Rapid review on protective immunity post COVID-19 vaccination: update 3

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Introduction

What do we know about protective immunity acquired from vaccination evidenced by breakthrough infections and markers of immunity ≥6 months post vaccination?

Understanding the extent and limits of protective immunity against COVID-19 has important implications for the COVID-19 pandemic and response. Immunity arising from infection with coronaviruses in general varies tremendously, from a few months for the seasonal coronaviruses associated with the common cold, to 2-3 years for the emerging coronaviruses such as SARS-

CoV-1 and MERS[1]. For SARS-CoV-2 (COVID-19), it is known that most people develop immune responses after receiving a full primary vaccination series (2 doses unless the primary series is a 1 dose vaccine e.g. Janssen), however, for how long and to what extent immune responses protect individuals from infection is not yet clear.

Previous versions of this report from February, April and August 2021 summarized the evidence on protective immunity post infection and post vaccination together and can be requested through ocsoevidence-bcscdonneesprobantes@phac-apsc.gc.ca. Due to the expanding evidence base, reviews on protective immunity post infection and post vaccination have been done separately in update 3 (Oct 2021) and will be done separately for subsequent updates. A separate review has been completed to look at protective immunity from SARS-CoV-2 infection, including the evidence on reinfection and correlates of long-term immunity post-infection (≥12 months). The current review addresses protective immunity from the primary series of vaccines, including the evidence on breakthrough infections and correlates of long-term immunity (≥6 months) from vaccination in individuals with or without a history of prior infection.

With the number of partially and fully vaccinated individuals increasing around the world, real-world data and research on infections is starting to emerge. There is some heterogeneity across studies in how "fully-vaccinated" and "breakthrough infection" are defined. In this review, articles were included if they reported data based on the CDC case definition of breakthrough infection: a person has SARS-CoV-2 RNA or antigen detected on a respiratory specimen ≥14 days after completing the primary series of a COVID-19 vaccine (e.g., two weeks post second dose of a two-dose vaccine or two weeks post first dose of a one-dose vaccine)[2]. Since the last update of this review, research on third doses and "booster doses" have been accumulating. As such, this review also captured data on breakthrough infections following third doses or boosters following the primary series.

There are also challenges in assessing long-term immunity against COVID-19 post-vaccination. This arises because immune responses are variable, not everyone vaccinated for COVID-19 develops detectable antibody levels and not all people with antibodies specific to SARS-CoV-2 antigens mount sufficient protective immunity. Evidence suggests that both neutralizing antibodies, B-cell (i.e., immune cells that produce virus targeting antibodies) and memory T-cell (i.e., immune cells that guide the cell mediated adaptive immune responses) activity specific to SARS-CoV-2 are currently the best indicators of protective immunity. However, the variation and interplay of antibodies, B and T-cell responses to infection and/or vaccination, as well as the variety of detection techniques complicates the assessment of long-term immunity.

This rapid review summarizes the evidence from recent studies on breakthrough infection post-vaccination, persistence of antibodies and other immune markers for ≥6 months following vaccination published before October 22, 2021. Due to the abundance of human data, animal models of disease and in vitro studies were not included.

Key points

There were 42 studies on breakthrough infection and 36 on the kinetics and durability of antibodies and other immunity markers at ≥6 months post-vaccination. The review is divided into two sections and two populations including breakthrough infections in people that were vaccinated with (n=3) and without (n=41) history of prior SARS-CoV-2 infection. As well as studies that capture immune response markers ≥6 months post full vaccination in people with (n=10) and without (n=26) history of prior infection. No studies captured evidence on immune correlates ≥6 months after a breakthrough infection following vaccination.

Breakthrough infections post primary series COVID-19 vaccination

Forty-two studies including randomized controlled trials, prospective cohorts and case control studies were summarized to estimate total number of breakthrough infections (i.e., asymptomatic and symptomatic) following a full primary vaccine series (Table 1).

- Breakthrough infections confirmed by RT-PCR among people with no history of COVID-19 occurred at variable rates (0.2-6.6%) across prospective studies conducted December 2020-August 2021 following full vaccination with the Comirnaty (Pfizer), Spikevax (Moderna), or Vaxzevria (AstraZeneca) vaccines[3, 4, 5, 6, 7, 8]. Studies that included infections determined via antigen detection reported higher breakthrough rates (8.6-26%)[9, 10].
- Vaccine effectiveness (VE) against overall infection were similar for original variants and Alpha (B.1.1.7)[11, 12, 13, 14, 15, 16, 17] and Beta (B.1.351) [12, 14, 17, 18]. Recent data has suggested that there are more breakthrough infections due to Delta (B.1.617.2) compared to other variants of concern (VOC) and the original variant[9, 15, 16, 19, 20, 21, 22, 23, 24]. VE estimates against Delta infections were lower compared to Alpha and higher for mRNA vaccines (Comirnaty/Spikevax: 66-79% Delta vs. 90-92% Alpha) than viral-vector based vaccines (Vaxzevria/Janssen: 51-67% Delta vs. 72-79% Alpha)[5, 16, 25, 26]. For more information on VE estimates against VOCs please refer to the living review maintained by COVID-END[27].
- Vaccinated individuals with a history of SARS-CoV-2 infection prior to vaccination had higher levels of protection against breakthrough infection compared to vaccinated individuals without a prior infection[11, 25, 28].
- There was a lot of variability in the risk of breakthrough infection between studies which are likely due to a combination of factors, such as what SARS-CoV-2 variants are circulating, stage of the epidemic within the study area, the level of immunity in the

study population, vaccine effectiveness, type of vaccine, administration protocol (e.g., interval between doses) and length of time since vaccination.

Immune response markers ≥6 months post full vaccination in individuals not previously infected

Twenty-six studies reported on circulating antibodies (n=26) or cellular immune activity (n=4) at 6-8 months post vaccination in participants that did not contract COVID-19 prior to vaccination, (Table 2).

Four studies on Comirnaty (Pfizer) and one study on Spikevax (Moderna) reported memory B-cell or T-cell responses at 6 months following a completed primary series of COVID-19 vaccination:

- Elevated T-cell (n= 3 studies) or B-cell (n= 2 studies) responses were detected in the majority of individuals at 6 months (42%-90% for T-cells)[29, 30]. Longitudinal sampling in some studies showed responses were still increasing and diversifying from earlier time points[29, 30, 31] or were reported as being maintained at 6 months[29].
- Two studies indicated decreasing CD8+ T-cells and increasing CD4+ T-cells at 6 months, which indicates development of immune memory B-cells[29, 30].
- One out of two studies that measured correlations at 6 months between T-cell levels and presence of antibodies showed a correlation[29], while the other did not find any correlations[30].

Twenty-six studies reported on circulating antibodies 6-9 months post primary vaccine series in people who had not had COVID-19 infection. The majority of studies reported that antibody levels had declined from peak, but were detectable for Spike (S) IgG and Receptor Binding Domain (RBD) IgG and neutralizing antibodies (NAb). There is some evidence that antibody titers are correlated with protective immunity, but the exact level of protection is uncertain[32, 33]:

- Studies comparing Comirnaty and Spikevax find that Spikevax recipients had higher initial antibody titers with slower declines up to 6 month post vaccination samples[34, 35].
- NAb titers were maintained in the majority of individuals in the 6-9 month post vaccination samples (57%-100%)[29, 36, 37, 38] and S-IgG or RBD-IgG was positively correlated with NAbs[29, 39, 40].
- NAb titers among nursing home residents who received Comirnaty were notably lower (30%) compared to NAb titres among 84% of the healthcare workers (HCWs) working in the nursing home who also received Comirnaty[38].
- Immunocompromised individuals had slightly lower seropositivity or titers than non-immunocompromised controls (79-90.2% vs 84-100% respectively) 6 months post a two dose primary series of vaccination with Comirnaty[40, 41, 42, 43]. These populations included

patients with cancer, dialysis, and multiple sclerosis with anti-S IgG seropositivity 6 months after vaccination at 90.2% for chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL) vaccinated with Comirnaty[42], 79% for patients with cancer receiving Comirnaty[43], and 56.1%-85.9% for patients on dialysis receiving either Comirnaty, Spikevax, or Janssen[35].

- Individual factors associated with seropositivity or NAb titers included a negative correlation of antibody titers with increasing age, but in most cases antibodies were still detectable at 6 months in individuals vaccinated with Comirnaty (n=4 studies), Spikevax (n= 2), and Jansen (n=1)[36, 37, 38, 40, 44, 45, 46, 47]. One study reported no difference (less than 10% difference in S-IgG levels) between those over 60 and under 60 years of age who received Comirnaty[48].

Immune response markers in previously infected individuals ≥6 months post primary series of COVID-19 vaccinations

Ten studies reported on immune response markers in previously infected individuals greater or equal to six month post primary series of COVID-19 vaccinations, Table 3. Cellular immune markers in vaccinated individuals who did not have COVID-19 infection history compared to vaccinated individuals who were previously infected showed the latter maintained their T-cell levels better in two studies and the frequency of B-cell populations or decay rates for T-cells was found to be the same in another study [29, 30, 39].

Antibody S-IgG and RBD-IgG titers) and NAb titers were generally higher in vaccinated individuals who were previously infected compared to individuals without history of prior infection[38, 39, 47, 49]:

- NAb titers were similar in vaccinated people with (81-100%) and without history of prior infection (57-100%) [29, 36, 37, 38].
- In three studies, at 6-7 months post vaccination, previously infected vaccinated individuals had a smaller decline in spike specific antigens and NAbs than those vaccinated who did not have a history of prior infection[39, 47, 50], while four studies reported no difference or higher antibody decay rates among those previously infected then vaccinated[29, 34, 38, 46].

The specific relationship between the correlates of immunity and protection against SARS-CoV-2 infection is not fully understood and additional data is needed to fill knowledge gaps.

Overview of the evidence

Breakthrough infection studies: Only data in which breakthrough infections occurred ≥14 days after completing the primary series of a COVID-19 vaccine were included in this review (as per

the CDC definition of breakthrough infection). This review focuses on the highest level of evidence: randomized controlled trials, prospective cohort studies and case control studies. Double-blind placebo-controlled trials are the gold standard for measuring the impact of an intervention, but do not necessarily provide an accurate estimate of how effective the vaccination will be in the real-world, nor are they as likely to occur during an ongoing pandemic scenario. Observational studies provide a real-world assessment of an intervention, but may also be at risk of more biases. These include the retrospective nature of case control studies and reliance on self-reported symptoms in many cohort studies. In cohort studies, people who get vaccinated may differ in health seeking behaviour (i.e., getting tested for SARS-CoV-2) than people who do not get vaccinated. Using a test-negative case control design can help minimize this type of bias, as both groups are seeking testing. Prospective cohort design in which participants are tested on a longitudinal basis also helps to minimize bias. Retrospective cohorts of medical record data or routinely collected surveillance data on COVID-19 were excluded from this review so the review could focus on studies with a lower risk of bias.

Long-term immunity studies mainly include longitudinal evidence from observational studies, particularly of prospective cohort, large case series and cross-sectional design, which are at moderate to high risk of selection biases and confounding factors. For example, most studies reported clinical infection severity among study participants, but many did not analyse or control for risk factors such as age, that may explain some of the heterogeneity in correlates of immunity. Differences in study participant demographics, baseline immune status, length of time from infection to vaccination, clinical severity of infections, investigated immune outcomes, follow-up time and measurement methods likely contributed to some of the observed heterogeneity. Variability may have come from the application of different antibody and immune cell detection methods with different test sensitivity and specificity parameters. All of these factors make it difficult to compare results across studies[51].

Knowledge gaps:

- Lack of understanding of how strong the correlation is between markers of immunity (e.g., neutralizing antibody titers) and protection from infection or severe disease and how vaccine mediated protection may be different than protection post infection.
- The role of specific antibodies, B-cells and T-cells in the preventing or clearing infection have not been definitively identified in humans.
- The majority of evidence on protective immunity against VOCs is on Alpha. Prospective studies are needed on the other emerging VOCs, particularly Delta and Omicron.
- Further evidence is required on waning immunity over time for all combinations of vaccinated and/or previously infected individuals, as well as what demographic variables and other risk factors may impact waning immunity.

Breakthrough infections post full vaccination

Although COVID-19 vaccines have been shown to be very effective at preventing severe disease, some vaccine breakthrough cases are expected. Evidence on the extent of vaccine protection against infection or severe illness from various VOCs is rapidly emerging and our understanding of vaccine immunity is evolving. The definition for breakthrough infection used in this review was based on the CDC case definition for breakthrough infection[2]: a person who has SARS-CoV-2 RNA or antigen detected on a respiratory specimen collected ≥14 days after completing the primary series of a COVID-19 vaccine (e.g., two weeks post second dose of a two-dose vaccine or two weeks post second dose of a one-dose vaccine). Studies that only included estimates of symptomatic or severe infection following vaccination, rather than the total number of breakthrough infections (i.e., asymptomatic and symptomatic) were excluded. High level points are listed below and detailed outcomes for each study are located in Table 1.

