness coincided with increasing incidence of the Delta variant. The remaining two studies only presented graphical displays of vaccine effectiveness over time with neither showing a decline over time.
- 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 variants of concern.

- The evidence suggests that COVID-19 vaccination provides a high level of protection against severe disease, symptomatic infection and any infection. Despite this, there may still be a risk to health services as this protection may not be sufficient to prevent healthcare workers from becoming infected, particularly when combined with high incidence rates in the community. This could result in staffing pressures due to absences or in the transmission of infection within healthcare settings to vulnerable populations from infected staff.
- 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] 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 the 26 December 2020 in a sequenced manner, starting with those at greatest risk of severe illness and death, followed by those at very high or high risk of exposure and transmission receiving priority for the available vaccines. The first group to receive the vaccine included adults aged ≥65 years 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 26 October 2021, 7.3 million vaccine doses have been administered in Ireland, with an estimated 92.1% 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 the second or final dose of their respective vaccination schedule is complete. The dosing schedule for each vaccine, and additional vaccine identifiers are detailed in Table 1.

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

Vaccine	Number of doses required	Days from final dose to being considered fully vaccinated	Other Vaccine Identifiers
BNT162b2 **Pfizer/BioNTech.**[16, 17]	2	7	• Comirnaty • Tozinameran
mRNA-1273 **Moderna.**[15]	2	14	• Spikevax • CX-024414 • TAK-919
ChAdOx1 **AstraZeneca/Oxford.**[18]	2	14	• 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 a recent 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 the previous evidence summary:

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

This evidence summary focuses on the duration of protective immunity for healthcare workers following COVID-19 vaccination.

2 Methods

This review aimed to examine the change in efficacy and effectiveness of COVID-19 vaccination over time for healthcare workers. This review is a limited update of a previous review and a detailed summary of the methods used is provided in the protocol, available here.[23]

A systematic search of published peer-reviewed articles and non-peer-reviewed preprints was undertaken. Previous searches of the Medline and Embase databases and the Europe PMC preprint server up to 30 September 2021 were updated to 18 October 2021. A previous search of the preprint server MedRxiv up to 31 August 2021 was also updated to 18 October 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] Where available, vaccine efficacy and 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 using R 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), healthcare workers, and residents and staff of long term care facilities). ▪ Depending on data availability, results from relevant subgroups (for example age group, or immunocompromised).
Intervention	**Included:** Vaccines against COVID-19 which are licensed and distributed in Ireland: ▪ ChAdOx1 (AstraZeneca)^ ▪ Ad26.COV2.S (Janssen). ▪ mRNA-1273 (Moderna). ▪ BNT162b2 (Pfizer/BioNTech). Studies which include vaccine regimens with extended intervals between first and second doses or heterologous vaccine regimens were 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] Outcomes were extracted for study-defined time points since vaccination. Changes in absolute and relative efficacy or effectiveness were noted. Disaggregated data by variant was extracted if reported. **Excluded**: ▪ Outcomes relating to time points in the period when individuals are waiting for the second dose of a two-dose schedule and in the period immediately after full vaccination, but before immunity is expected to occur.
Types of studies	**Included:** ▪ Randomised controlled trials. ▪ Non-randomised controlled trials. ▪ Quasi-experimental studies. ▪ Prospective and retrospective cohort studies. ▪ Case-control studies. ▪ Test-negative case control studies. ▪ Analytical cross sectional studies. ▪ Studies where the median time from administration of the final regimen dose to outcome ascertainment is ≥ eight weeks~ or studies which report outcomes eight weeks after administration of the final regimen dose. **Exclude:** ▪ 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 was included and extracted.

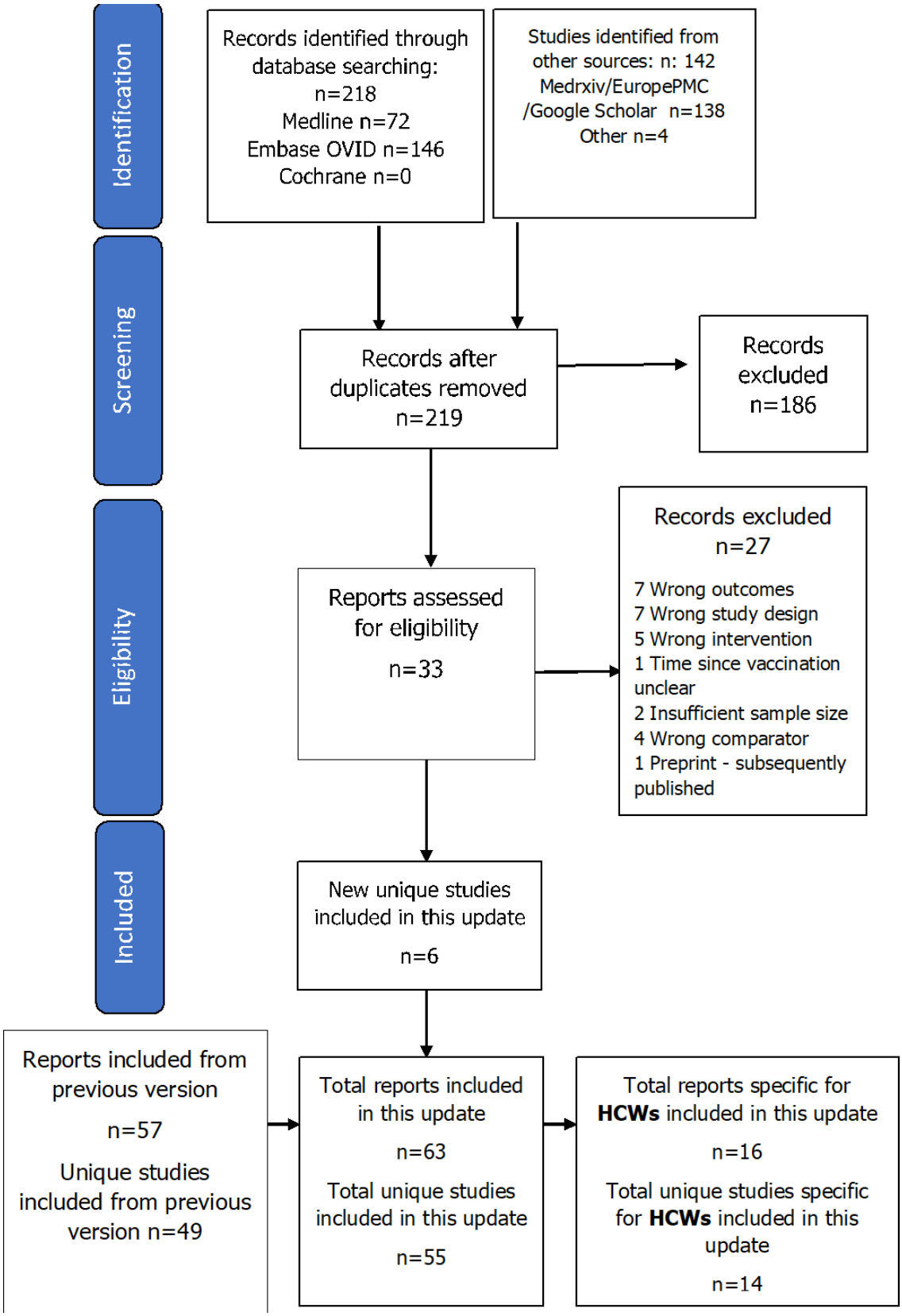
*Safety outcomes were considered beyond the scope of this review. Outcomes related to immunogenicity (where there is no long-term efficacy/effectiveness data) and transmission were not included in the review.
^Brands of ChAdOx1 which are not licensed in Ireland (for example Covishield) were included.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

3 Results

An overview of the updated search findings since the previous version of this review (that is, updated searches from 30 September 2021) are presented in the PRISMA diagram (Figure 1). The database search of Embase, Medline and Cochrane on 18 October 2021 returned 218 citations. An additional 138 citations were identified from MedRxiv/EuropePMC/Google Scholar, and four from other sources. Following removal of duplicates, the titles and abstracts of 219 citations were screened for relevance. This resulted in 33 reports eligible for full-text review where a further 27 records were excluded. Following the screening process, an additional six papers were added to the 57 previous reports describing 49 studies, yielding a total of 63 papers describing 55 unique studies that met the inclusion criteria. There were 16 reports describing 14 studies that concerned healthcare workers. Seven of the included papers were only available as preprints.