Vaccines used in the included studies on breakthrough infections included Comirnaty (Pfizer-BioNTech/ BNT162b2), Spikevax (Moderna/mRNA-1273), Vaxzevria (AstraZeneca/Covishield/ChAdOx1-S/AZD1222), Janssen (Johnson & Johnson/Ad26.COV2.S), and Bharat Biotech (Covaxin /BBV152)).

Five studies detailing findings from randomized controlled trials of vaccine efficacy reported that breakthrough infection within 0.5-6 months following two doses of vaccine is relatively low. The primary endpoints for many RCTs were symptomatic COVID-19 cases at least one week after 2nd dose; thus, did not meet our inclusion criteria:

- Spikevax (Moderna): In a US RCT with 5 months follow-up, infections were recorded in 2% of vaccinated individuals compared to 9.5% of unvaccinated (placebo) individuals[52]. Efficacy of the Spikevax vaccine against infection was 82.0% (95%CI 79.5-84.2) and did not wane over a 5 month period following the second dose[52].
- Vaxzevria (Astra Zeneca): In a UK RCT with up to 6 months follow-up, infections were recorded in 4% of vaccinated individuals compared to 8% of controls (who were vaccinated with the meningococcal vaccine MenACWY) [53, 54, 55]. The vaccine efficacy ranged from 73.5% (95%CI 55.5-84.2) in an early analysis of the trial data (May-Nov 2020) to 50.9% (95%CI 41.0-59.0) in a later analysis of the trial data (Oct 2020-Jan 2021)[53, 54, 55].
- BBV152 (Covaxin): In a trial from India with a 2-month follow-up period, infections occurred in 0.2% of the vaccine group and 0.9% or the placebo group[56]. Efficacy against asymptomatic infection, symptomatic infection, and Delta infection was 63.6% (95%CI 29.0–82.4), 77.8% (95%CI 65.2–86.4), and 65.2% (95%CI 33.1–83.0), respectively [56].

Thirty-seven observational studies of real-world vaccine effectiveness (VE) also demonstrate that breakthrough infection from original variants and the Alpha variant following two doses of vaccine is low during short term follow-up (0.5 -7 months). However, some VOCs are showing more concerning trends:

- Overall, unvaccinated subjects were at a significantly higher risk of developing infection as compared to fully vaccinated subjects (Vaxzevria RR=2.5; Vaxzevria and Comirnaty OR=2.7-10.9; Comirnaty HR=9.1)[3, 8, 9, 19, 26, 57, 58].
- Breakthrough infections were low following vaccination with the Comirnaty, Spikevax, and Vaxzevria vaccines.
    - Five prospective cohort studies of HCWs, with follow-up ranging from 2-6 months post vaccination with Comirnaty or Spikevax, reported that the incidence of RT-PCR confirmed infection was lower in the vaccinated HCWs (0.2-6.3% across studies) compared to the unvaccinated HCWs (2.2-7.5% across studies)[3, 4, 5, 6, 7]. For Vaxzevria in India, the incidence was 6.6% (vaccinated HCWs) vs. 43.8% (unvaccinated HCWs)[8].
    - Estimates of breakthrough infection were higher in studies that identified infections by the detection of SARS-CoV-2 antigen in a respiratory specimen. One prospective cohort study of HCWs in the US conducted between Mar-Aug 2021 found a high proportion of Comirnaty breakthrough infections (detected by SARS-CoV-2 nucleocapsid seroconversion) at 26.0% (59/227), similar to the unvaccinated HCWs at 23.5% (4/17)[10]. Another study (conducted between Jan-May 2021 in India), which characterized vaccine breakthroughs by either the detection of SARS-CoV-2 RNA or antigen, reported infection in 8.6% of fully vaccinated HCWs (Vaxzevria) vs. 21.5% of unvaccinated HCWs[9].
- Among HCWs in a prospective cohort, post infection immunity (85%) and post vaccination immunity (90%, Comirnaty or Vaxzevria 15-42 days post second dose) offered similar protection compared to the incidence of infections in the unvaccinated and not previously infected group[11]. Another cohort of HCWs found that infection after vaccination was rare (1.1% of HCWs, 20/1818) and significantly less frequent compared to reinfection after initial infection (9.5%, 8/84)[59]. In a UK general population study up to August 2021 there was no evidence that effectiveness of Vaxzevria was different than protection afforded by previous infection without vaccination ($p=0.33$), but protection from vaccination with Comirnaty was greater than protection from infection ($p=0.04$), and those previously infected and then vaccinated had the highest protection against new infection ($p<0.006$)[25].
- Comirnaty, Spikevax, and Vaxzevria VE against infection in the US, UK, and Israel were ≥80% between Dec 2020-Apr 2021[3, 5, 6, 11, 15, 25, 60, 61, 62]. However, lower vaccine

effectiveness of these vaccines has been reported in more recent studies: Comirnaty and Spikevax in the US was 66-74% in July/August 2021, Janssen in the US was 51% in July/August 2021, Comirnaty and Vazevria VE in the UK was 67-80% in May 2021, Spikevax and Vaxzevria VE in Spain was 66% Jan-Apr 2021, Comirnaty and Spikevax VE in Qatar was 54-87% Dec 2020-Jul 2021, Vaxzevria and Covaxin VE in India was 54-83% Jan-Jun 2021, and Coronavac/Biotec VE in China was 59% between May-Jun 2021 [5, 19, 23, 25, 26, 58, 63, 64, 65, 66]. This variability in VE may be related to multiple factors, such as stage of epidemic within the study area, level of immunity in the study population, administration protocols (e.g., interval between doses), length of time since vaccination, and an increase/change in VOCs.

- Preliminary evidence indicates that VE against infection is similar for original variants and Alpha[11, 12, 13, 14, 15, 16, 17]. VE against Beta may be slightly less compared to Alpha, but the difference was not statistically significant[12, 14, 17, 18]. A study from the US (Feb-Apr 2021) found that VOCs were overrepresented in mRNA breakthrough cases compared to cases in the unvaccinated population[67]. The frequency of all VOCs in breakthrough cases increased by 1.47-fold compared with that of SARS-CoV-2 sequences taken from a general sample of infections in the same area[67].
- Genomic analysis has revealed a rise of Delta variant in breakthrough infections since Apr 2021[9, 15, 19, 20, 21, 22] and studies have shown reduced vaccine effectiveness against the Delta variant compared to other variants; however, these results may be affected by increasing Delta cases, easing of public health restrictions, and increased time since primary series of vaccines during the analysis periods.
    - There was a higher risk of Delta breakthrough infection compared to Alpha in a study from Portugal (aOR=1.96, 95%CI 1.2-3.1)[21]. VE estimates against Delta infection were lower compared to Alpha in studies from Scotland (Comirnaty: 79% vs. 92%; Vaxzevria: 60% vs. 72%)[16] and the US (Comirnaty/Spikevax: 66%% vs. ~90%)[5]. One longitudinal household study from the UK, found that VE when Delta was dominant was not significantly different than when Alpha was dominant (Comirnaty: 80% vs. 78%; Vaxzevria: 67% vs. 79%)[25].
    - An increase in breakthrough infections has been particularly evident in Qatar[23, 24]. The percentage of all daily diagnosed SARS-CoV-2 infections that were vaccine breakthroughs (Comirnaty and Spikevax) increased over time and reached 36.4% in September 2021[24]. VE against infection declined to 20% 5-7 months after second dose of Comirnaty or Spikevax[24]. The dominant variant during the entire study period was Beta, but a similar pattern of waning of protection was also demonstrated for the recently dominant Delta variant.

- Evidence of waning immunity was modest in the US, with Delta VE decreasing from 94.1% (90.5-96.3%) 14-60 days after vaccination to 80% (70.2-86.6%) 151-180 days after vaccination[15].

Previously infected individuals that received a full primary series of vaccines have high levels of protection (n=3 studies):

- Vaccinating previously infected HCWs (96% reduction in incidence compared to the naïve group) was not significantly more protective than those fully vaccinated (90%) 15-42 days post vaccination or previously infected (85%)[11].
- A case control study of the general population in Kentucky found that previously infected individuals who were not vaccinated had 2.34 times the odds of reinfection compared with those who were fully vaccinated with Janssen, Comirnaty, or Spikevax[28].
- In a large longitudinal study of households in the UK, protection against infection was significantly higher for vaccinated individuals with prior infection than vaccinated individuals without prior infection (Comirnaty p=0.006 / Vaxzevria p<0.0001)[25].
- While not included in-depth in this review as they did not meet the specified inclusion criteria, multiple studies have also found that vaccinated individuals with a history of SARS-CoV-2 infection show high levels of protection from breakthrough infection[68, 69, 70].

One study was identified that investigated breakthrough infections following a booster dose after a primary series (n=1):

- Booster doses were reported in a study from Israel investigating third shots of Comirnaty[71]. Breakthrough infections in August occurred in 5.5% of individuals that had received 2-doses in January vs. 3.6% of individuals that received the booster in August[71]. Across a test-negative and matched case control analysis within the same study, they estimated a 70-84% reduction in the odds of testing positive 14-20 days after the booster compared to protection from the two dose primary series administered 6 months ago[71].

Immune response markers

This section summarizes 26 studies reporting on immune response markers longitudinally measured up to 8 months following vaccination in individuals with (n=10) and without (n=26) history of previous SARS-CoV-2 infection. The included studies were limited to studies that reported on >30 participants ≥6 months after vaccination with no prior (Table 2) or in those vaccinated after recovery from COVID-19 (Table 3).Twenty-six studies looked at circulating serum antibody levels after vaccination, and four studies reported on multiple cellular and humoral immune markers (i.e., B-cells and/or T-cells and antibodies) in the same sample of naïve – vaccinated individuals. Ten studies also reported immune markers in previously infected and vaccinated individuals.

Currently approved vaccines in Canada, Comirnaty (Pfizer-BioNTech/ BNT162b2), Spikevax (Moderna/mRNA-1273), Vaxzevria (AstraZeneca/Covishield/ChAdOx1-S/AZD1222), Janssen (Johnson & Johnson/Ad26.COV2.S), and Bharat Biotech (Covaxin /BBV152)), have been developed to target Spike protein including the RBD of SARS-CoV-2 and thus studies focus on positivity for these markers of immunity rather than nucleocapsid, membrane or envelope proteins[72, 73].

The majority of included studies were prospective cohorts or randomized controlled trials that took samples from vaccinated individuals over time. High-level points are listed below and detailed outcomes for each study are located in Table 2 and Table 3. Overall, there was considerable variability across outcomes and studies due to differences in study participants, frequency and duration of follow-up, investigated immune outcomes and measurement methods, which limit the synthesis of results across studies. Studies of infection prior to vaccination frequently did not report the interval from recovery to vaccination or infection severity and post vaccination immune correlates. Furthermore, the evidence is limited for associations between measured long-term immune markers and protection from infection in specific populations, such as children, the elderly, the immunocompromised (e.g., individuals with HIV) and immunosuppressed populations (undergoing cancer treatment or taking immunosuppressant treatments) from both the wild-type and emerging VOCs.

Outcomes reported included both cellular and humoral markers of immunity and a brief background to these markers is provided:

- Cellular immune markers include memory B-cells (i.e., immune cells that produce virus targeting antibodies) and memory T-cells (i.e., immune cells that guide the cell mediated adaptive immune responses) are considered to be indicators of long-term immunity[1, 74, 75]. T-cells are immune cells classified by surface receptors CD4+ or CD8+. The primary role of T-cells can be separated into the production of antibodies via B-cell activation (CD4+ T-cells) or the destruction of infected cells presenting certain antigens (CD8+ T-cells)[76]. Memory B-cells are a type of B lymphocyte that forms part of the adaptive immune system. The included studies isolated peripheral blood mononuclear cells (PBMCs) from serum samples then measured T-cell or B-cell numbers, phenotypes or activity after simulation with various SARS-CoV-2 peptide sequence pools (i.e., amino acids that make up viral proteins)[77, 78]. The variability and/or the lack of detail on peptide sequences used in stimulation studies limit the comparability of study results. Studies also report Interferon-γ (IFNγ), interleukin-2 (IL-2), and/or Tumor Necrosis Factor α (TNFα) from commercial kits to measure T-cell activity against antigens based on secreted cytokines[77].
- Humoral immunity, also called antibody-mediated immunity, generally refers to circulating antibodies that are directed at viral antigens[1, 74]. Among included studies,

circulating antibodies in serum samples were measured by antibody affinity assays, pseudovirus neutralization assays, flow cytometry, and other molecular biology-based techniques. Variation between assays was noted in several studies with large disagreement between results in some analyses; this is a source of between study heterogeneity[79, 80, 81, 82]. An example of this was a diagnostic test accuracy study that reported the Euroimmun assay had missed 40% of positives in 8 month samples compared to Roche assays [81]. The range of reported antibody outcomes included total antibodies, neutralizing antibodies (NAbs), antibody class (i.e., IgG, IgM, IgA) which were occasionally described by subclass (i.e., IgG1, IgG3), and/or binding affinity to SARS-CoV-2 viral antigens. Many studies often specified the viral antigen targets of the measured Ig antibodies, which mainly included viral structural proteins: spike (S) protein, S1 or S2 subunit of the S protein and receptor binding domain (RBD) proteins for vaccinated individuals as opposed to other targets, such as nucleocapsid (N), envelope (E), or membrane (M) proteins which are not present in many vaccines[73].

Immune response markers ≥6 months post primary series of vaccination in individuals with no history of prior COVID-19

Preliminary data on long-term markers of immunity ≥6 months post vaccination in individuals not previously infected, included 18 studies post Comirnaty vaccination, eight post Spikevax , two post Janssen, one Coronavac (Sinopharm), and two inactivated SARS-CoV-2 (not approved for use) vaccine studies. Most studies measured immune response markers up to 6 months. There were only 3 studies with data to 7 months and 1 studies with data to 8-9 months. Key results from included studies are listed below and detailed outcomes for each study are located in the Table 2.

Key outcomes from B-cell and T-cell immune responses at 6 to 7 months post vaccination (n=4) with Spikevax and Comirnaty demonstrate detectable and durable cellular immune responses[29, 30, 31, 39]:

- Two studies (Comirnaty n=2 and Spiekvax n=1) indicated stable or increasing antigen specific memory B-cell populations, which is a significant indication of an effective immune response[29, 31]. One US based study of a general population noted class switching between IgA+ and IgM+ B-cells 1 to 3 months after Comirnaty vaccination towards an increasing number and variety of antigen specific IgG+ B-cells[29].
- Reactivation of B-cells collected at 6 months showed strong S-IgG production, which was correlated to Spike+ memory B-cells detected by flow cytometry [29]. Additionally, humoral immunity (Spike and RBD-IgG) was correlated with cellular immune markers CD4+ and Th1 at 6 months[29]. Another study reported no correlation between antibodies and cellular immune markers[30].

- At six months after Comirnaty vaccination effector T-cell and TH1 levels were stable indicating durable memory T-cell responses which may have a limited change in magnitude or composition in response to booster vaccines[29]:
    - Two studies of Comirnaty vaccinated individuals indicated decreases in IFN-γ CD8+ T-cells with increases in IFN-γ CD4+ T-cells (memory B-cells) at 6 months which is a good indication of an effective immune response to vaccination[29, 30].

Key outcomes from humoral immune responses at 6 months post full vaccination (n=26 studies) reported the following:

- After 2 doses of Spikevax, the spike IgG antibodies and NAbs remained detectable and stable up to 6 months (n=8)[29, 35, 36, 49, 83, 84, 85].
    - Two publications from the same Spikevax (Moderna) trial report that antibodies remained detectable up to 6 months after the second dose and NAbs were present for almost all participants, however, lower levels of neutralization activity were observed in people over 55 years [36]. The other publication reported on neutralization of VOCs which ranged from 96% with Alpha and Delta to 54% with Beta[44].
    - A randomized control trial found Spikevax NAbs neutralized the original variant at 6 months, however 30%-45% of samples did not neutralize Beta, Gamma and Delta[83].
    - Among American patients on dialysis in a retrospective cohort, 14.1% of Spikevax recipients had seroreverted based on S-IgG levels at 6 months[35].
- After 2 doses of Comirnaty, Spike IgG, RBD IgG antibodies and NAbs decreased from peak at 1 to 3 months after the second dose but remained detectable at 3-7 months (n=18)[30, 31, 35, 38, 39, 40, 42, 43, 45, 46, 47, 48, 49, 86].
    - At 6 months 83.9-99% had detectable RBD-IgG antibodies[45, 47].
    - One study of 17 individuals with Comirnaty vaccinated and not previously infected indicated all individuals had detectable antibodies at 6 months [50].
    - NAb titers were highly maintained for at least 6 months in healthy populations (57%-100%)[29, 36, 37, 38].
- High risk populations that completed the primary series of Comirnaty with ≥6 months follow-up were reported in seven studies:
    - NAbs in nursing home residents at 6 months post vaccination were detectable in 30% of residents that did not have a history of COVID-19 infection[38]. There was also an 84% reduction in NAb, S-IgG and RBD-IgG titers at 6 months post vaccination[38]. A second study in nursing home residents found 100% of nursing home residents who had detectable antibodies (RBD IgG/IgM) at baseline had detectable antibodies at 6 months[30].

  - A US retrospective cohort that received Comirnaty reported 43.9% of patients on dialysis had seroreverted based on S-IgG at 6 months post vaccination[35].
  - A prospective cohort of patients with solid tumor had lower positive serology at 6 months compared with healthy controls (79% vs 84%) and 15% of patients with cancer had seroreverted[43].
  - An Israeli prospective cohort study of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) patients exhibited high level of response to vaccine with 90.2% anti-S IgG positive antibodies compared to 100% of healthy controls, 9.8% of CLL/SLL patients had seroreverted[42].
  - A cross-sectional study of 414 multiple sclerosis (MS) patients receiving treatment had lower S-IgG titers than MS patients not receiving treatment or heathy controls [41].
  - In one Israeli prospective cohort study found the probability of having low NAb titers (NAb titer <16) 6 months after being fully vaccinated was highest among immunosuppressed men ≥65 compared to healthy adults[40].
- Janssen:
  - In a randomized control trial of the Janssen vaccine 7 to 9 months after first dose resulted in higher levels of detectable NAbs for adults aged 18 to 55 (95%-100%) compared to older adults >65 (68-69%)[37]. 93% of adults and 86% of older adults had detectable S-IgG at 6 months[37].
  - A second US retrospective cohort study indicated that dialysis patients reached the lower limit of S-IgG detection at 6 month follow-up[35].
- Other vaccines:
  - 6 months after 2 doses of inactivated SARS-CoV-2 vaccine NAbs and S protein antibodies decline to 35.6%-51.7% and 52.1%-52.7% depending on the dosing schedule, respectively[87]. At 8 months another study reported NAbs were present in 48% of those vaccinated[88].
  - A single CoronaVac (Sinopharm) study found that NAbs declined from 100% to 12-22% at 6 months[89].
- Studies looking to find associations between immunity markers and demographic variables reported inconclusive results. Two studies indicated no difference in responses due to age, sex, or dose schedule[43, 88] while seven indicated lower antibody responses for older vaccine recipients at 6 months post second dose of vaccine[36, 37, 38, 40, 44, 45, 48].

Immune response markers in previously infected individuals ≥6 months post primary series of COVID-19 vaccination

Preliminary data on long-term markers of immunity ≥6 months post vaccination in individuals with evidence of a previous infection was included in 10 studies post Comirnaty vaccination,

three post Spikevax, and one post Janssen. High level points are listed below and detailed outcomes for each study are located in Table 3.

Two studies of the Comirnaty vaccine indicate T-cell titers were higher among previously infected vaccinees and they were more likely to have detectable T-cells at month 6 to 7 compared to those that had not had COVID-19 prior to vaccination[30, 39]. One US prospective cohort study of Spikevax and Comirnaty vaccine found T-cell responses were not significantly elevated in previously infected vaccinees compared to those that had not had COVID-19 prior to vaccination at 6 months[29].

- One Swedish prospective cohort study of 66 previously infected Comirnaty vaccinated healthcare workers indicated vaccinated individuals with a history of COVID-19 had at least 2-fold higher neutralization titers for Alpha, Beta, Gamma, and Delta than vaccinated individuals with no history of COVID-19[39].
- NAb titers were not dissimilar in previously infected vaccinees (81% - 100%)[29, 38] compared vaccines with no history of infection (57%-100%)[29, 36, 37, 38]. Larger differences in NAbs were seen among nursing home residents (65% in previously infected vaccinated individuals vs 30% in vaccinated individuals with no history of infection)[38].
- Two studies (Comirnaty and Spikevax) found no difference in either the decay rate post vaccination of S or RBD-IgG in previously infected and uninfected individuals[29, 34]. One prospective cohort study conducted in Italy of Comirnaty vaccinated healthcare workers reported antibody decay was faster among previously infected compared to uninfected individuals[46] and two prospective cohort studies of the Comirnaty vaccine reported slower declines in RBD-IgG, IgA, and IgM over time towards 6 months in the vaccinate and previously infected group compared to those with no history of infection[47, 50].

Review literature

Three relevant rapid and systematic reviews include COVID-19 research from up to July 2021 on correlates of immunity from vaccinated individuals (Table 4). These are included as resources for research on time points for immune markers earlier than 6 months and analyses of factors that correlate with a strong immune response to vaccination. There are also systematic reviews reinfection data including summaries of confirmed reinfections typically reported as case reports which are not included in this review.

Methods

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with

the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a Refworks database and an excel list that can be searched. Targeted keyword searching was conducted within these databases to identify relevant citations on COVID-19 and SARS-COV-2. Three separate searches were conducted to identify citations relevant to reinfection, breakthrough infections and immunity. Search terms used included:

Breakthrough terms (efficacy or effective* or breakthrough) across studies with the vaccine tag

immunity terms (month* or longitudinal) across studies with the immunology tag.

This review contains research published up to October 22, 2021.

Each potentially relevant reference was examined to confirm it had relevant data and relevant data was extracted into the review.

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Evidence tables

Table 1: Randomized controlled trials, prospective cohort and case control studies evaluating vaccine breakthrough infections (n=42)

Study	Method	Key Outcomes
Trials (n=5)		
El Sahly (2021) [52] **new** Randomized controlled trial US Jul 2020-Mar 2021	Phase 3, observer-blinded, placebo-controlled clinical trial of Spikevax. Included adult volunteers who were at high risk for Covid-19 or its complications and randomly assigned in a 1:1 ratio two intramuscular injections of Spikevax or placebo, 28 days apart, at 99 centers across the United States. The primary end point was prevention of Covid-19	• Infection occurred in 1,339/14,164 (9.5%) of participants in the placebo group and 280/14,287 (2.0%) of participants in the Spikevax group, for an efficacy of was 82.0% (95%CI 79.5-84.2). • The efficacy did not wane up to 4 months after the second injection and beyond.

Study	Method	Key Outcomes
	illness with onset at least 14 days after the second dose in participants who had not previously been infected. Asymptomatic infections were identified by seroconversion (antibody specific to nucleocapsid protein) as scheduled visits (months 1 and 2). Efficacy was estimated with a stratified Cox proportional-hazards model. Incidence rates and vaccine efficacy were estimated by 1 minus the hazard ratio (Spikevax vs. placebo), and the corresponding 95% confidence interval was based on the total number of cases adjusted according to total person-time. The duration of follow-up from the second dose was ~5 months.	
Feng (2021) [53] **new** RCT UK May 2020-Feb 2021	Data from a randomized efficacy trial of the Vaxzevria vaccine in the United Kingdom (COV002) was analyzed to determine the antibody levels associated with protection against SARS-CoV-2. Using data from this efficacy trial, the authors assessed the correlation between immune markers at 28 days post the second dose of Vaxzevria vaccination and symptomatic and asymptomatic infections. Participants with symptoms were assessed in clinic with a nose and throat swab taken for nucleic acid amplification testing. Additionally, participants were asked to complete a nose and throat swab at home each week, which was	• Among 4,372 participants that received Vaxzevria, there were a total of 174 breakthrough cases of SARS-CoV-2 infection (3.9%) during a 4-6 month follow-up period. Among 4,194 controls that received MenACWY vaccine there were 333 SARS-CoV-2 infections (7.9%). • The risk of symptomatic COVID-19 decreased with increasing levels of anti-spike IgG (P=0.003), anti-RBD IgG (P =0.018), pseudovirus neutralization titer (P=0.005), and live-virus neutralization titer (P<0.001). In contrast, there were no significant associations between any of the assays and protection against asymptomatic infection.