Of the 14 studies identified, one was an RCT, and the remaining 13 were of observational study designs. 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

Two papers describing the results of one RCT that included healthcare workers were identified (summarised in Table 3). [27, 28]

El Sahly et al. published an updated analysis of the mRNA-1273 (Moderna) trial originally published by Baden et al.[27] with a median follow-up of 26 weeks (IQR 24 to 28) after dose two.[28] The mRNA-1273 (Moderna) overall vaccine efficacy estimate for the prevention of symptomatic infection was 94.4% (95% CI 90.3 to 96.8%) for healthcare workers. Similar vaccine efficacy estimates were found for emergency response providers, personal care and in-home service providers, and pastoral/social/public health workers. For the total study population, vaccine efficacy estimates for severe and symptomatic disease were 98.2% (95% CI 92.8 to 99.6) and 93.2% (95% CI 90.9 to 94.8), respectively.

Information on protection over time specifically for healthcare workers was not available in this study. For the total study population which included healthcare workers, there was no evidence of waning efficacy for symptomatic disease, with vaccine efficacy of 91.8% (95% CI 86.9 to 95.1), 94.0% (95% CI 91.2 to 96.1) and 92.4% (95% CI 84.3 to 96.8) for the intervals ≥14 days to < two months, two months to < four months, and at ≥ four months after dose two, respectively.

No deaths attributed to COVID-19 occurred in fully vaccinated individuals in this study. The vaccine efficacy against death was estimated as 100% (95%CI: NE–100 – the lower bound of the 95% CI could not be calculated). Three COVID-19 deaths occurred in the placebo group, and one death occurred in a partially vaccinated individual (received one dose of mRNA-1273 (Moderna) vaccine).

The risk of bias assessment of this RCT indicated that it was considered to be at low risk of bias across all the domains examined.

Figure 2 Risk of bias summary for included RCTs

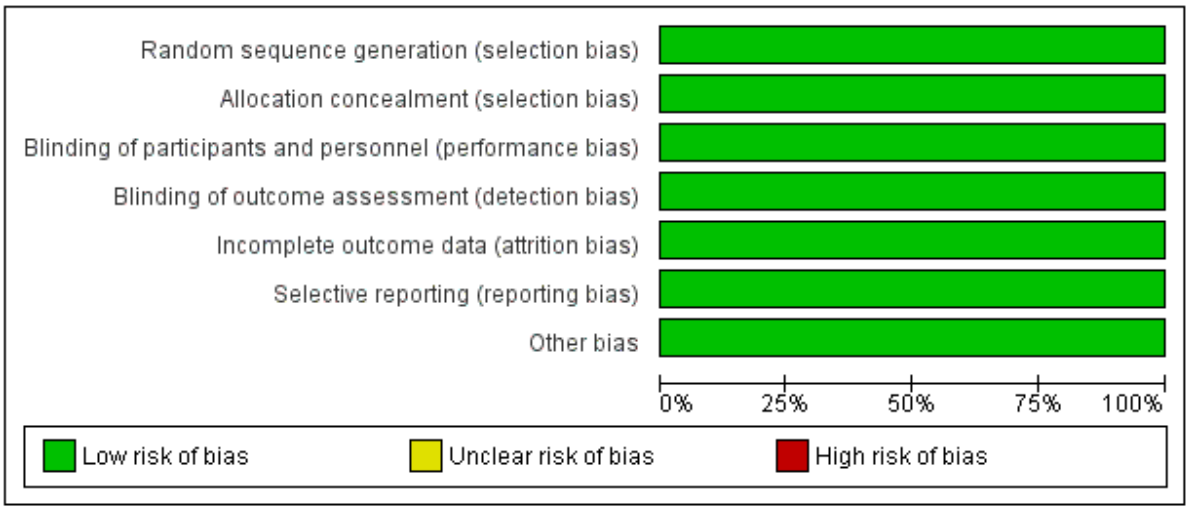


Table 3 Summary of RCTs reporting data for primary outcomes (vaccine efficacy against COVID-19 related severe disease and mortality), secondary outcomes (vaccine efficacy against any symptomatic SARS-CoV-2 infection) and change in efficacy over time

Author, Country	Exposure	Sample Size	Time since final vaccination	Primary outcomes: overall follow up (VE (95%CI)		Secondary Outcomes: overall follow-up VE (95%CI)		Change in vaccine efficacy over time VE (95%CI)	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
Baden,[27] peer-reviewed US	mRNA-1273 (Moderna)	**N:** 28,207 (25.1% of participants were HCWs) Intervention: 14,134 Control:14,073	Median: 9 weeks (Range 0 – 13.9)	VE for total study population: 100% (NE to 100)	NR	NR	Overall population outcomes: 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 for overall population.	Low
El Sahly, [28] US Follow up of Baden [27]	mRNA-1273 (Moderna)	**N:** Efficacy population - 28,451 FAS – 30,346 Proportion of HCWs included in study: Healthcare workers – 3,806 (25.2%)	Median – 26.1 weeks (IQR 37.5 to 32.1).	VE for total study population: 98.2% (92.8 to 99.6)	VE for total study population: 100% (NE to 100)	VE for total study population : 82.0% (79.5 to 84.2)	Overall population outcomes: VE: 93.2 (90.9 to 94.8) *HCW outcomes:* *Healthcare Providers* VE: 94.4 (90.3 to 96.8)	Overall population outcomes: Symptomatic infection over time (PP) ≥14 days to <2 months: VE 91.8% (86.9 to 95.1) 2 months to <4 months: VE 94.0% (91.2 to 96.1) ≥ 4 months: VE 92.4% (84.3 to 96.8	Low

Author, Country	Exposure	Sample Size	Time since final vaccination	Primary outcomes: overall follow up (VE (95%CI)		Secondary Outcomes: overall follow-up VE (95%CI)		Change in vaccine efficacy over time VE (95%CI)	Risk of bias
				Severe Disease	Mortality	Any infection	Symptomatic infection		
		Emergency Response – 302 (2.0%) Personal Care and In-Home Services – (940) 3.1% Pastoral, Social or Public Health Workers (1,039) 3.4%					*Emergency Response providers* VE: 93.0 (70.6 to 98.4) *Personal care and in-home service providers* VE: 93.5 (72.8 to 98.5) *Pastoral, social, or public health workers* VE: 97.6 (82.2 to 94.2)	Changes in vaccine efficacy over time not specifically reported for HCW population.	

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

3.2 Vaccine effectiveness

Characteristics of included studies

Of the 13 observational studies, 12 were cohort studies,[29-41] and one was a test negative case-control study.[42] Ten studies exclusively enrolled healthcare and other frontline workers; one study presented data from a mixture of HCWs and residents of LTC facilities and one presented data from the general population, which included HCWs.