Study	Method	Key Outcomes
	used to detect asymptomatic infections.	
Emary (2021) [54] Randomized controlled trial UK Oct 2020- Jan 2021	Volunteers (aged ≥18 years) who were enrolled in phase 2/3 vaccine efficacy studies in the UK (COV002), and who were randomly assigned (1:1) to receive Vaxzevria or a meningococcal conjugate control (MenACWY) vaccine, provided upper airway swabs on a weekly basis and also if they developed symptoms of COVID-19 disease were included. Those receiving two standard doses (SD/SD group), or a low dose followed by a standard dose (LD/SD group) were included in the analysis. The efficacy analysis included symptomatic COVID-19 in seronegative participants with a NAAT positive swab more than 14 days after a second dose of vaccine. Asymptomatic infections and those with unknown symptoms detected through weekly swabbing were a secondary outcome.	• Between Oct 1, 2020, and Jan 14, 2021, 520/8534 participants developed SARS-CoV-2 infection. This included 173/4244 (4.1%) vaccinated individuals and 347/4290 (8.1%) controls. The overall efficacy estimate for all cases (n=520) was 50.9% (95%CI 41.0-59.0). • There were 75 cases of Alpha, including 21 in the vaccinated group and 54 in the control group, for a vaccine efficacy of 61.7% (95%CI 36.7-76.9). • There were 144 cases of other variants, including 27 in the vaccinated group and 117 in the control group, for a vaccine efficacy of 77.3% (95%CI 65.4-85.0). • Of the cases for which there were no sequence results (n=301), SARS-CoV-2 infection was noted in 125 vaccinated individuals and 176 controls.
Voysey (2021) [55] **new** RCT UK	This study presents data from three single-blind randomised controlled trials—one phase 1/2 study in the UK (COV001), one phase 2/3 study in the UK (COV002), and a phase 3 study in	• Vaxzevria vaccine efficacy. • There were 131 cases of symptomatic COVID-19 in LD/SD or SD/SD recipients who were eligible for inclusion in the primary efficacy analysis more

Study	Method	Key Outcomes
May 2020-Nov 2021	Brazil (COV003)—and one double-blind phase 1/2 study in South Africa (COV005). Only the UK (COV002) study included symptomatic and asymptomatic cases, thus only these findings are summarized herein. This trial included individuals working in professions with high possible exposure to SARS-CoV-2, such as health and social care settings and elderly (>59 years). MenACWY vaccine was used as the control. Those who met symptomatic criteria had a clinical assessment and a swab taken for a nucleic acid amplification test. To test for asymptomatic infections, participants provided a weekly self-administered nose and throat swab for NAAT testing. Efficacy against SARS-CoV-2 more than 14 days after a second dose of Vaxzevria vaccine was calculated from a Poisson model.	than 14 days after the second dose of vaccine: 30 (0.5%) cases among 5807 participants in the vaccine arm and 101 (1.7%) cases among 5829 participants in the control group, resulting in vaccine efficacy of 70.4% (95.8% CI 54.8–80.6) • In participants who received two standard-dose vaccines, vaccine efficacy was 62.1% (95% CI 41.0–75.7), whereas in those who received a low dose as their first dose of vaccine, efficacy was higher at 90.0% (67.4–97.0; $p_{interaction}$=0.010).
Ella (2021) [56] Preprint Randomized controlled trial India Nov 2020-Jan 2021	Phase 3 clinical trial in 25 Indian hospitals to evaluate the efficacy of the BBV152 COVID-19 vaccine. Healthy adults received two intramuscular doses of vaccine (n=12,221) or placebo (n= 12,198) administered four weeks apart. The primary outcome was laboratory-confirmed symptomatic COVID-19, occurring at least 14 days after the second dose. However, in addition to symptomatic follow-up, a series of post-dose 2 nasopharyngeal swabs were collected on-site for detection of asymptomatic	• 24 infections occurred in the vaccine group (0.2%, N=12,221) and 106 occurred in the placebo group (0.9%, N=12,198). • Efficacy against asymptomatic SARS-CoV-2 infections was 63.6% (95%CI 29.0–82.4). • Efficacy against symptomatic SARS-CoV-2 infections was 77.8% (95%CI 65.2–86.4). • Among 50 Delta confirmed cases, 13 and 37 participants were in the vaccine and placebo arms, resulting in vaccine efficacy of 65.2% (95%CI 33.1–83.0) against Delta.

Study	Method	Key Outcomes
	COVID-19 infection at monthly intervals (n=8,721)	
Observational studies (n=37)		
Moncunill (2021) [4] Preprint **new** Prospective cohort Spain Mar 2020- Aug 2021	This cohort included randomly selected HCWs at baseline. Participants were recruited at the peak of the first wave of the pandemic in Spain and attended several follow-up visits to assess antibody kinetics and information on infection. At month 12, most of the participants had received two doses of either mRNA vaccine (Comirnaty or Spikevax). They collected information on new SARS-CoV-2 infection episodes in this cohort until 6 months after vaccination (M18) through the Occupational Health department at the hospital.	• Among the 159 participants fully vaccinated with two doses, 10 (6.3%) vaccine breakthroughs were detected by rRT-PCR after 15 days post-second dose with a median of 144.5 days (49-189 days) post-vaccination. Among the 53 individuals non-vaccinated at M12, 4 (7.5%) had a SARS-CoV-2 infection in the same period of time.
Fowlkes (2021) [5] **new** Prospective cohort US Dec 2020-Aug 2021	Data from the HEROES-RECOVER Cohorts, a network of prospective cohorts among frontline workers, is reported. Workers were tested weekly for SARS-CoV-2 infection by reverse transcription–polymerase chain reaction (RT-PCR) and upon the onset of any COVID-19–like illness. Reports vaccine effectiveness (VE) estimates for Comirnaty and	During the total 35 week study period: • 2,976 participants contributed a median of 177 fully vaccinated days with 34 infections. 80.6% of breakthrough infections were symptomatic. • 4,136 participants (with no previous infection) contributed a median of 20 unvaccinated days per participant, during which 194

Study	Method	Key Outcomes
	Spikevax, and examines whether VE differs for adults with increasing time since completion of all recommended vaccine doses. Cox proportional hazards models were used to calculate ratios of unvaccinated to fully vaccinated (≥14 days after receipt of all recommended COVID-19 vaccine doses) infection rates, adjusted for occupation, site, and local viral circulation, and weighted for inverse probability of vaccination using sociodemographic characteristics, health information, frequency of close social contact, and mask use.	SARS-CoV-2 infections were identified. 89.7% of these infections were symptomatic. • Adjusted VE against infection was 80% (95%CI 69%–88%). The VE was 85% among participants for whom <120 days had elapsed since completion of full vaccination compared with 73% among those for whom ≥150 days had elapsed (difference was not statistically significant). During time period when Delta was dominant: • 2,352 fully vaccinated participants contributed a median of 49 days per participant, with 24 infections (75.0% symptomatic). • 488 unvaccinated participants contributed a median of 43 days with 19 SARS-CoV-2 infections (94.7% symptomatic). • Adjusted VE was 66% (95% 26%–84%) during Delta predominance compared with 91% (95% CI = 81%–96%) during the months preceding Delta predominance.
Laing (2021) [10] Preprint **new** Prospective cohort US Jan-Aug 2021	HCWs who had no history of COVID-19 were enrolled and followed in the Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) study. Participants were asked to obtain nasopharyngeal SARS-CoV-2 PCR testing upon experiencing symptoms. Asymptomatic infections were determined by nucleocapsid protein (NP) seroconversions (antigen testing) assessed monthly over 6 months	• Of vaccinated subjects, 26.0% (59/227) developed NP seroconversion between March and August of 2021. Two of these cases had symptomatic, PCR-positive vaccine breakthrough infection. The rest were deemed asymptomatic/pauci-symptomatic cases. • In the unvaccinated cohort, four (23.5%) participants were

Study	Method	Key Outcomes
	post full Comirnaty vaccination. Excluding individuals infected prior to January 31 of 2021, the study followed 227 participants fully vaccinated with BNT162b2 and 17 unvaccinated participants.	diagnosed with SARS-CoV-2 infection.
Novazzi (2021) [7] **new** Prospective cohort Italy Mar-Aug 2021	Fully vaccinated HCWs (all considered fully vaccinated in February 2021) who worked in 8 wards deemed to be at "high risk" had a mandatory RT-PCR test every 2 weeks (n=789), and those in 8 "moderate-risk" wards were tested every 4 weeks (n=1,387). If SARS-CoV-2 RNA was detected, the HCW was tested daily until 2 consecutive swabs were negative for SARS-CoV-2.	• During the 6 month study period, 33 (1.5%) asymptomatic and 8 (0.4%) symptomatic breakthrough infections were discovered. • All 33 asymptomatic case patients tested negative the day after the initial positive result, thus time to viral clearance was only 1 day. In contrast, symptomatic cases cleared after a mean of 11 days. The mean IgG level after vaccination was twice as high in the asymptomatic as the symptomatic group.
Shamier (2021) [20] Preprint **new** Prospective cohort Netherlands Apr 2020-Jul 2021	Healthcare workers were followed for primary and breakthrough infections (Comirnaty, Spikevax, Vaxzevria, or Janssen). Compared virological characteristics of first RT-PCR positive samples collected from HCWs with breakthrough infections (occurring between Apr-Jul 2021) to first RT-PCR positive samples from the same cohort of HCWs prior to the onset of vaccination (Apr-Dec 2020). Infections were classified as breakthrough infections if the date of the first positive SARS-CoV-2 RT-PCR was more than 14	• 161 breakthrough infections were identified from 22,169 vaccinated HCWs. • 90.5% of breakthrough infections for which a SARS-CoV-2 lineage could be identified were Delta.

Study	Method	Key Outcomes
	days after completion of all recommended vaccine doses.	
Issac (2021) [8] Preprint **new** Prospective cohort India Jan-Jul 2021	Prospectively evaluated 324 employees working in hospital throughout the study period of 170 days (January 27, 2021 - July 15, 2021). Of this population, 243 (75%) completed the full primary cycle of vaccination, i.e., completed 14 days post-vaccination with 2 doses of Vaxzevria vaccine, and 80 (25%) were not vaccinated. All the employees were under surveillance after vaccination to quantify the breakthrough infections (the symptomatic suspected cases, as well as the high-risk contacts of infected cases, were confirmed using RT-PCR screening). The cohorts were compared using a binary logistic regression and a time-dependent cox proportionality hazard model. The event time observed was the number of days from the second dose until a COVID-19 infection was confirmed. Covariates tested were age, sex, and contact exposure status.	• A total of 51 employees tested positive for COVID-19. 16 were fully vaccinated (breakthrough infections, all symptomatic, non requiring hospitalization) and 35 were unvaccinated. Thus, the percentage of infected in the vaccinated group was 6.58% and that in the unvaccinated group as 43.75%. • The median time between the second dose and the laboratory-confirmed COVID-19 infection was 65 (IQR: 20 - 91 days). • Cox proportionality model showed that age, sex, and the contact exposure status of the cohort were not significant factors for getting infected after being vaccinated, while binary logistic regression shows that a significant relationship exists between the incidence of infection and the unvaccinated status (p = 0.001, OR= 4.3). • Completing the full course of the vaccination decreased the risk of infection with the SARS-CoV-2 virus by 84.96%.
Ronchini (2021) [59] Preprint **new** Prospective cohort Italy	Healthcare workers at hospital sites in Milan were followed. Antibody testing was done every 4 weeks. PCR test was done after a positive serological test, in case of symptom, after holidays and every 2 weeks for medical doctors. Vaccinations started in January 2021 (follow-up time max	• Probability of infection after vaccination was less frequent compared to reinfection after natural infection. • 1.1% (20/1818) of fully vaccinated HCWs became infected >14 days after 2nd dose of Comirnaty.

Study	Method	Key Outcomes
May 2020-Jun 2021	for breakthrough infection was 5 months).	• Frequency of reinfection was 9.5% (8 reinfections out of 84 natural infections pre-vaccine roll-out).
Pouwels (2021) [25] **new** Prospective cohort UK Dec 2020-May 2021	Investigated the effectiveness of Comirnaty and Vaxzevria vaccines in a large, community-based follow-up study of randomly selected households (n=221909 Alpha Dec 1, 2020- May 16, 2021, n= 358983 Delta May 17– Aug 1, 2021). RT–PCR tests were performed after a pre-determined schedule, irrespective of symptoms every week for the first month and then monthly for 12 months from enrollment. At each visit, enrolled household members provided a nose and throat self-swab following instructions from the study worker. Outcomes investigated: variation in vaccine effectiveness by time from second vaccination, long-term health conditions, age and prior infection and assessed viral burden in new PCR-positive cases occurring ≥14 d after second vaccination using Ct values. Adjusted analysis for risk factors that also affect vaccination: patient-facing healthcare work, long-term health conditions, background 'force of infection', infection rates varying by age, calendar time and geographical region. Follow-up post second vaccination was median (IQR)	• There were 1,736 PCR positive cases >14 days after vaccination (1,415 (82%) of whom had ≥1 prior negative swabs after their second vaccination). • During the Alpha dominant time period (Dec 2020-May 2021) previously infected VE 60% (95%CI 50-68%), VE 14 days post 2nd dose of Comirnaty and Vaxzevria were 78% (95%CI 68–84%) and 79% (95%CI 56–90%), respectively. • During the Delta dominant time period (May 2021) previously infected VE 72% (95%CI 58-82%), VE among naïve/previously infected and vaccinated with Comirnaty 80% (95%CI 77–83%)/ 93% (95%CI 87-96%) and Vaxzevria 67% (95%CI 62–71%)/ 88% (95%CI 83-92%), respectively. There was no difference between VE for Alpha and Delta periods, but VE for previously infected and vaccinated individuals was significantly higher (p=0.006 Comirnaty / <0.0001 Vaxzevria). • There was no evidence that effectiveness varied by dosing interval (<6 weeks vs. ≥6 weeks) • There was no evidence that the effectiveness of two Vaxzevria doses differed from the protection afforded by previous

Study	Method	Key Outcomes
	Vaxzevria 41 days (27–57), Comirnaty 59 d (35-86).	natural infection without vaccination (p = 0.33), whereas two Comirnaty doses afforded greater protection (p = 0.04). • Protection against new PCR-positive cases was significantly higher for vaccinated individuals with prior infection than vaccinated individuals without prior infection for both vaccines (p<0.006). • Protection was higher in younger adults (18-34 vs. 35-64, p<0.001). • Over a 3 month follow-up a 22% (95%CI 6-41%) decline in VE per month for Comirnaty and 7% decline (95%CI 18% decline – 2% incline) for Vaxzevria.
Kale (2021) [9] Preprint Prospective cohort India Jan-May 2021	The study was conducted on HCWs (n=1858) receiving two doses of Vaxzevria vaccine. Serial blood samples were collected to measure SARS-CoV-2 IgG and neutralizing antibodies. A vaccine breakthrough infection was defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from an individual who had received either one or two doses of vaccine. Fully vaccinated was defined as HCWs who received two doses of vaccine and developed infection after 14 days of the second dose. 46 RT-PCR positive samples from breakthrough infections were subjected to whole genome sequencing (WGS).	• 1346/1858 (72.4%) HCWs were fully vaccinated. • Infection occurred in 116/1346 (8.62%) fully vaccinated HCWs vs. 47/219 (21.46%) of unvaccinated HCWs. • The non-vaccinated subjects were at a significantly higher risk of developing infection as compared to fully vaccinated subjects (RR 2.49 (95%CI 1.83-3.39) p=<0.001). • Genomic analysis revealed an alarming rise of Delta variant (B.1.617.2) in breakthrough infections (n=32/46 samples sequenced; 69.6%). • Reinfection after vaccination (i.e. infection in previously infected and vaccinated individuals) was documented in 4 (0.06%) HCWs, 6-8 months after the previous infection. These included two

Study	Method	Key Outcomes
		participants who had received 2 doses of Covishield (ChAdOx1) vaccine and 2 who had received a single dose of the vaccine.
Wickert (2021) [57] Preprint Prospective cohort US Mar-May 2021	Vaccine effectiveness at preventing infection was estimated by comparing infection risk as a function of time since vaccination in a cadet population (n=4200). Weekly surveillance testing using the Sofia SARS Antigen Fluorescent Immunoassay (FIA) provided infection point prevalence estimates. Asymptomatic individuals identified during surveillance testing and symptomatic individuals received RT-PCR based tests. Infection risk as a function of vaccination time status was determined by comparing the total person-days within the observation period and the total infection count, per 10,000 person-days for each vaccination group. At the end of the study period, 36% of cadets were fully vaccinated (defined as 14 days after the 2nd dose of Comirnaty).	• 2 cases of COVID-19 occurred in fully vaccinated cadets during the study period. • A statistically significant eleven-fold reduction of infection risk (OR 10.9) was observed in fully vaccinated cadets (p = 7x10-7). • The Alpha strain increased in prevalence during the study period. Both of the two breakthrough infections were Alpha variants.
Muhsen (2021) [3] Preprint Prospective cohort Israel Dec 2020-Apr 2021	Long-term care facility (LTCF) HCWs underwent weekly nasopharyngeal SARS-CoV-2 RT-PCR testing. Fully vaccinated (14+ days after second dose of Comirnaty; n=6960) and unvaccinated HCWs (n=2202) were followed until SARS-CoV-2 acquisition, or end of follow-up. Hazard ratios were calculated via	• 40 fully vaccinated HCWs acquired SARS-CoV-2 (median follow-up, 66 days; cumulative incidence 0·6%) vs. 84 unvaccinated HCWs (median follow-up 43 days; cumulative incidence, 5·1%). • Hazard ratio was 0·11 (95% CI 0·07, 0.17) and unadjusted

Study	Method	Key Outcomes
	Cox proportional hazards regression models, adjusting for socio-demographics and residential-area COVID-19 incidence.	vaccine effectiveness=89% (95% CI 83%, 93%). • During the study period the Alpha variant was most common.
Thompson (2021) [60] Prospective cohort US Dec 2020-Apr 2021	Prospective cohorts of healthcare personnel, first responders, and other essential and frontline workers (n=3,975) completed weekly SARS-CoV-2 testing. Self-collected mid-turbinate nasal swabs were tested by qualitative and quantitative RT-PCR. HCWs were considered fully vaccinated 14 days after second dose of either Comirnaty or Spikevax mRNA vaccines. Hazard ratios were estimated by the Andersen-Gill extension of the Cox proportional hazards model, which accounted for time-varying vaccination status.	• SARS-CoV-2 was detected in 204 (5.1%) participants, including 5 fully vaccinated individuals. • Adjusted mRNA VE of full vaccination was 91% (95%CI 76%–97%) against symptomatic or asymptomatic SARS-CoV-2 infection.
Martínez-Baz (2021) [63] Prospective cohort Spain Jan-Apr 2021	This study followed all individuals aged ≥ 18 years covered by the Navarre Health Service, who had been close contacts of laboratory-confirmed COVID-19 cases from January to April 2021. Close contacts were tested by RT-PCR for SARS-CoV-2 initially and 10 days after the last contact. Cox regression provided estimates of the crude and adjusted relative risks. Adjusted models included age groups, sex, major chronic condition, contact setting	• The cohort included 20,961 close contacts, 491 of which were fully vaccinated. • There was 62 cases of breakthrough infections among 512 close contacts (61 vaccinated with Comirnaty and 1 with Spikevax). • Comirnaty VE against SARS-CoV-2 infection was 66% (95%CI 57-74). • Median time from vaccination to breakthrough infection was 43 days.

Study	Method	Key Outcomes
	(household or other) and month. Contacts were considered fully vaccinated 14 days after second dose of Comirnaty or Spikevax.	
Thompson (2021) [61] Prospective cohort US Dec 2020-Mar 2021	Prospective cohorts of health care personnel, first responders, and other essential and frontline workers in eight U.S. locations were included. Active surveillance for symptoms consistent with COVID-19–associated illness occurred through weekly text messages, e-mails, and direct participant or medical record reports. Participants self-collected a midturbinate nasal swab weekly, regardless of COVID-19–associated illness symptom status and collected an additional nasal swab and saliva specimen at the onset of COVID-19–associated illness. Vaccine effectiveness was analyzed in participants with full immunization of two doses of mRNA COVID-19 vaccines (Comirnaty and Spikevax.	• Overall, 3,950 participants in the vaccine effectiveness analytic sample were analyzed. • Three PCR-confirmed infections occurred during 78,902 person-days with full immunization (≥14 days after second dose; incidence rate = 0.04/1,000 person-days). • Vaccine effectiveness of full immunization with two doses of mRNA vaccines was 90% (95% CI = 68%–97%) protective against RT-PCR–confirmed SARS-CoV-2 infection.
Katz (2021) [6] Preprint **new** Prospective cohort Israel Dec 2020-Feb 2021	Followed HCWs in 6 hospitals to estimate the effectiveness of the Comirnaty COVID-19 vaccine in preventing SARS-CoV-2 infection. Participants filled out weekly symptom questionnaires and provided weekly nasal specimens. VE against PCR-confirmed SARS-CoV-2 infection was calculated using the Cox Proportional Hazards model. Estimated VE >14 days after receipt of the second	• Of the 1,250 participants in the analysis, 998 (79.8%) were vaccinated before or at enrollment. • Fully vaccinated individuals contributed 61,620 Person Days of follow-up and unvaccinated participants contributed 10,027. • Breakthrough infections occurred among 4 vaccinated participants. Infections occurred among 9 unvaccinated participants.

Study	Method	Key Outcomes
	vaccine dose. Only included participants who were seronegative at enrollment and did not have PCR-confirmed SARS-CoV-2 infection at or prior to enrollment.	• Adjusted VE was 94.5% (95%CI 82.6%-98.2%).
Lumley (2021) [11] Prospective cohort UK Sep 2020-Feb 2021	Healthcare workers (HCWs) (n=13,109) were followed to investigate and compare the protection from SARS-CoV-2 infection conferred by 2 doses of vaccine (by either Comirnaty vaccine or Vaxzevria vaccine) with onset at least 14 days after the second injection. Protection from prior infection was also examined (Results in Table 1). Staff remained at risk of infection until the earliest of the study end, or a positive PCR test. To assess the impact of the Alpha variant on (re)infection risk, they analysed PCR-positive results with and without S-gene target failure (SGTF), and those confirmed as Alpha on genome sequencing. Protection was calculated as 100*(1-IRR).	• In total there were 940 previously seronegative HCWs followed after a second dose of either Comirnaty vaccine or Vaxzevria vaccine (39,222 person-days follow-up). • Vaccination reduced the incidence of any PCR-positivity compared to the unvaccinated group by 90% more than 14 days post 2nd vaccine dose (aIRR=0.10, 95%CI 0.02-0.38; p<0.001), by 85% (aIRR= 0.15, 95%CI 0.08–0.26, p<0.001) post-natural infection and by 96% in vaccinated previously seropositive HCWs (aIRR=0.04 (95%CI: 0.01-0.27; p=0.001). There was no statistical difference in protection between the three groups. • Effect of VOC estimates were only calculated after a first dose of vaccine. There was no evidence that SGTF or Alpha changed the extent of protection against any PCR-positive infection in previously seronegative HCWs after a first vaccine (p>0.05).

Study	Method	Key Outcomes
Patalon (2021) [71] Preprint **new** Test negative case control Israel Jan-Aug 2021	The study population consisted of Maccabi Healthcare Services (MHS) members, aged 40+, who received either two or three doses of the Comirnaty vaccine. Second doses were typically administered in January and booster doses in August, end of follow up was August 21st, 2021. Participants were excluded if they tested positive for SARS-CoV-2 before the start of the follow-up period. A test-negative case control analysis sought to estimate the reduction in the odds of a positive test at different time intervals following receipt of the booster (third) dose (0-6 days, 7-13 days, 14-20 days) compared to two-dose only vaccinees. Covariates included the 10-year age category, biological sex, time since receipt of the 2nd dose, and comorbidities. A matched case control design was also conducted. Cases were defined as individuals with a positive PCR test occurring after August 1, 2021, among those 40 years of age or older who did not have a previous positive test recorded and who received at least two doses of the vaccine. Up to 20 controls per case were drawn from the entire population.	• During the period when the booster was available (August 2021), 8,285/149,379 total tests (5.5%) were positive for SARS-CoV-2 in the two-dose group and 1,188/32,697 (3.6%) were positive in the three-dose group. • Across the test-negative and matched case control analyses, they estimated a 48-68% reduction in the odds of testing positive for SARS-CoV-2 after 7-13 days and 70-84% 14-20 days after the booster compared to two doses.
Chemaitelly (2021) [24] **new** Test negative case control	Estimate vaccine effectiveness against any SARS-CoV-2 infection for Comirnaty. Authors define breakthrough as any infection following any dose no matter the time frame but present study	• Between December 21, 2020, and September 5, 2021, a total of 907,763 people completed the two-dose regimen of Comirnaty and 494,859 completed the two-dose regimen of SpikeVax.