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	
Alali,[29] Preprint Kuwait Retrospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech)	**N:** 3,246 HCWs 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,[30] 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 (65.0 to 92.0) >69 days 81.0 (42.0 to 94.0)	VE: 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
Emborg,[31] Preprint Denmark	BNT162b2 (Pfizer/BioNTech)	425,799 HCWs (112,824 vaccinated)	Median 9.6 weeks (IQR 8.3, 10.3)	VE: not estimated due to small numbers	VE: not estimated due to small numbers	VE: 80 (77 to 83)	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	
Retrospective cohort study								
Thompson,[39]& Peer-reviewed US prospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech) 67% mRNA-1273 (Moderna) 33%	Vaccinated HCWs 2,510 (161,613 person days) Unvaccinated HCWs 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,[43]& published report (CDC), (update of Thompson) US prospective cohort study (crossover)	BNT162b2 (Pfizer/BioNTech) 65% mRNA-1273 (Moderna) 33% Ad26.COV2.S (Janssen) 2%	Vaccinated 2,976 HCWs (455,175 person days) Unvaccinated 4,135 HCWs (181,357 person days)	Median 27 weeks (fully vaccinated) IQR (18.4 to 29.9 weeks)	NR	NR	VE: 80 (69 to 98)	NR	Fair
Ghosh,[33] Peer-reviewed India Cohort Study with crossover	ChAdOx1 (AstraZeneca) (Covishield®)	**N:** 1,595,630 HCWs End study: 82.2% fully vaccinated.	Mean 8.4 weeks, range NR	NR	VE: 98.5 (0 to 99.9) 95% CI is wide due to low number of events.	VE: 91.8 (88.8 to 94.0)	NR	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	
Giansante, [34] Peer reviewed Italy Retrospective cohort study	BNT162b2 (Pfizer/BioNTech) 96% mRNA-1273 (Moderna) NR	**N:** 9,839 (All the staff of the Bologna health trust (not only HCWs). 7,190 (73%) were HCWs.	Mean 11.67 weeks (sd NR)	15 cases hospitalised in unvaccinated, 0 cases in fully vaccinated.	NR	Overall population VE: 84.8 (73.2 to 91.4) Only HCWs VE: 84.4 (95% CI: 69.7 to 92.0)	Overall population VE: 87.1 (69.3 to 94.6) Only HCWs VE: 86.5 (62.9 to 95.1)	Poor
Issac,[35] 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 [36] Preprint Israel, Prospective Cohort Study Covid-19 Vaccine Effectiveness in Healthcare Personnel in 6 Israeli Hospitals (CoVEHPI)	BNT162b2 (Pfizer/BioNTech)	N: Total – 1,250 HCWs Vaccinated – 998 (79.8%) Unvaccinated – 252 (20.2%)	Median – 11.1 weeks (10.5 to 10.8 weeks)	NR	NR	VE (≥14 day after second/final dose): 94.5 (95% CI: 82.5 to 98.2)	VE(≥7 days after second/final dose): 97.0 (72.0 to 99.7)	Fair
Muhsen,[37]	BNT162b2 (Pfizer/BioNTech)	vaccinated 6,960 HCWs	Median 11.4 weeks IQR NR	NR	NR	VE: 89 (83 to 93)	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	
Preprint Israel Prospective cohort study		unvaccinated 2,202 HCWs						
Naito,[38] Peer-reviewed Japan **Retrospective cohort study**	BNT162b2 (Pfizer/BioNTech)	N: 8,749 HCWs	Maximum follow up 15.6 weeks	NR	NR	VE: not estimated June: 16 cases among unvaccinated population 0 cases among fully vaccinated population July: 11 cases among unvaccinated population 3 cases among fully vaccinated	NR	Poor
Pilishvili,[42] 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 HCWs Controls – 3,449 HCWs	Median – 6.0 weeks (range 1 to 23.5 weeks)	Hospitalisation in cases fully vaccinated: 4 (2%) Partially vaccinated: 1 (1%) Unvaccinated 21: (3%)	NR	NR	<u>Any COVID vaccine</u> VE: 90.4 (87.0 to 92.9) <u>BNT162b2</u> VE: 88.8 (84.6 to 91.8) <u>mRNA-1273</u> VE: 96.3 (91.2 to 98.4)	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	
Uschner,[40] Preprint US Prospective cohort study	BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2.S (Janssen)	**N: 16,020** (Fully vaccinated adults 18 years and older) 34% HCWs	Median 24 weeks for infected participants (IQR 17, 28.4) Median 23.6 weeks for non-infected participants (IQR 17.4, 29.9)	NR	NR	VE: not estimated, HR reported *Ad26.COV2.S (Janssen) vs BNT162b2 (Pfizer/BioNTech)* HR = 2.23 (1.40 to 3.56) *mRNA-1273 (Moderna) vs BNT162b2 (Pfizer/BioNTech)* HR = 0.69 (0.50 to 0.96).	VE: not estimated	Poor
Yassi,[41] 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 to 8.9)	NR	NR	VE: 79.2 (64.6 to 87.8)	NR	Poor

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.

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

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

* Quality Appraisal is provided in detail in Appendix A.

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

Author, Country Study Design	Exposure	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)	Quality appraisal
Bianchi,[30] 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)	VE against **symptomatic infection** 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
Fowlkes,[43] 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 HCWs (181,357 person days) vaccinated 2,976 HCWs (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% (68 to 93) 120–149 days: 81% (34 to 95) 150+ days 73% (9 to 86)	Fair
Pilishvili, [42] US Test negative case control	BNT162b2 (Pfizer/BioNTech) (Cases: 78%, Controls 79%) mRNA-1273 (Moderna) (Cases: 21%, Controls 20%)	N: Cases – 1,482 HCWs Controls – 3,449 HCWs	Median – 6.0 weeks (range 1 to 23.5 weeks)	VE against **symptomatic infection** 1-2 weeks 92.7% (89.1 to 95.0) 3-4 weeks 96.6% (92.7 to 98.5) 5-6 weeks 91.8% (83.6 to 96.0) 7-8 weeks 88.7% (79.9 to 94.1) 9-10 weeks 83.7% (68.3 to 91.6) 11-12 weeks 82.8% (68.5 to 90.4) 13-14 weeks 80.9% (61.0 to 90.4)	Good
Uschner,[40] Preprint US Prospective cohort study	BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2.S (Janssen)	**N:** 16,020 (Fully vaccinated adults 18 years and older) 34% HCWs	Median 24 weeks for infected participants (IQR 17, 28.4) Median 23.6 weeks for non-infected participants	Kaplan-Meier curves for cumulative incidence of **self-reported infection** over time are presented for vaccine type, rural/urban setting, and age group. These showed higher cumulative incidences for those vaccinated with BNT162b2 (Pfizer/BioNTech) and Ad26.COV2.S (Janssen), and for those aged greater than 65 or between 18 and 44.	Poor

Author, Country Study Design	Exposure	Sample Size	Time since final Vaccination	Change in vaccine effectiveness over time VE (95% CI)	Quality appraisal
			(IQR 17.4, 29.9)		
Yassi,[41] 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.	Poor

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

Description of studies

Fourteen papers describing thirteen studies were identified that examined vaccine effectiveness in healthcare workers which are further detailed in Appendix B. Given the number of studies identified, this section focuses on the five 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.[39, 43] Participants were swabbed and tested for SARS-CoV-2 infection regardless of symptom or vaccination status. Vaccine effectiveness estimates are adjusted for baseline sociodemographic and health characteristics, and participant's virus exposure. Thompson et al.[39] 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, vaccine effectiveness was estimated at 91% (95% CI 76 to 97) ≥14 days after the second dose. Vaccine effectiveness for severe disease or mortality was not reported.

Fowlkes et al.[43] 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, 65% had received the BNT162b2 (Pfizer/BioNTech) vaccine, and 33% had received the mRNA-1273 (Moderna) vaccine. Vaccine effectiveness 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. As the 95% CIs are overlapping, differences in vaccine effectiveness over time are not statistically significant and could be due to poor precision. The authors noted that the observed decline in point estimates corresponded to both an increase in the prevalence of the Delta variant and an increase in time since vaccination. 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.[42]

Pilishvili et al. conducted a test negative case control study to examine the effectiveness of mRNA vaccines in HCWs across 25 US states.[42] Cases (n=1,482) were defined as a positive RT-PCR or antigen-based test 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 RT-PCR test for SARS-CoV-2 regardless of symptoms and were matched by week of test date and site. Results were adjusted for sociodemographics, underlying conditions and exposure to a person with COVID-19. The median time since final vaccination dose was six weeks (range 1 to 24).

Vaccine effectiveness for symptomatic infection more than seven days after the second dose was 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 HCWs 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 three and four, the authors considered that wide and overlapping confidence intervals did not support a conclusion of waning immunity, but that the data suggested longer-term monitoring of vaccine effects is warranted. Digitised estimates taken from the figure presented in the publication estimate the effectiveness as 96.6% (95% CI 92.7 to 98.5) at 3-4 weeks and 80.9% (95% CI 61.0 to 90.4) at 13-14 weeks after dose two.

Emborg et al.

In a preprint, Emborg et al.[31] 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 vaccination threshold required for inclusion in this review. Results for the cohort of HCWs included in the analysis are presented here.

The analysis included 426,000 HCWs, of whom 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 study from 27 December 2020 to 11 April 2021. 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 approximately 79,000 person years of follow-up in the unvaccinated group. Vaccine effectiveness against confirmed SARS-CoV-2 infection was estimated at 80%.

Israeli studies

Two studies were conducted in HCWs in Israel. Katz et al.[36] reported on a prospective cohort study of 1,250 HCWs across six hospitals, with a 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. The study was conducted over a three month period, with enrolment between late December 2020 and mid-February 2021. All sequenced infections were confirmed to be the Alpha variant of COVID-19.

In a preprint of a prospective cohort study of 6,960 fully vaccinated healthcare workers in long term care facilities, Muhsen et al. [37] calculated a vaccine effectiveness of 89% (95% CI: 83 to 93) against any infection for BNT162b2 (Pfizer/BioNTech) over a median follow-up of 11.4 weeks. The study was undertaken over a four-month period during which the Alpha variant was the dominant variant in Israel, with follow-up ending in April 2021.

Neither study presented data on mortality or severe disease outcomes.

Summary of studies of poor quality

The remaining eight studies were considered to be of poor quality.

In a preprint, Uschner et al.(40) examined the effectiveness of the BNT162b2 (Pfizer/BioNTech) (70%), mRNA-1273 (Moderna) (25%), and Ad26.COV2.S (Janssen) (5%) vaccines among adults in six healthcare settings in North Carolina. The proportion of healthcare workers in this cohort was 34%. The primary outcome was weeks until the first self-reported infection occurring ≥ 14 days after vaccination. The cumulative incidence was 5.2% at 34 weeks following full vaccination. Vaccine effectiveness for the total cohort for the Ad26.COV2.S (Janssen) and mRNA-1273 (Moderna) vaccines were presented relative to BNT162b2 (Pfizer/BioNTech), with hazard ratios of 2.23 (95% CI: 1.40 to 3.56) and 0.69 (95% CI: 0.50 – 0.96), respectively, with a hazard ratio less than one indicating higher effectiveness.

Bianchi et al.[30] 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. The study matched vaccinated HCWs 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. Results for mortality or severe disease outcomes were not reported. Results for any SARS-CoV-2 infection and symptomatic disease were 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, vaccine effectiveness 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.[41] examined vaccine effectiveness 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. Results for mortality or severe disease outcomes were not reported. Vaccine effectiveness ≥7 days after the 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, but no decline in vaccine effectiveness was observed.

In a preprint, Alali et al.[29] 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 among 3,246 healthcare workers. The mean time since the final vaccination was 15 weeks. Results for mortality or severe disease outcomes were not reported. Vaccine effectiveness against symptomatic infection ≥ 7 days after the second dose was 94.5% (95% CI 89.4% to 97.2%).

Both Indian studies of Covishield (an alternative brand name of the ChAdOx1 (AstraZeneca) vaccine) in HCWs were considered to be of poor quality. Ghosh et al.[33] analysed vaccine effectiveness 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.[35] analysed vaccine effectiveness in 324 HCWs in a secondary care hospital who had at least 15 weeks follow-up. Neither study reported results for mortality or severe disease outcomes. Vaccine effectiveness for any infection was 91.8% (95% CI 88.8 to 94.0) and 84.9% (95% CI not reported) for Ghosh et al.[33] and Issac et al.,[35] respectively. There was no adjustment for age or other important confounders in either analysis.

Giansante et al. reported vaccine effectiveness in healthcare workers among staff in a health trust in Italy.[34] A cohort of 9,839 HCWs were followed up for a mean of 11.7 weeks after receiving either BNT162b2 (Pfizer/BioNTech) (96%) or mRNA-1273 (Moderna) vaccines. Results for mortality or severe disease outcomes were not reported. Vaccine effectiveness of 86.5% (95%CI: 62.9 to 95.1%) and 84.4% (95%CI: 69.7 to 92.0%) were reported for symptomatic or any infection, respectively.

Naito et al.[38] reported effectiveness among staff in a hospital in Japan that had been vaccinated with BNT162b2 (Pfizer/BioNTech) over a maximum follow up period of 15.6 weeks. Of the 2,809 frontline staff vaccinated, no fully vaccinated staff members were diagnosed with COVID-19 over a three month period. Three staff members were subsequently diagnosed as the incidence of the delta variant increased, with all three confirmed to have been infected with the delta variant.

3.3 Summary of findings

Primary outcome: COVID-19 related mortality and severe disease

There was very limited evidence (efficacy or effectiveness) related to the primary review outcomes of mortality and severe disease for vaccinated HCWs. There were no COVID-19 associated deaths among the vaccinated participants in the one relevant RCT for the mRNA-1273 (Moderna) vaccine.[28] This is compared with three deaths among those who received the placebo in this RCT, but it was not specified if those were HCWs or not. Vaccine efficacy was estimated at 100% for the prevention of COVID-19 associated death, though the low numbers and limited follow-up warrant caution in interpreting this estimate.

Only one observational study reported deaths among those who were vaccinated. This large Indian study of almost 1.6 million HCWs reported 37, 16, and seven deaths occurring among those who were unvaccinated, partially vaccinated, and fully vaccinated with Covishield® (ChAdOx1 – AstraZeneca), respectively.[33] Vaccine effectiveness relating to the prevention of COVID-19 related mortality was estimated to be 98.5% (95% CI: 0.0-99.9) over a period of 19.3 weeks. The wide confidence interval was attributed to low event numbers and the authors cautioned that this prevents the drawing of meaningful conclusions from these data.

There was also limited evidence available for the occurrence of severe disease. In the updated RCT, El Sahly et al. reported a vaccine efficacy of 98.2% (95% CI: 92.8 to 99.6%) for prevention of severe illness (defined as confirmed COVID-19 with at least one clinical sign of severe systemic illness). This corresponded to 106 severe cases in the placebo group and two in the mRNA-1273 (Moderna) group.[28] Only

two observational studies reported hospitalisation of vaccinated HCWs, with one and four participants hospitalised, respectively.[30, 42]

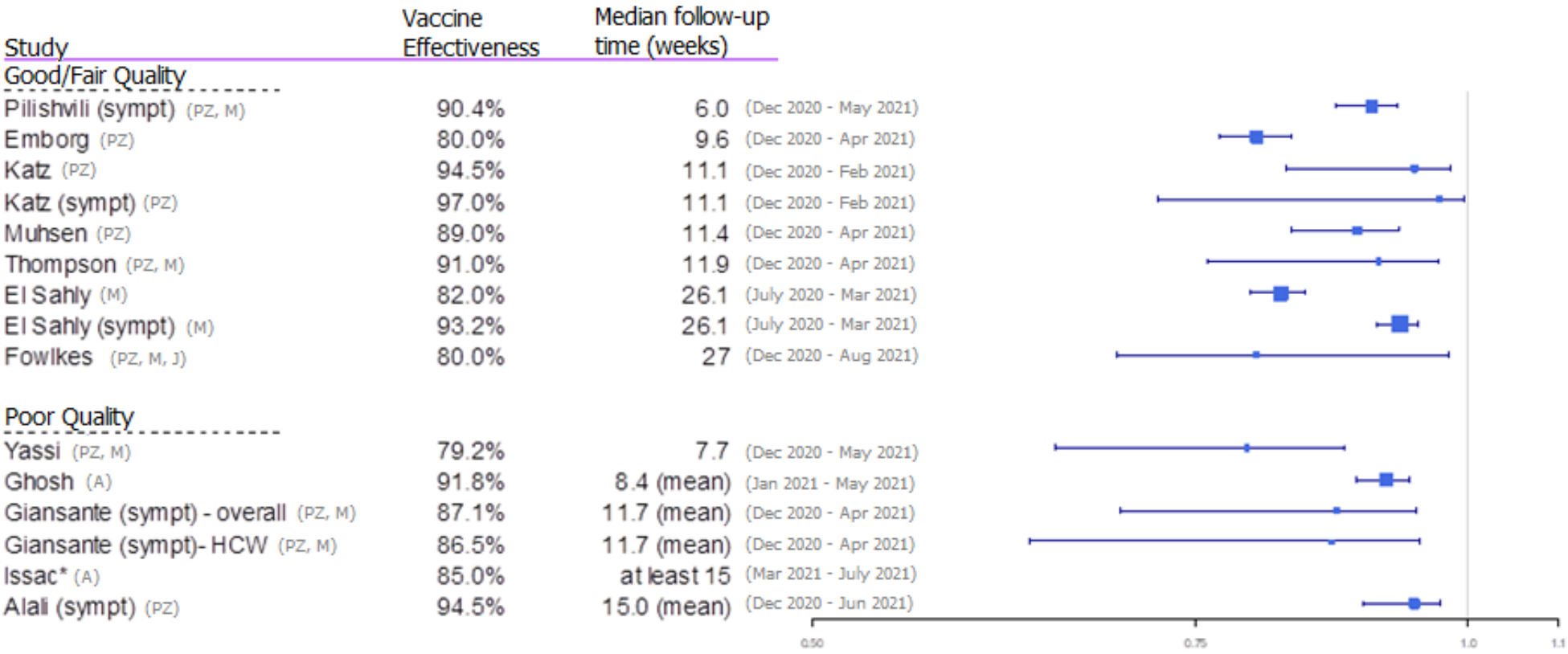
Secondary outcome: symptomatic and any infection

RCT data for the secondary review outcomes were limited to the mRNA-1273 (Moderna) vaccine with up to six months of follow-up data. Vaccine efficacy for included HCWs for preventing symptomatic infection was 94.4%; this was similar to that estimated among the total population of 93.2%.[28]

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 and the risk of outcome ascertainment bias. Vaccine effectiveness for the prevention of symptomatic or any infection exceeded 79% (ranging from 79.2 to 97.2%) for all vaccines across the included studies (Figure 3), with the BNT162b2 (Pfizer/BioNTech) vaccine being the most frequently reported (in 11 studies) and the Ad26.COV2.S (Janssen) vaccine being the least frequently reported (in two studies). The reporting of pooled figures at varying time points by different studies may impact the reliability of findings for specific vaccines and or overall effectiveness.