Study	Method	Key Outcomes
Qatar Dec-Sep 2021	findings separately for post 1st and 2nd dose and beyond. Comirnaty effectiveness was assessed against Alpha, Beta, and Delta infections separately to investigate whether declining effectiveness could have been confounded by exposure to different variants over time. Case participants (PCR-positive persons) and controls (PCR-negative persons) were matched one to one according to sex, 10-year age group, nationality, reason for SARS-CoV-2 PCR testing, and calendar week of PCR test.	• At the end of the study period, a total of 10,543 Comirnaty breakthrough infections had been recorded among participants who received two doses. 106 were categorized as "severe". • The percentage of all daily diagnosed SARS-CoV-2 infections that were vaccine (Comirnaty or Spikevax) breakthrough infections increased gradually over time and reached 36.4% on September 5, 2021. Most vaccine breakthrough infections (77.2%) were recorded for the Comirnaty vaccine. • VE reached its peak at 77.5% (95%CI 76.4-78.6) in the first month after the second dose. • Effectiveness declined gradually thereafter, with the decline accelerating after the fourth month to reach approximately 20% in months 5 through 7 after the second dose. • Estimated effectiveness against infection with each VOC showed a pattern similar to that seen against any SARS-CoV-2 infection. Thus, it is unlikely that waning of protection was confounded by exposure to different variants at different time points.
Bruxvoort (2021) [15] Preprint **new**	Whole genome sequencing was conducted for SARS-CoV-2 positive specimens to determine Spikevax effectiveness against Delta, Mu and other VOCs. Test-	• Among Delta cases, 232 (11.4%) were fully vaccinated. Among matched controls, 4,588 (45.3%) were fully vaccinated. In comparison, 0.9% of Alpha cases

Study	Method	Key Outcomes
Test negative case control US Mar-Jul 2021	positive cases (n=8,163) were matched 1:5 to test-negative controls on age, sex, race/ethnicity, and specimen collection date. Conditional logistic regression was used to compare odds of vaccination among cases versus controls, adjusting for confounders. Analyses of VE by time since receipt of second dose of Spikevax (14-60 days, 61-90 days, 91- 120 days, 121-150 days, 151-180 days, and >180 days) were conducted for Delta (overall and by age), non-Delta variants, and unidentified variants.	and 24.4% of Alpha controls were fully vaccinated. • Overall two-dose VE against infection was 86.7% (95%CI 84.3-88.7%) against Delta, 98.4% (96.9-99.1%) against Alpha, 90.4% (73.9%-96.5%) against Mu, 95.5-97.6% against other identified variants (e.g., Epsilon, Gamma, Iota), and 79.9% (76.9-82.5%) against unidentified variants (cases where WGS failed). • VE against Delta was lower among individuals aged ≥65 years (75.2%, 59.6-84.8%) than those aged 18-64 years (87.9%, 85.5-89.9%). • Only 5 fully vaccinated Delta cases were hospitalized. No fully vaccinated non-Delta cases were hospitalized. • Evidence of waning immunity was modest: • Delta VE: 94.1% (90.5-96.3%) 14-60 days after vaccination to 80.0% (70.2-86.6%) 151-180 days after vaccination. • Non-Delta VE: 98.6% (97.3-99.3%) at 14-60 days to 88.7% (73.2-95.2%) 121-150 days after vaccination. • Unidentified variants VE: 83.6% (79.5-86.9%) at 14-60 days to 68.5% (51.3-79.6%) 151-180 days after vaccination.

Study	Method	Key Outcomes
Tang (2021) [23] Preprint **new** Test negative case control Qatar Dec 2020-Jul 2021	Between December 21, 2020 and July 21, 2021, 877,354 individuals completed the two-dose regimen of Comirnaty and 409,041 completed the two-dose regimen of Spikevax. Vaccine effectiveness was estimated against documented infection (defined as a PCR-positive swab regardless of the reason for PCR testing or presence of symptoms) with the Delta variant. Cases and controls were matched one-to-one by sex, 10-year age group, nationality, reason for SARS-CoV-2 polymerase chain reaction (PCR) testing, and calendar week of PCR test.	• By the end of the study, 249 Delta breakthrough infections had been recorded among the 877,354 individuals who received two doses of Comirnaty (4 severe) and 26 breakthrough infections had been recorded among the 409,041 individuals who received SpikeVax (0 severe). • Comirnaty effectiveness against infection with Delta was 53.5% (95%CI 43.9- 61.4%). The corresponding effectiveness for Spikevax was 84.8% (95%CI 75.9-90.8%), and for vaccination with either mRNA vaccine, it was 57.2% (95%CI 48.9-64.1%).
Barlow (2021) [26] **new** Test negative case control US Jul 2021	Estimate the effectiveness of vaccination against SARS-CoV-2 infection during July 2021 (when Delta was dominant). 500 case control pairs were matched (n=1000). Cases included a random sample of individuals that tested positive for SARS-CoV-2 in July 2021 and were reported by electronic laboratory report, were >15 years of age, and had no prior known SARS-CoV-2 infections. Controls were age and postal code matched individuals that tested negative for SARS-CoV-2 during July 2021. Vaccinations were considered invalid if they were administered <14 days prior to the case's positive test collection date.	• 202/500 (40.4%) "cases" and 323/500 (64.6%) "controls" were fully vaccinated. • Both mRNA immunizations (Comirnaty and Spikevax) had similar protective effects against infection (OR 0.3, 95%CI 0.15-0.35, p<0.001). VE for mRNA vaccines was 74% (95%CI 65-82%) • Janssen protective effect was slightly reduced (OR 0.5, 95%CI 0.24-1.02, P=0.60) for a VE of 51% (95%CI -2-76%). • Note: Vaccine interval (last dose to case test date) was 102 days (IQR 74-136) in cases.

Study	Method	Key Outcomes
Singh (2021) [58] **new** Test negative case control India Apr-Jun 2021	Vaccine effectiveness of vaccination was investigated. The vaccines administered at the time were Vaxzevria and Covaxin. This case control study was conducted among people aged ≥45 years. The cases were the COVID-19 patients who were admitted or visited the All India Institute of Medical Sciences (AIIMS) flu clinic. The controls were the individuals tested negative for severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) at the Virology laboratory. This was an unmatched case control study, but logistic regression analysis was adjusted for age, sex, occupation, COVID-inappropriate behaviour score, chronic co-morbidity, H/O hospitalisation, ILI, prior COVID-19 and high-risk contact with a case or suspect.	• A total of 577 cases and 1154 controls were selected during the study period and considered for the final analyses. 33 cases (14.1%) vs. 201 (85.8%) of controls were fully vaccinated. 26 (78.8%) cases had symptomatic infection. • aVE was 83.0% (95%CI 73.0–89.0%) for preventing SARS-CoV-2 infection. The adjusted odds ratio for infection among fully vaccinated individuals was 0.17 (95%CI 0.11-0.27). Four out of every five fully vaccinated individuals are estimated to be protected from SARS-CoV-2 infection. • A sub-group analyses of the cases found that the length of hospital stays (LOS) and the severity of the disease were significantly lower among vaccinated compared to unvaccinated individuals.
Li (2021) [66] **new** Test negative case control China May-Jun 2021	Estimate vaccine effectiveness of two SARS-CoV-2 inactivated vaccines (China National Biotec Group SARS-CoV-2 vaccine and the CoronaVac vaccine) against infection or pneumonia associated with the Delta variant. Defined the second-dose vaccination (fully vaccinated) as having elapsed for more than 14 days after the second dose upon the clinical diagnosis (for cases) or the last contact with the cases (for contacts).	• Seventy-four test-positive cases and 292 test-negative controls were included in the final analysis. Of the 74 cases, 10 (13.5%) were breakthrough infections. • After adjusting for age and sex, the overall VE for two-dose vaccination was 59.0% (95%CI 16.0%-81.6%) against infection.

Study	Method	Key Outcomes
Sheikh (2021) [16] Test negative case control Scotland Apr-Jun 2021	Estimate vaccine effectiveness (Comirnaty and Vaxzevria) against risk of SARS-CoV-2 infection. S gene-positive detection was used as a proxy for Delta identification and S-gene negative detection was representative of Alpha. Vaccine effectiveness estimates were obtained from a generalised additive logistic model adjusting for age, temporal trend when the swab was taken, and number of previous tests using splines plus sex and deprivation.	• There were 19,543 confirmed SARS-CoV-2 infections over the period of interest. 7723 (39.5%) of these cases were in those who were S gene-positive (i.e., Delta cases). • Breakthrough S gene-negative (Alpha) infection occurred in 104/53575 individuals vaccinated with Comirnaty and 100/32588 individuals vaccinated with Vaxzevria. Alpha infection occurred in 5828/119419 unvaccinated individuals tested. Breakthrough S gene-positive (Delta) infection occurred in 208/53679 individuals vaccinated with Comirnaty and 231/32719 vaccinated with Vaxzevria. Delta infection occurred in 3672/117263 unvaccinated individuals tested. • Comirnaty VE was 92% (95% CI 90–93) against S gene-negative (Alpha) and 79% (75–82) S gene-positive (Delta). • Vaxzevria VE was 73% (95% CI 66–78) for S gene-negative cases (Alpha) versus 60% (53–66) for those S gene-positive (Delta). • This analysis is limited by an increasing trend in vaccination and Delta cases over time.

Study	Method	Key Outcomes
Butt (2021) [64] Test negative case control Qatar Dec 2020-May 2021	Determined the vaccine effectiveness of mRNA vaccines (Comirnaty and Spikevax) in preventing confirmed SARS-CoV-2 infection in pregnant women at a national referral hospital ≥14 days after the second dose of the vaccine. For each woman who tested positive, they identified up to 3 RT-PCR negative controls matched on age and reason for testing. Authors did not match the cases and controls for the time of testing.	• The study group in this analysis included 16 vaccinated and 370 unvaccinated cases ("test-positive" group) and 87 vaccinated and 747 unvaccinated controls ("test-negative" group). • Of the 16 vaccinated PCR-positive women, 2 were infected ≥14 days after dose 2. Vaccine effectiveness >14 days after the second dose was 86.8% (95%CI 47.5-98.5). • Of all infections diagnosed in these pregnant women, 74 were Alpha variant, 182 were Beta variant, and 130 were unknown variants.
Chemaitelly (2021) [12] Test negative case control Qatar Dec 2020-May 2021	With essentially only Beta and Alpha cases identified in the viral genome sequencing and the multiplex RT–qPCR variant screening conducted on cases between 8 March and 10 May 2021, an Alpha infection was proxied as an S-gene target failure case and a Beta infection as an S-gene target positive case. Spikevax COVID-19 Vaccine effectiveness analyses against Alpha were performed using independent samples of n=21,305 PCR-positive cases and n=21,305 PCR-negative controls while VE analyses against Beta were performed using n=44,737 PCR-positive cases and n=44,737 PCR-negative controls.	• 0 Alpha and 6 Beta breakthrough infections were recorded. • Effectiveness against Alpha infection was 100% (95% CI: 91.8–100.0%) ≥14 days after the second dose of Spikevax. • Effectiveness against Beta infection was 96.4% after the second dose of Spikevax (95% CI: 91.9–98.7%).

Study	Method	Key Outcomes
Pramod (2021) [65] Preprint Test negative case control India Jan-May 2021	Information on vaccination status (Covishield) of cases with COVID-19 among healthcare workers and an equal number of matched controls, (i.e., positive and negative for SARS-CoV-2 by RT-PCR), was obtained. The cases and controls were matched for age and date of testing (n=360 case control pairs). The groups were compared using multivariable conditional logistic regression to calculate odds ratios (OR), adjusted for gender, occupational role, presence of symptoms and presence of a comorbidity condition.	• 98 breakthrough infections were recorded among the 360 cases. • VE against COVID-19 >14 days post 2nd dose was 54% (27%-71%). • Delta was the dominant variant circulating in this area during the study period.
Abu-Raddad (2021) [17] Test negative case control Qatar Feb-Mar 2021	Data for SARS-CoV-2 were extracted from Qatar's nationwide digital-health information platform. Cases and controls were matched one-to-one by age, sex, nationality and reason for PCR testing. Effectiveness was estimated against documented infection with the Alpha or Beta variants.	• 333,764 individuals received at least one Comirnaty vaccine dose, of whom 250,619 completed two doses. • ≥14 days after the second dose, among cases with Alpha, 50 were vaccinated (breakthrough infections) and 16,354 were unvaccinated. Among cases with Beta, 179 were vaccinated and 19,396 were unvaccinated. • Effectiveness was 89.5% (95% CI: 85.9–92.3) against Alpha and 75.0% (95% CI: 70.5–78.9) against B.1.351.

Study	Method	Key Outcomes
Thiruvengadam (2021) [19] Preprint Test negative case control India Apr-May 2021	Determined the vaccine effectiveness of Vaxzevria vaccine in preventing confirmed infection during a surge of Delta infections in India. Cases were RT-PCR positive for SARS-CoV-2 infection (n=2766). The controls (n=2377) were selected randomly from the individuals who tested negative and were matched in numbers for each calendar week of testing during the study period. Defined complete vaccination as when the participant had completed at least 14 days after the second dose of the vaccine. Adjusted odds ratio (aOR) was estimated by a multivariable logistic regression model which included confounders.	• Genomic analysis determined that 90% (121/133) of the infections for which sequence data was available were due to the Delta variant. • Among cases, 3.1% were fully vaccinated compared with 7.1% among controls giving an adjusted OR of 0.37 (95%CI 0.28, 0.48); • The vaccine effectiveness was 63.1% (95%CI 51.5-72.1) vaccine effectiveness against SARS-CoV-2 infection. • Only one breakthrough infection led to severe disease.
Andrejko (2021) [62] Test negative case control US Feb-Apr 2021	Enrolled cases (testing positive, n=525) and controls (testing negative, n=498) from among the population whose SARS-CoV-2 molecular diagnostic test results were reported to the California Department of Public Health. Participants were matched on age, sex, and geographic region. Assessed participants' self-reported history of mRNA-based COVID-19 vaccine receipt (Comirnaty and Spikevax). Participants were considered fully vaccinated two weeks after second dose receipt.	• Among cases, 20 (3.8%) were fully vaccinated with either Comirnaty or Spikevax. Among controls, 86 (16.3%) were fully vaccinated. • Two weeks after second dose receipt, VE was 87.0% (95%CI 68.6-94.6%) and 86.2% (68.4-93.9%) for Comirnaty and Spikevax, respectively.