Infection despite vaccination was more frequently reported during the periods of Delta predominance.[38, 40] Among healthcare workers, the vaccine effectiveness against infection was 66% (95% CI: 26%–84%) during the Delta predominant period compared with 91% (95% CI: 81%– 96%) during the months preceding Delta predominance.[32] For the general population, with the BNT162b2 (Pfizer/BioNTech) vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the Alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the Delta variant. With the ChAdOx1 nCoV-19 (AstraZeneca) vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the Alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the Delta variant.[44] However, this also coincided in all cases with a longer time since vaccination.

Figure 3 Forest plot of vaccine effectiveness against symptomatic or any infection across observational studies of healthcare workers stratified by study quality

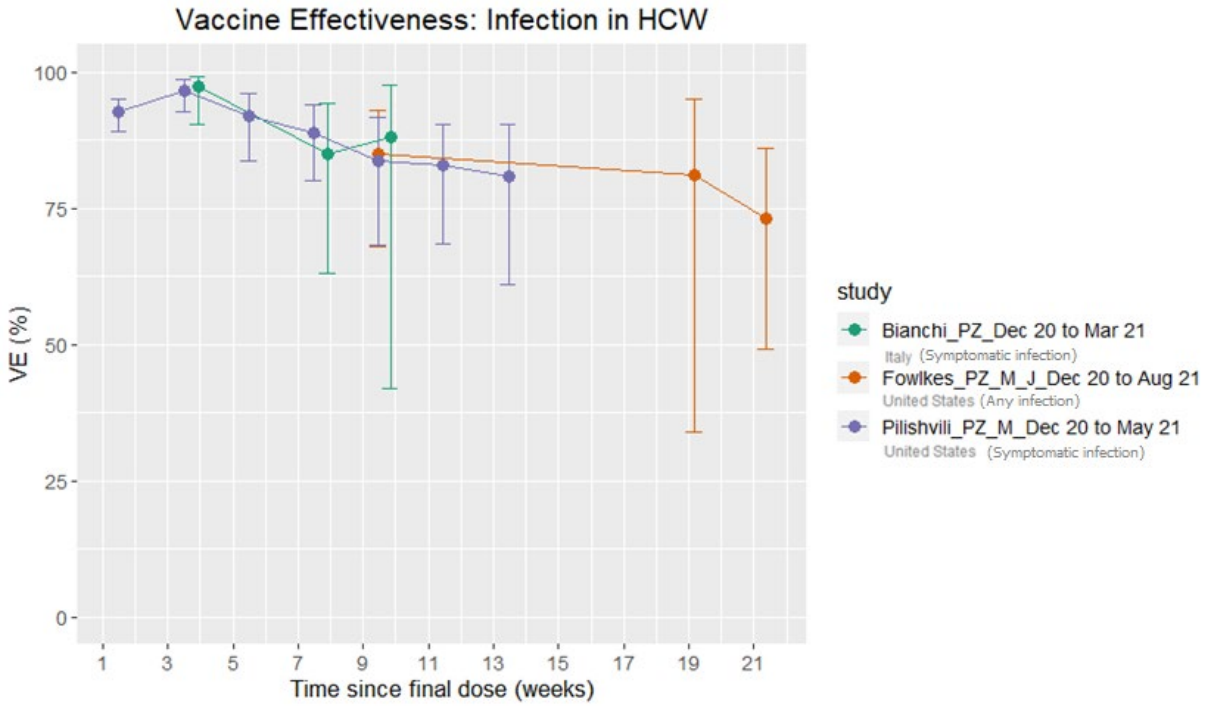


Abbreviations: A – ChAdOx1 (AstraZeneca), HCW – healthcare workers, J – Ad26.COV2.S (Janssen), PZ – BNT162b2 (Pfizer/BioNTech), M – mRNA-1273 (Moderna), sympt – symptomatic. *95% CI were not available for the study by Issac et al.

Vaccine effectiveness over time

Vaccine effectiveness over time was presented in five studies. Data from two American studies and a preprint of an Italian study provided trends in vaccine effectiveness over time since complete vaccination up to 21.4,[32] 14,[42] and 9.6 weeks.[30] Point estimates for vaccine effectiveness against symptomatic or any infection decreased with time for all of these studies (Figure 4). However, the confidence intervals were wide and overlapped across time points. Consequently, it is not possible to conclude if there is evidence of waning immunity from these data. Additionally, the time points associated with the decline of vaccine effectiveness are also associated with the increasing incidence of the Delta variant, further reducing the ability to determine waning vaccine effectiveness. The lowest reported vaccine effectiveness estimate was 73% for any infection at the longest follow-up time point of approximately 5.4 months.[32] The remaining two studies only presented graphical displays of vaccine effectiveness over time, with neither showing a decline over time.[40, 41]

Figure 4: Vaccine effectiveness against symptomatic or any infection over time across observational studies of healthcare workers



Abbreviations: HCW – healthcare workers, J – Ad26.COV2.S (Janssen), PZ – BNT162b2 (Pfizer/BioNTech), M – mRNA-1273 (Moderna).

Quality of included effectiveness studies

Quality appraisal was conducted using the NIH Quality Assessment Tools.[25] The quality appraisal of the included studies are described in Appendix A (Tables App.A1 and App.A2). Of the 13 observational studies, two[31, 42] were rated as good quality, three[32, 36, 37] were appraised as being of fair quality, and eight as poor quality.[29, 30, 33-35, 38, 40, 41]

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

Outcome ascertainment bias can be a concern in vaccine effectiveness studies as individuals aware of their vaccinated status may have altered their testing behaviour. Routine testing regardless of vaccination or symptom status 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.[31] was rated as good quality for this reason. However, as the majority of studies did not report on mortality or severe disease outcomes, they may be at risk of this bias.

Seven of the 13 studies are currently published as preprints[29-31, 35-37, 40] 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

Sixteen relevant papers reporting on 14 unique studies were identified as part of this review with the median duration of follow-up ranging from six to 26 weeks. There was very limited evidence (efficacy or effectiveness) related to the primary review outcomes of mortality and severe disease for vaccinated healthcare workers. The one included RCT reported no deaths among fully vaccinated participants and reported a vaccine efficacy of 98.2% for prevention of severe illness with a median follow-up of 26 weeks. [27, 28] Only one observational study reported COVID-19 associated deaths.[33] Two observational studies reported a small number of hospitalisations of vaccinated staff. [30, 42]

There was evidence to suggest that overall vaccine efficacy and effectiveness for symptomatic disease for HCWs is similar to that of the general population. The included RCT reported a vaccine efficacy estimate of 94.4% (95% CI 90.3 to 96.8%) for HCWs and 93.2% (95% CI 90.9 to 94.8%) for the general population. [27, 28] The observational study that reported results separately for HCWs and the general population reported effectiveness estimates of 86.5% and 87.1%, respectively. [34]

The overall effectiveness of vaccination and its duration is of particular importance in relation to healthcare workers as this subgroup of the population has a greater potential for exposure to SARS-CoV-2 in light of their work. There are also patient safety concerns as a consequence of the infection of healthcare workers, due to the risk of onward transmission to vulnerable patients and staffing pressures that would result from staff absence due to illness or infection.

Data from RCTs were limited in this review, with only one trial reported in two papers. This RCT focused exclusively on the mRNA-1273 (Moderna) vaccine and there were no RCTs identified that specifically included healthcare workers for the BNT162b2 (Pfizer/BioNTech), ChAdOx1 (AstraZeneca), or Ad26.COV2.S (Janssen) vaccines.

Observational studies included in this review predominately reported outcomes and follow-up for those vaccinated with BNT162b2 (Pfizer/BioNTech), with very few (two of thirteen) studies reporting assessment of the Ad26.COV2.S (Janssen) vaccine. When the Ad26.COV2.S (Janssen) vaccine was included in a study, it was the vaccine least commonly administered.[32, 40] Two included studies indicate higher effectiveness for mRNA-1273 (Moderna) compared to the other vaccines, but low numbers of individuals fully vaccinated with the alternative vaccines resulted in difficulties in comparing their effectiveness.[40, 42] The undertaking of comparative effectiveness trials would be beneficial to resolve these difficulties, such as the one

undertaken by Hulme et al. which showed similar effectiveness for BNT162b2 (Pfizer/BioNTech) and ChAdOx1 (AstraZeneca) up to 20 weeks after the first dose of each was administered.[45]

In studies that reported outcomes for healthcare workers as part of a wider population, most outcomes were not reported separately for healthcare workers; therefore, risks specific to healthcare workers, such as rates of severe disease or mortality could not be determined. When vaccine effectiveness was reported for healthcare workers (such as for symptomatic infection in the included RCT[28]) it was similar to that of the general population, with both estimates being high at 94.4% (95% CI: 90.3 to 96.8%) and 93.2% (95% CI: 91.0 to 94.8%) for healthcare workers and the general population, respectively.

There was limited reporting of the primary review outcomes of severe disease or mortality, with the majority of the studies reporting only on the secondary review outcomes concerned with infection. Individuals who were aware of their vaccination status may alter their test-seeking behaviour, which can lead to the risk of outcome ascertainment bias in observational studies. This is less of a concern for outcomes such as COVID-19 associated hospitalisation and mortality. This potential risk of bias needs to be considered when interpreting the results of this review.

The longest time that vaccine effectiveness was reported specifically for healthcare workers in this review was 21.4 weeks.[32] The majority of results come from studies with follow-up times of less than four months (only two studies had longer follow up time – Pilishvili et al. and HEROS-RECOVER)[32, 42].

Where reported, declines in vaccine effectiveness were small and indicate a high level of protection for healthcare workers remains for up to six months after they have completed their vaccine regimen. However, despite this high level of protection, there may still be risks to the health service in terms of staff illnesses, particularly during times of increased incidence rates within the community and the resultant increased risk of exposure.

Strengths and Limitations

The main strength of the review is that the review examines clinical outcomes in preference to biochemical metrics such as antibody titres which may not necessarily predict effectiveness over time.[46] This also ensures that outcomes that are of greater relevance to the public and policymakers are reported.

This review is subject to a number of important limitations. These relate to the type of review conducted ('rapid review'), which was limited by time constraints, 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 additional and longer-term studies are published.

Seven of the 16 papers identified are only published as preprints, 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.[46]

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.

Estimating changes in effectiveness over time in real world observational studies is difficult for a number of reasons, such as the emergence of new variants or changing levels of societal restrictions designed to minimise the spread of COVID-19. Consequently, vaccine effectiveness may be influenced by factors not directly related to the vaccine itself.

5 Conclusion

This evidence summary aimed to assess the duration of vaccine efficacy and effectiveness against COVID-19 and identify any evidence of waning of vaccine derived immunity among healthcare workers.

Although a small decline in vaccine effectiveness over time was noted, there remained a high level of protection afforded by COVID-19 vaccines against severe disease and infection for up to six months post-vaccination. It is not possible to determine if the observed decline is related to waning immunity, the effect of the increase in the incidence of the more transmissible Delta variant, changes in the behaviour of vaccinated individuals, or as a result of alterations to societal restrictions and or other factors.

Despite the high level of protection, there may still be a risk to health services as this protection may not be sufficient to prevent healthcare workers from becoming infected, particularly when combined with high incidence rates in the community. This could result in staffing pressures due to absences or in the transmission of infection within healthcare settings to vulnerable populations from infected staff.

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Appendix A 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.A1: Quality appraisal of cohort studies

	Healthcare and Frontline Workers											
Quality appraisal criteria	**Alali (2021) (29)**	**Bianchi (2021) (30)**	**Emborg (2021)(31)**	**Fowlkes (2021) (43)– updated analysis of Thompson (2021)(47)**	**Ghosh (2021) (33)**	**Giansante (2021)(34)**	**Issac (2021)(35)**	**Katz (2021)(36)**	**Muhsen (2021)(37)**	**Naito (2021) (38)**	**Uschner (2021) (40)**	**Yassi (2021) (41)**
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	X	✓	✓	X	✓	✓	✓	✓	X	CD	X
3. Was the participation rate of eligible persons at least 50%?	✓	CD	✓	✓	NR	✓	✓	✓	X	CD	CD	CD

	Healthcare and Frontline Workers											
Quality appraisal criteria	**Alali (2021) [29]**	**Bianchi (2021) [30]**	**Emborg (2021) [31]**	**Fowlkes (2021) [43]– updated analysis of Thompson (2021) [47]**	**Ghosh (2021) [33]**	**Giansante (2021) [34]**	**Issac (2021) [35]**	**Katz (2021) [36]**	**Muhsen (2021) [37]**	**Naito (2021) [38]**	**Uschner (2021) [40]**	**Yassi (2021) [41]**
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	✓	✓	✓	✓	X	✓	✓

	Healthcare and Frontline Workers											
Quality appraisal criteria	**Alali (2021)** [29]	**Bianchi (2021)** [30]	**Emborg (2021)** [31]	**Fowlkes (2021)** [43]– **updated analysis of Thompson (2021)** [47]	**Ghosh (2021)** [33]	**Giansante (2021)** [34]	**Issac (2021)** [35]	**Katz (2021)** [36]	**Muhsen (2021)** [37]	**Naito (2021)** [38]	**Uschner (2021)** [40]	**Yassi (2021)** [41]
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	CD	✓
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. For exposures that can vary in amount or level, did the study examine different	✓	✓	✓	✓	✓	✓	✓	X	X	✓	X	✓

	Healthcare and Frontline Workers											
Quality appraisal criteria	**Alali (2021)** [29]	**Bianchi (2021)** [30]	**Emborg (2021)** [31]	**Fowlkes (2021)** [43]– updated analysis of Thompson (2021)[47]	**Ghosh (2021)** [33]	**Giansante (2021)**[34]	**Issac (2021)**[35]	**Katz (2021)**[36]	**Muhsen (2021)** [37]	**Naito (2021)** [38]	**Uschner (2021)** [40]	**Yassi (2021)** [41]
levels of the exposure as related to 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?	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓
10. Was the exposure(s) assessed more than once over time?	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	X	✓

	Healthcare and Frontline Workers											
Quality appraisal criteria	**Alali (2021)** [29]	**Bianchi (2021)** [30]	**Emborg (2021)** [31]	**Fowlkes (2021)** [43]– updated analysis of Thompson (2021)[47]	**Ghosh (2021)** [33]	**Giansante (2021)**[34]	**Issac (2021)**[35]	**Katz (2021)**[36]	**Muhsen (2021)** [37]	**Naito (2021)** [38]	**Uschner (2021)** [40]	**Yassi (2021)** [41]
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	CD	✓	CD	✓	CD	CD	CD	✓	✓	X	CD	CD
12. Were the outcome assessors blinded to the exposure status of participants?	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD
13. Was loss to follow-up after baseline 20% or less?	✓	✓	✓	X	✓	✓	✓	✓	CD	CD	CD	✓
14. Were key potential confounding variables measured and	X	X	✓	✓	X	X	X	X	X	✓	X	X

	Healthcare and Frontline Workers											
Quality appraisal criteria	**Alali (2021)** [29]	**Bianchi (2021)** [30]	**Emborg (2021)** [31]	**Fowlkes (2021)** [43]– **updated analysis of Thompson (2021)** [47]	**Ghosh (2021)** [33]	**Giansante (2021)** [34]	**Issac (2021)** [35]	**Katz (2021)** [36]	**Muhsen (2021)** [37]	**Naito (2021)** [38]	**Uschner (2021)** [40]	**Yassi (2021)** [41]
adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?												
Quality Rating†	**Poor**	**Poor**	**Good**	**Fair**	**Poor**	**Poor**	**Poor**	**Fair**	**Fair**	**Poor**	**Poor**	**Poor**
Comment	No adjustment for confounders.	No adjustment for any potential confounders. Insufficient descriptions of population.	Primary review outcomes are less susceptive to outcome ascertainment bias.	Insufficient information given regarding loss to follow-up since original report by Thompson.	Limited adjustment for confounders. Limited description of population provided. Potential for outcome ascertainment bias.	Limited adjustment for confounders. Potential for outcome ascertainment bias.	No adjustment for confounders.	Some concerns regarding confounding.	Some concern regarding confounding.	No adjustment for confounders.	Self-reported vaccination status and lack of control for important confounders. Also lack of information on recruitment of participants.	Very limited adjustment for confounders. Insufficient information given on whether testing differed by vaccination status.

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

The quality appraisal of a case control study was assessed using: 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.A2: Quality appraisal of case control studies

	Healthcare and Frontline Workers
Quality appraisal criteria	**Pilishvili (2021) [42]**
1. Was the research question or objective in this paper clearly stated and appropriate?	✓
2. Was the study population clearly specified and defined?	✓
3. Did the authors include a sample size justification?	✓
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	✓
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	✓
6. Were the cases clearly defined and differentiated from controls?	✓
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	N/A
8. Was there use of concurrent controls?	✓
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

Quality appraisal criteria	Healthcare and Frontline Workers Pilishvili (2021) [42]
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	✓
Quality Rating†	Good
Comment	

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

Appendix B Data Extraction

Randomised Control Trials

Moderna

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Baden (2021)[27] **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	**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 %	**Severe Disease:** **≥14 days after second dose** *Severe Disease~* VE – 100% (95% CI NE to 100) *Hospitalisations #* Intervention – 0 Control – 9 *ICU admissions #* Intervention – 0 Control - 2 **Adjustments:** NA **Mortality** $ *COVID-19 related death* Intervention – 0	**Confirmed RT-PCR ≥14 days after second/final dose** *Symptomatic@* (PP) VE = 94.1% (95% CI 89.3 to 96.8%) *Symptomatic@* (FAS) VE = 93.6% (95% CI 88.6 to 96.5) **Adjustments:** N/A **Variants of Concern:** NR **Subgroups:** *Symptomatic infection by age @* ≥18 to <65 yr.