Study	Method	Key Outcomes
Kislaya (2021) [21] Preprint **new** Case-case Portugal May-Jul 2021	Utilized RT-PCR positive cases notified to the National Surveillance System and electronic vaccination register to calculate the odds of vaccine breakthrough in Delta cases compared to Alpha SARS-CoV-2 cases. This was estimated by conditional logistic regression adjusted for age group, sex, and matched by the week of diagnosis. Whole-genome sequencing (WGS) or spike (S) gene target failure (SGTF) data were used to classify Delta and Alpha. Participants were considered fully vaccinated two weeks after second dose receipt of mRNA vaccine (Comirnaty or Moderna).	• Individuals infected with the Delta variant were more frequently vaccinated than individuals infected with the Alpha variant (12% vs. 5%). Individuals who were fully vaccinated had higher odds of breakthrough infection in the Delta cases when compared to the Alpha cases (OR 1.96, 95%CI 1.22-3.14).
Cavanaugh (2021) [28] Case control US May-Jul 2021	Among Kentucky residents infected with SARS-CoV-2 in 2020, vaccination status of those reinfected during May–June 2021 was compared with that of residents who were not reinfected. A case-patient was defined as a Kentucky resident with laboratory-confirmed SARS-CoV-2 infection in 2020 and a subsequent positive NAAT or antigen test result during May 1–June 30, 2021. Control participants were Kentucky residents with laboratory-confirmed SARS-CoV-2 infection in 2020 who were not reinfected through June 30, 2021. Case-patients and controls were matched on a 1:2 ratio based on sex, age, and date of initial	• 246 case-patients were included and matched with 492 controls. • Among case-patients, 20.3% were fully vaccinated, compared with 34.3% of controls. Kentucky residents with previous infections who were unvaccinated had 2.34 times the odds of reinfection compared with those who were fully vaccinated (95% CI=1.58–3.47).

Study	Method	Key Outcomes
	positive SARS-CoV-2 test. Case-patients were considered fully vaccinated if a single dose of Janssen (Johnson & Johnson) or a second dose of an mRNA vaccine (Comirnaty or Spikevax) was received ≥14 days before the reinfection date.	
Chau (2021) [22] Preprint Case control Vietnam Mar 2020-Jun 2021	Studied breakthrough infections during an outbreak among healthcare workers of a major infectious diseases hospital. Used available data on neutralizing antibodies from a vaccine study for case control analyses. Matched cases with the controls by age and gender.	• Between 11th–25th June 2021 (week 7–8 after dose 2), 69 fully vaccinated healthcare workers tested positive for SARS-CoV-2, of which 62 participated in the study. • 49 were (pre)symptomatic with one requiring oxygen supplementation. All recovered uneventfully. 23 complete-genome sequences were obtained and they all belonged to the Delta variant. • Neutralizing antibody levels after vaccination and at diagnosis of the cases were lower than those in the matched uninfected controls.
Duerr (2021) [13] Case control US Feb-Apr 2021	Compared the SARS-CoV-2 genomes of 76 breakthrough cases after full vaccination with Comirnaty, Spikevax, or Janssen to unvaccinated controls (n=1,046) in metropolitan New York, including their phylogenetic relationship, distribution of variants, and full spike mutation profiles. Unmatched and matched statistical analyses considering age, sex, vaccine type, and study month as covariates were conducted. Breakthrough infection was defined as infection	• Recorded 101 cases of vaccine breakthrough infection between Feb 1-Apr 30, 2021, representing 1.4% of the 7147 total SARS-CoV-2 positive cases in the healthcare system and 0.08% of the fully vaccinated population in the medical records. 76 cases yielded full SARS-CoV-2 genomes for analysis. • 7/76 breakthrough infections required hospitalization and one died.

Study	Method	Key Outcomes
	occurring >14 days after inoculation with the second dose of the mRNA vaccines, or with the single dose COVID-19 Janssen vaccine.	• Most breakthrough infections (57/76) occurred with Alpha or Iota variants. • Both unmatched and matched statistical analyses demonstrated equal variant distributions between vaccinated and unvaccinated in chi-squared and McNemar tests (p>0.1) highlighting a high vaccine efficacy against Alpha and Iota variants.
McEwen (2021) [67] Case control US Feb-Apr 2021	Examined SARS-CoV-2 genomes isolated from individuals identified as vaccine breakthrough cases (n=20) and compared them with the background of SARS-CoV-2 sequences from Washington over the same time interval (n=5174). Vaccine breakthrough was defined as testing positive via RT-PCR >2 weeks post second dose of Comirnaty or Spikevax vaccines).	• All breakthrough cases received mRNA-based vaccines (14 Comirnaty, 5 Spikevax). 15 out of 18 cases reported symptoms but none required hospitalization. Specimens were collected at an average of 67.7 days after vaccination (range 39–112 days) • All 20 (100%) of vaccine breakthrough cases were classified as VOCs: 8 (40%) Alpha, 1 (5%) Beta, 2 (10%) Epsilon (B.1.427), 8 (40%) Epsilon (B.1.429), and 1 (5%) Gamma. In contrast, during the same time interval, 68% of cases sequenced represented VOCs, with 31% Alpha, 1% Beta, 3% Epsilon (B.1.427), 27% Epsilon (B.1.429), and 7% Gamma. • Overall, VOCs were overrepresented in breakthrough cases, with the frequency of all VOCs in breakthrough cases increased by 1.47-fold compared with the control group (95%CI, 1.45–1.50, p=0.001).

Study	Method	Key Outcomes
		• Variants Epsilon (B.1.427), Epsilon (B.1.429), and Alpha were 3.38-fold (0.90–12.71, p=0.119), 1.51-fold (0.88–2.59; p =0.203), and 1.29-fold (0.75–2.20; p=0.468) more common in breakthrough cases compared with controls. • Together, variants that have been reported to be associated with immune evasion (Beta, Epsilon, and Gamma) were identified in 60% of breakthrough cases and 36.7% of control cases, a 1.63-fold change (95%CI, 1.14–2.34, p=0.037).
Mor (2021) [18] Preprint Case control Israel Dec 2020-Mar 2021	Used logistic regression, with variant type as the dependent variable, vaccination status (Comirnaty) as the main explanatory variable, controlling for age, sex, subpopulation, place of residence and time of sample, to estimate the odds ratio for a vaccinated case to have the Beta versus the Alpha variant, within vaccinated and unvaccinated persons who tested positive. Information (including sequencing results) on confirmed COVID-19 cases in the country was retrieved from the Israeli Ministry of Health's databases.	• The national database contained the sequencing results of 11,624 samples obtained from distinct individuals, of which 596 vaccinated and 2515 unvaccinated cases were eligible for analysis. • There were 19 cases of Beta variant (3.2%) among those vaccinated more than 14 days before the positive sample and 88 (3.5%) among the unvaccinated. The estimated odds ratio of breakthrough infection caused by Beta compared to Alpha was 1.29 (95%CI 0.66-2.50, p=0.46). • Assuming the efficacy against the Alpha variant was 95%, the estimated efficacy against the Delta variant was 94% (95%CI 87-97%).

Study	Method	Key Outcomes
Kustin (2021) [14] Case control study Israel Jan 2020-Mar 2021	Examined the distribution of SARS-CoV-2 variants observed in infections of vaccinated individuals and matched infections of unvaccinated individuals. The authors conducted the analysis with breakthrough infections defined as individuals who had a positive PCR test that was performed at least one week after the second vaccine dose (denoted as full effectiveness, FE). However, they also provide case numbers that were infected post 14 days of 2nd dose. Conducted PCR and viral genome sequencing on 149 paired "fully vaccinated" individuals and 247 pairs of "partially vaccinated" individuals (only 1 dose).	• Alpha was the predominant strain of virus in Israel over the entire sampling period, with increasing frequency over time. The Beta strain was at an overall frequency of 1.6% in the total sample. • There were no statistically significant differences in the rates of Alpa infection in "fully vaccinated" cases vs. unvaccinated controls (OR: 6:4, p=0.38). • There was a significantly higher proportion of Beta in "fully vaccinated" cases vs. unvaccinated controls (OR: 8:1, p=0.02). • 79 (49%) of the "fully vaccinated" individuals tested positive on days 7-13 post second dose and 76 (51%) tested positive >14 days post second dose. • Of the eight "fully vaccinated" cases with Beta, one was detected exactly 14 days after the second dose and the rest were infected 7-13 days after the second dose. No Beta cases were seen >14 days.

Abbreviations: AIM, activation induced marker; AB, Alberta; ELISA, enzyme linked immunoassay; est, estimate; HCW, healthcare worker; LTE, letter to the editor;

Table 2: Immune responses ≥6 months after the primary series of COVID-19 vaccination in individuals with no history of prior COVID-19 (n=26)

Study	Method	Key outcomes
Circulating antibody, B-cell and T-cell immune responses (n=4)		
7 months		
Haverall (2021) [39] Preprint **new** Prospective cohort Sweden Apr 2020 – Feb 2021	Healthcare worker binding antibodies (IgG), T-cell responses, and neutralizing antibodies against wild-type and Delta were assessed using longitudinally collected blood samples from the COMMUNITY (COVID-19 Immunity) study for up to 7 months. At the last time measurement data was available for 246 naïve individuals (66 previously infected) who received the Comirnaty vaccine. S-IgG binding antibodies were determined by multiplex antigen bead array, IFN-γ T-cells through IGRA assay as well as T-SPOT® Discovery SARS-CoV-2 kit, and neutralizing antibodies were through pseudotyped virus assays, and for a subset of 17 naïve vaccinated live virus micro-neutralization. Outcomes related to infected then vaccinated individuals is located in Table 3.	T-cells at 7 months: • IFN-γ T-cell titers were lower at 7 months than at 3 months (GMT 18.7 VS 26.8). Antibodies at 7 months: • Comparing 7 month to 6 week S-IgG binding titers had a 6.6-fold decrease. • Pseudo typed neutralization titers had 3.3-fold decrease from week 6 to month 7. • S-IgG titers were strongly correlated to both wild-type and Delta neutralizing antibody titers. VOC at 7 months: • Delta NAbs had 4.6-fold decrease from week 6 to month 7. • Pseudotyped neutralizing antibodies at 7 months was not significantly different from to wild-type titers (GMT 4.8 vs 4.7). • Live virus neutralization for Delta was slightly higher capacity to inhibit binding compared to wild-type.