Time Period*:* 27 July 2020 to 21 November 2020. **Variants of Concern:** NR **Publication status**: Peer-reviewed		**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%[+]	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 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 = 95.6 (95% CI 90.6 to 97.9) ≥65 years VE = 86.4 (95% CI 61.4 to 95.2) ≥65 to ≤75 VE = 82.4% (95% CI 46.9 to 93.9) 75 and older [€] VE = 100% (95% CI NE, 100%) *Symptomatic infection by risk for severe COVID-19 [@]* At risk * VE = 90.9% (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) <u>≥ 2 risk factors *,%</u> 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% 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 - is defined 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) [28] **Title:** Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase **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	**Intervention/Exposure**: mRNA-1273 **Comparator/Control:** Placebo (Saline) **Time since final vaccination dose:** Median – 21.08 weeks (Duration of follow up from 0 to 220 days for 113 participants).	**Description:** Adults at least 18 years old with no known history of SARS-CoV-2 infection and whose locations or circumstances put them at appreciable risk of acquiring SARS-CoV-2 infection or who were at high risk for severe disease. **N:** Efficacy population - 28,451 FAS – 30,346 **Proportion of HCWs included in population:** Healthcare workers – 7,649 (25.2%) Emergency Response – 598 (2.0%) Personal Care and In-Home Services – 940 (3.1%) Pastoral, Social or Public Health Workers – 1,039 (3.4%) **Age:** (FAS) Mean – 51.4 (Range 18-95) **Male** (FAS) = 52.6% **Co-morbidities** (FAS)**:** Chronic Lung Disease – 4.8%	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* [%] VE = 98.2% (95% CI 92.8 to 99.6) *Hospitalisation*[*] Intervention – 1 Placebo – 27 *ICU admissions* Intervention – 0 Placebo - 4 **Adjustments:** N/A **Mortality** *COVID-19* VE = 100% (95% CI NE to 100) **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Confirmed RT-PCR infection (PP)** **≥14 days after second/final dose** [$] *Outcomes relevant to overall population:* *Symptomatic* VE = 93.2% (95% CI 90.9 to 94.8) *Asymptomatic* VE = 63.0% (95% CI 56.6 to 68.5) *Any* VE =82.0% (95% CI 79.5 to 84.2) *Outcomes relevant to HCW population:* *Symptomatic* *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)

				Pastoral, social, or public health workers VE = 97.6 (95% to 82.2 to 94.2) **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[$](PP) by comorbidity or risk group</u> *Chronic Lung Disease* VE = 87.2% (95% CI 63.8 to 95.5) **Efficacy/effectiveness over time** <u>To prevent symptomatic confirmed RT-PCR infection COVID-19[$](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 17.1 weeks or 113 patients at 31.3 weeks.
* Due to SARS-CoV-2 % Severe COVID-19 was defined as confirmed COVIC-19 plus one clinical sign of severe systemic illness				

$ Per protocol. COVID-19 cases were defined by at least 2 systemic symptoms (temperature ≥38°C, chills, myalgia, headache, sore throat, or new olfactory or taste disorders), or at least 1 respiratory sign or symptom (cough, shortness of breath, or clinical or radiologic evidence of pneumonia), and were confirmed by positive SARS-CoV-2 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.

Observational studies

Study characteristics	Intervention and Comparators	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Alali (2021)[29] **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	**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%	**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

Country: Kuwait **Setting:** Single 900-bed Public Hospital **Time Period:** 24 Dec 2020 to 15 June 2021 **Study Design:** Retrospective Cohort Study (with crossover) **Publication status**: Preprint		**Special populations**: HCWs: 100%		**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)[30] **Title:** BNT162B2 mRNA Covid-19 Vaccine Effectiveness in the	**Exposure**: BNT162b2 (Pfizer) **Comparator/Control:** No vaccine	**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	**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).	**Confirmed RT-PCR infection** **days after second/final dose** **Efficacy/effectiveness over time.**

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 **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	**Time since final vaccination dose:** Median 19.86 weeks	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) **Male** = *mRNA-1273 (Moderna)* 40.5% *Unvaccinated* 37.7% **Co-morbidities:** NR	**Adjustments:** NA **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	*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 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 2 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 Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Emborg (2021)[31] **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 **Variants of Concern:** NR	**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 84 (77; 90)	**Severe Disease:** **≥7 days after second/final dose** *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 VE: 23% (95% CI:-54% to 62%)	**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		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 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	**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): Thompson (a) (2021)[39] **Title:** Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines **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:	**Intervention/Exposure*** BNT162b2 vaccine (Pfizer-BioNTech) : 67% mRNA-1273 vaccine (Moderna): 33% **Comparator/Control:** unvaccinated **Time since final vaccination dose:** Fully Vaccinated: Median 11.86 weeks Unvaccinated: median 2.71 weeks	**Description:** Healthcare workers, first responders, frontline and essential workers. Swabbed weekly regardless of symptoms. previously seropositive status is considered a confounder **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%	**Severe Disease:** **≥14 days after second/final dose** *Severe Disease* 3 unvaccinated participants were hospitalized (no further analysis reported) *Hospitalisation* NR *ICU admissions* NR **Adjustments:**NR **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time.** NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection** **≥14 days after second dose** *Any* VE 91% (95% CI 76 to 97) **Adjustments:** Adjusted VE 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

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		**Male** = 38% **Co-morbidities:** ≥1 chronic conditions: 31%		**Subgroups** <u><50 years</u> 90% (95%CI 69–97) <u>≥50 years</u> 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)[43] **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	**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:**	**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)	**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* <u>*Vaccine Effectiveness*</u> Overall: 80% (95% CI 69 to 98) *Symptomatic* 89.7% of infections in unvaccinated were

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: 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)	Median 27 weeks (fully vaccinated) IQR (18.4 to 29.9 weeks)	**Age:** NR **Male** = NR **Co-morbidities:** NR		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* 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)

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): Ghosh (2021)[33] **Title:** COVISHIELD (AZD1222) Vaccine effectiveness among healthcare and frontline 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 Jan 2021 to 30 May 2021 (Interim Analysis) **Study Design***:* Cohort Study with Cross over **Variants of Concern:** NR **Publication status**: Peer-reviewed.	**Exposure**: ChAdOx1 (Covishield®) **Control:** No vaccination **Time since final vaccination:** Mean 8.38 weeks	**Description:** Healthcare workers and frontline workers of the Indian Armed forces (regardless of previous serological or previous COVID positive status) **N:** 1.6 million. 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	**Severe Disease:** NR **Mortality:** *All cause* VE: 98.53% (95% CI: 0.00 to 99.99) **Adjustments**: None **Subgroups:** NR **Effectiveness over Time:** NR	**RT-PCR or antigen Confirmed SARS-CoV-2 infection >14 days after second dose.** *Any* **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) [34] **Title:** COVID-19 vaccine effectiveness among the staff of the Bologna Health Trust, Italy, December 2020 – April 2021 **NCT:** N/A **DIO:10.23750/abm.v92i4.11896** **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:**	**Exposure**: mRNA vaccine **Control:** unvaccinated **Time since final vaccination dose:** Mean 11.67 weeks (sd NR)	**Description:** All the staff of the Bologna health trust (not only healthcare workers) Excluded: Subjects with a previously documented SARS-CoV-2 infection and subjects vaccinated with non-mRNA vaccines. Individuals with 0 follow-up days after vaccination **N:** 9,839 subjects (all staff of the Bologna health trust not only healthcare workers). 7,190 (73%) were health workers. **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	**Severe Disease:** **≥7 days after second/final dose** *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*	**Confirmed RT-PCR SARS-CoV-2 infection** **≥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:** Similar VE estimates were found when considering only healthcare workers. In healthcare workers: VE any infection

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			2 cases in unvaccinated and 0 in vaccinated **Efficacy/effectiveness over time:** NR	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): Issac (2021)[35] **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	**Exposure:** ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca) **Comparator/Control:** No vaccine **Time since final vaccination dose:** At least 15 weeks	**Description** HCWs in secondary care hospital. No information is given regarding previous infection. **N:** 324 healthcare workers *Vaccinated* 243 *Unvaccinated* 80 **Age:** *Vaccinated* mean 35.28 (SD ± 10.02) *Unvaccinated* mean 30.26 (SD ± 6.26)	**Severe Disease:** **≥14 days after second:** NR **Adjustments:** N/A **Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 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

Study Design: Prospective cohort study **Country**: India **Setting:** Secondary care hospital in South Indian state of Kerala **Time Period:** April 01 to 15 July 2021 **Variants of Concern:** NR **Publication status**: Preprint		**Male** = *Vaccinated* 20.16% Unvaccinated 3.75% **Co-morbidities:** 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 Effectiveness.

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Katz (2021)[36] **Title:** Covid-19 Vaccine Effectiveness in Healthcare Personnel in six Israeli Hospitals (CoVEHPI) **DOI:** doi.org/10.1101/2021.08.30.21262465;	**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.	**Severe Disease:** **≥7 days after second/final dose[Delete** *Severe Disease* NR *Hospitalisation* none of the symptomatic participants required hospitalization *ICU admissions* 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

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 **Publication status**: Pre-print		**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% Immunosuppression – 3%	**Adjustments:** NA **Mortality:** NR **Variants of Concern** NR **Subgroups** NR **Efficacy/effectiveness over time.** NR	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:** 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, 2 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:** 3 samples from infections identified in the primary analysis, and 2 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 7 days before and 5 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	Population and Patient demographics	Primary outcome results	Secondary outcome results

	Exposure and Controls			
Author (Year): Muhsen (2021)[37] **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 **DOI:** http://dx.doi.org/10.2139/ssrn.3885633 **NCT:** N/A **Study Design***:* Prospective Cohort Study (No Crossover) **Country**: Israel **Setting:** health care workers (HCWs) of LTC facilities **Time Period:** December 2020 – 11 April 2021 **Variants of Concern:** Alpha Dominant **Publication status**: Preprint	**Intervention/Exposure**: BNT162b2 vaccine (Pfizer/BioNtech) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Median fully vaccinated: 11.4 weeks Unvaccinated: 6.1 weeks	**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. *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	**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* 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 Effectiveness

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Naito (2021)[38] **Title:** Real-world evidence for the effectiveness and breakthrough of BNT162b2 mRNA COVID-19 vaccine at a medical center in Japan **DOI:** doi.org/10.1080/21645515.2021.1984124 **NCT:** N/A **Study Design**: Retrospective cohort study **Country**: Japan **Setting:** Hospital **Time Period**: Feb 1, 2020 and Jul 30, 2021 **Variants of Concern:** The Delta variant spread in the Tokyo metropolitan area	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) **Comparator/Control:** Unvaccinated **Time since final vaccination dose:** Maximum follow up 15.57 weeks	**Description:** All hospital employees, university faculty, students and administrative staff (medical staff) at Juntendo University Hospital. 2,809 frontline medical staff ultimately received vaccination. **N:** 8,749 **Age:** Mean age: 37.1 (SD 14.9) **Male** = 50.3% **Co-morbidities/Special Populations:** NR **Outcome measurement:** Temperature checks occur daily at the workplace, with symptoms suspicious for COVID-19 undergoing further examination.	**Severe Disease:** **14 days after final dose** NR	**Confirmed RT-PCR SARS-CoV-2 infection 14 days after final dose** *Any* June 19 cases Unvaccinated - 16 Fully vaccinated – 0 July [$] Unvaccinated – 11 Fully Vaccinated – 3 **Adjustments:** NR **Variants of Concern:** *Any* July 11 unvaccinated cases with mixed alpha and delta variants. **Subgroups**

began in early June **Publication status**: Peer-reviewed				NR **Efficacy/effectiveness over time.** NR
$ For medical staff who did not receive vaccines in March and April, vaccination using BNT162b vaccines started from July 1. An additional 13 cases were confirmed from those staff in July.				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Pilishvili (2021) [42] **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	**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:** Health care 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%)	**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	**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

clinics), and long-term care facilities (32%). **Time Period***:* 28 December 2020 to 19 May 2021 **Variants of Concern:** NR **Publication status**: Peer reviewed.		*Control* N=574 (17%) **Co-morbidities:** *Cases* Asthma –14% Immunocompromising condition [%] – 4% COPD – 0.3% *Controls* Asthma – 18% Immunocompromising condition [%] – 4% COPD – 1%	**Mortality:** NR **Variants of Concern:** NR **Subgroups**: NR **Efficacy/effectiveness over time:** NR	exposures to persons with COVID-19. **Variants of Concern:**NR **Subgroups** ≥1 underlying condition or risk factor[#] VE: 90.3% (95%CI 86.4% to 93.0%) ≥2 underlying conditions or risk factors[#] VE: 88.5% (95%CI 83.2% to 92.2%) ≥3 underlying 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 PCR testing, other nucleic acid amplification testing, or antigen-based testing

† Case participants were defined as health care personnel who had at least one Covid-19–like symptom and a positive result for SARS-CoV-2 on 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): Uschner (2021)[40] **Title:** Breakthrough SARS-CoV-2 Infections after Vaccination in North Carolina **DOI:**	**Intervention/Exposure**: BNT162b2 (Pfizer/BioNTech) mRNA-1273 (Moderna) Ad26.COV2.S (Janssen) **Comparator/Control:** • Age group • Vaccine type	**Description:** Fully vaccinated adults 18 years and older **N:** 16,020 **Age:** 18-44 – 33%	**Severe Disease:** **≥14 days after second/final dose** NR	**Confirmed RT-PCR or Antigen SARS-CoV-2 infection ≥14 days after second/final dose** *Any*

doi.org/10.1101/2021.10.10.21264812 **NCT:** NCT04342884 **Study Design***:* Prospective observational Study **Country**: US **Setting***:* Six healthcare systems **Time Period***:* January 15, 2021 to September 24, 2021 **Variants of Concern:** The study period included a statewide surge in cases driven by the Delta variant, with a comparable number of new cases as during the winter of 2020-21 **Publication status**: Pre-print Supplementary Appendix: No	• Healthcare worker/non-healthcare worker **Time since final vaccination dose:** Infected participants: Median: 24 weeks (IQR 17 to 28.4) Non-infected participants: Median: 23.6, IQR = (17.4-29.9)	45-64 – 47% 65+ - 20% **Male** = 26% **Co-morbidities/Special Populations:** **HCWs – 34%** **Outcome measurement:** The primary outcome was weeks until first self reported infection (positive SARS-CoV-2 antigen or nucleic acid amplification test) occurring ≥ 14 days after vaccination		310 (1.9%) self-reported a positive SARS-CoV-2 viral test at least 2 weeks following full vaccination Event rate was 7.3 breakthrough infections per 100,000 person-years Cumulative incidence was 5.2% at 34 weeks following full vaccination *Symptomatic* In 289 (92%) of cases **Adjustments:** Multivariate analyses were adjusted for; vaccination quarter before estimating HRs for breakthrough infection after vaccination. Age, sex, race/ethnicity, HCW status, vaccination brand, prior COVID-19 infection, Vaccination rate in county of residence (<60% or ≥60%), county classification (Urban, suburban or rural), mask usage **Variants of Concern:** NR **Subgroups** *Any infection by age[@]*

				>45 years vs. 18-44 years HR = 0.65 (0.51 to 0.82) 65+ years vs 18-44 years HR = 0.59 (0.39 to 0.9) *Any infection by vaccine type* Ad26.COV2.S vs BNT162b2 HR = 2.23 (1.40 to 3.56) mRNA-1273 vs BNT162b2 HR = 0.69 (0.50 – 0.96). HCWs vs non- HCWs HR = 1.33 (0.95 to 1.85) (p=0.0965) **Efficacy/effectiveness over time.** KMCs are presented for overall estimates, by vaccine and county setting
@ 92% of infections were symptomatic infections, defined as one or more self-reported symptom suggestive of COVID-19 ± 3 days from the date of a positive test				

Study characteristics	Intervention and Comparators Or Exposure and Controls	Population and Patient demographics	Primary outcome results	Secondary outcome results
Author (Year): Yassi (2021)[41] **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:** https://doi.org/10.1371/journal.pone.0254920**0** **NCT:** N/A **Study Design***:* Cohort study with crossover **Country**: Vancouver, Canada **Setting:** Healthcare provider.	**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) **Male** = NR **Co-morbidities:** NR	**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 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

Time Period: 15 December 2020 to 13 May 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				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 Effectiveness; VOC – Variants of concern.

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