Study	Method	Key outcomes
6 months		
Giménez (2021) [30] LTE **new** Prospective cohort Spain Feb – Sept 2021	Forty-six (10 previously infected) nursing home residents from a prior study that captured both B and T cell responses after Comirnaty vaccination were reassessed between 179 to 195 days for total RBD and N antibodies (IgG and IgM) (n=45) using the Roche Elecsys® electrochemiluminescence assay as well as IFNγ-producing-CD8+ and CD4+ T cells measured through flow cytometry. Outcomes related to infected then vaccinated individuals are in Table 3.	T-cell at 6 months: • 73% (34/46) of individuals had T-cells responses. 48.5% (16/33) lost T-cell responses. • 61.5% (8/13) of initially negative individuals gained detectable T-cells. • 25% (9/36) of naïve-vaccinated individuals had detectable IFN-γ CD8+cell and 39% (25/36) had IFN-γ CD4+ T-cells. • IFN-γ CD8+ T cell frequencies decreased from follow-up while CD4+ T-cells increased, suggesting CD4+ T cells may develop later than CD8+ T cells in nursing home residents. • No correlation was found between anti-RBD antibodies and IFN-γ CD4+ or CD8+ T cells. Antibodies at 6 months: • 100% of individuals who had detectable antibodies at baseline had detectable antibodies at follow-up. • 83% (29/35) of naïve-vaccinated individuals had decreasing RBD antibodies from baseline to 6 months.
Goel (2021) [29] **new** Prospective cohort US	Longitudinal antibody (1, 3, 6 months after second dose) and memory B and T cell responses including against VOCs (Alpha, Beta, Delta) after mRNA vaccination (Comirnaty or Spikevax) were measured in 45	B-cells at 6 months: • Spike and RBD positive memory B-cell increased up to 6 months for naïve – vaccinated individuals. • The phenotype of memory B-cells is described; IgG+

Study	Method	Key outcomes
Jan – Aug 2021	naïve and 16 recovered individuals. RBD and Spike IgG were measured by ELISA, NAbs were determined against pseudo typed variants, T-cell were detected with activation induced marker assay (AIM) and B-cells through using biotinylated proteins in combination with different streptavidin (SA)-fluorophore conjugates from peripheral blood mononuclear cell (PBMC) samples. Outcomes related to infected then vaccinated individuals is located in Table 3.	positive B-cells increased overtime whereas IgM+ and IgA+ cells declined, indicating class switching as immunity developed. • CD71+ B-cells declined as the 6-month mark approached indicating more mature resting B-cells. • At 6 months the memory B cells were capable of rapidly producing functional antibodies. • Variant-binding indicated variant specific B-cells exist up to 6 months with stronger responses for naïve vaccinated individuals than natural infection alone. T-cells at 6 months: • 90% (28/31) of naïve vaccinated individuals tested had detectable $CD4^+$ T-cell and this population had stabilized. 42% (13/31) had detectable CD8+ cells and this population continued to decline. • CD4+ cells and Th1 were correlated with antibodies. • Effector memory 1 (EM1; CD45RA-CD27+ CCR7-) cells stabilized in frequency from 3-6 months post-vaccination. • Effector T-cell was significantly associated with the durability of the overall CD4+ T cell response at 3 and 6 months. • Peak responses after the second dose of vaccine

Study	Method	Key outcomes
		predicted cellular and humoral immune response at 6 months. Antibodies at 6 months: • 100% had detectable S and RBD IgG. Titers decreased rapidly up to 3 months and then at a slower rate 3-6 months. The two-phase decay rates were not different between previously infected or naïve vacinees. NAbs at 6 months: • 88% (24/27) naïve vaccinated individuals had detectable NAbs at 6 months. • Decay rates were longer for NAbs (111-387 half-life days across study groups). • Antibodies (S and RBD-IgG) were highly correlated with NAbs. • NAbs were comparable between wild-type and Delta but were significantly lower for Beta.
Ciabattini (2021) [31] Prospective cohort Italy Jan-Aug 2021	Spike-specific memory B cells and humoral responses up to 6 months after vaccination with Comirnaty vaccine (2 doses- 3 weeks apart) was investigated in 145 HCWs aged 24-75 without a laboratory confirmed history of SARS-CoV-2 infection. Plasma samples were collected after first dose 21 days, after second dose 7 days, 21, 28, 90 and 160-180. Surrogate neutralization assays were used to assess whether the	Spike specific IgG antibodies: • Spike-specific antibody titers (IgG) and neutralizing activity were observed six months after second dose (GMT 3457, 95%CI 2768-4317), despite a significant progressive decline over time ($p \leq 0.001$ between days 28 and 160-180). No statistically significant difference was observed between days 90 and 180. • At 28 days post second dose neutralization was 100% after which time there was a steady

Study	Method	Key outcomes
	antibodies block the RBD-ACE2 interaction. ELISpot assays were used to measure spike-specific antibody secreting cells in restimulation experiments.	decrease in inhibition percentage. There was a moderate positive correlation between IgG titres and inhibition (r=0.6706, p<0.001) Spike specific memory B cells • As antibodies decreased, spike-specific memory B cells (CD19+), mostly IgG class, increased and persisted 6 months after vaccination. • Within the memory B cells detected at 6 months, only a low amount expressed IgM (3.2±3.6%) or IgA (8.9±6.3%), while the majority were switched to IgG (86±7%). • When PBMCs were restimulated in vitro, circulating memory spike-specific B cells were capable of reactivation and differentiation into IgG antibodies in 66% and IgM in 20% of vaccinated individuals.
Circulating antibody immune responses (n=22)		
Canaday (2021) [38] LTE Preprint **new** Prospective cohort US Jan-Jul 2021	Circulating antibodies and NAbs were measured in 120 nursing home residents and 92 HCWs 2 weeks and 6 months after a full primary series of Comirnaty vaccination. S and RBD-IgG were measured through ELISA and NAbs through pseudovirus neutralization assay. Outcomes related to previously infected then vaccinated individuals are in Table 3.	At 6 months: • Only 30% (22/73) of vaccinated and not previously infected nursing home residents had NAbs compared to 84% (54/64) of HCWs. This was a 54% seroreversion rate among residents. • NAbs, anti-spike and anti-RBD IgG levels decreased more than 84% between 2 weeks and 6 months post vaccination regardless of

Study	Method	Key outcomes
		prior COVID-19 infection status.
Eyran (2021) [50] Preprint **new** Prospective cohort Israel Jun 2020- Sep 2021	A subset of 20 COVID-19 recovered patients and 17 COVID-19 naïve individuals who received the Cominarty vaccine and were followed for samples 8, 35, 91, and 182 days (6 months) after the second dose to measure RBD Ig levels. Outcomes related to previously infected then vaccinated individuals are in Table 3.	Antibodies at 6 months: • All naïve vaccinated individuals reached the lower limit of detection for RBD IgG, IgM, and IgA.

Hsu (2021) [35]
Preprint
new
 	
Retrospective cohort
 	
US
Jan 2021-Jul 2021
	Dialysis patients (1567 with no prior history of COVID-19 and 299 with prior COVID-19) who attended a maintenance dialysis center and had both vaccine doses (441 Comirnaty/779 Spikevax/347 Janssen*) were analyzed for their long term Spike (S) -IgG responses. SARS-CoV-2 spike antigen was measured using the chemiluminescent assay ADVIA Centaur® XP/XPT COV2G.
	Outcomes related to previously infected then vaccinated individuals are in Table 3.
		Vaccinated naïve dialysis patients:
		• S-IgG titers declined towards 6 months, with the highest titers found among Spikevax recipients followed by Comirnaty, and Janssen.
		• Median Antibody titers at 6 months [IQR]
		  ○ Comirnaty =1.30 [0.15-3.59] U/L.
		  ○ Spikevax= 6.20 [1.74-20] U/L.
		  ○ Janssen = >1 U/L (lower limit of detection).
		• At 6 months 43.9% (76/174) of Comirnaty and 14.1% (12/85) of Spikevax recipients had IgG titers <1 U/L.
		• Those with an initial S-IgG titer of <20 U/L were more likely to serorevert at 6 months (HR 23.9 [95% CI: 16.1-35.5])

Study	Method	Key outcomes
Kontopoulou (2021) [47] Preprint **new** Prospective cohort Greece Feb-Sep 2021	RBD IgG responses after Comrinaty were investigated longitudinally from 2 weeks up to 6 months in a cohort of 252 HCWs (35 prior infection/217 no prior infection). IgG antibodies were assessed SARS-CoV-2 IgG II Quant assay. Outcomes related to previously infected then vaccinated individuals are in Table 3.	• At 6 months RBD IgG was detectable in 99% of the sample. • Older adults (60-69) had lower titers than adults <50 years old.
Remy (2021) [34] Preprint **new** Prospective cohort US Aug 2020- Oct 2021	A convenience sample of medical research company employees and household members (n=261) was used. Voluntary self-collected blood samples were measured for Spike IgG once per month up to 13 months. Persons who completed their primary series of vaccination (n= 21 Janssen, n= 78 Moderna, n=152 Pfizer) and 9 were unvaccinated. Forty-three participants reported prior positive PCR before vaccination, 9 reported a breakthrough infection and 24 reported a booster vaccination. Outcomes related to previously infected then vaccinated individuals are in Table 3.	6 months post vaccination: • At 6 months antibody signals were declining for all vaccines with Spikevax recipients having significantly slower decline in titer (0.06 signal unit declines per day) compared to Comirnaty (0.08 signal units per day), the regression slope <0, p<0.0001. Janssen recipients started with lower titers than those who received Comirnaty or Spikevax and its regression slope was not significantly different than 0. • Significant differences in antibody signals existed between sex. Up to 300 days post infection there was no pattern of S-IgG titers decreasing.

Study	Method	Key outcomes
Salvagno (2021) [46] Preprint **new** Prospective cohort Italy Jan-Aug 2021	787 HCWs who received the Comirnaty vaccine 3 weeks apart, had blood samples drawn before the first and second dose as well as 1, 3, and 6 months after the second dose to follow the kinetics of total antibodies as measured through the Roche Elecsys Anti-SARS-CoV-2 S chemiluminescent Immunoassay. Outcomes related to previously infected then vaccinated individuals are in Table 3.	Antibodies at 6 months: • At 6 months total antibodies were 57% (IQR: 35-71%) lower than the corresponding concentrations measured at the peak (1 month after the second dose). • 92.3% (576/624) naïve vaccinated had declines in antibody titers. • Older recipients (over 65) had two fold lower titers than those 65 and older.
Zhong (2021) [49] Preprint **new** Prospective cohort US Jun 2020-Sep 2021	1960 HCWs, 1887 HCWs with no prior infection (1530 Comirnaty/357 Spikevax), before vaccination, and 73 with prior infection (62 Comirnaty/11 Spikevax) were analyzed to determine IgG responses 1, 3, 6 months after vaccination other vaccines not specified). Anti spike (S) IgG was measured through the Euroimmun ELISA assay. Linear regression adjusted median IgG for time since vaccination, prior infection, vaccine, age and sex. Outcomes related to previously infected then vaccinated individuals are in Table 3.	At 6 months: • The adjusted median S-IgG level decreased to 4.55 (95% CI: 4.16-4.91) at 6 month from 7.28 (95% CI: 7.15-7.40) at 3 months, and 8.69 (95% CI: 8.56-8.80) at 1 month in the vaccinated group that was not previously infected with COVID-19.
Doria-Rose (2021) [36] LTE Randomized controlled trial US Aug 2020 – Mar 2021	Vaccine immunity was evaluated in 33 healthy adult participants in an ongoing phase 1 trial reported on antibodies 180 days post second dose of mRNA-1273 (Moderna). Vaccine schedule was two doses 28 days apart. Half-life was estimated using an exponential decay model and power-law model.	At 6 months antibody activity was high in all participants and mean binding antibodies were lower with increasing age geometric mean end-point titers (GMTs): • 92,451 (95%CI 57,148 - 149,562) 18 - 55 years • 62,424 (95%CI 36,765 - 105,990) 56 - 70 years • 49,373 (95%CI 25,171 - 96,849) 71+ years

Study	Method	Key outcomes
		Nearly all participants had detectable activity in a pseudoneutralization assay with 50% inhibitory dilution (ID50) GMTs: • 80 (95%CI 40 to 135) 18 - 55 years • 57 (95%CI 30 to 106) 56 - 70 years • 59 (95%CI 29 to 121) 71+ years All participants had activity on the live-virus focus-reduction neutralization nNeonGreen test ID50 GMTs with lower levels at increasing age: • 406 (95%CI 286 to 578) 18 - 55 years • 171 (95% CI, 95 to 307) 56 - 70 years (p=0.02) • 131 (95% CI, 69 to 251) 71+ years (p=0.004) Estimated means for half-life for binding antibodies after day 43 was 52-109 days, nAbs 69-173 days and live-virus neutralization 68 -202 days, which is consistent with data from previously infected patients up to 8 months.
Pegu (2021) [44] Prospective cohort US Aug 2020 – Apr 2021	The impact of SARS-CoV-2 variants on binding, neutralizing, and ACE2-competing antibodies elicited by the vaccine mRNA-1273 (Moderna) over seven months was evaluated. Vaccine schedule was two doses 28 days apart. Sera from a random sample of 8 volunteers in each of three age groups (18-55, 55-70, and 71+) was tested at four time points: 4 weeks after the first dose, and 2	• Binding and functional antibodies against all variants persisted in most individuals, albeit at low levels compared to WA1 and D614G, for 6-months after vaccination. Across all assays, B.1.351 (Beta) had the lowest antibody recognition with more than half of individuals maintaining neutralizing activity at Day 209. • Activity against all variants peaked two weeks after the

Study	Method	Key outcomes
	weeks, 3 months, and 6 months after the second dose (days 29, 43, 119, and 209 after the first dose, respectively). Three functional assays and two binding assays were used to assess the humoral immune response to the SARS-CoV-2 spike protein.	second dose (Day 43) with moderate declines over time through Day 209. • Using the lentivirus-based pseudovirus assay, all sera from Day 209 neutralized D614G and B.1.429 (Epsilon), but fewer sera neutralized the other variants, with 88%, 96%, 96%, 88%, 85%, and 54% of sera neutralizing WA1, B.1.1.7 (Alpha), B.1.617.2 (Delta), B.1.526 (Iota), P.1 (Gamma), and B.1.351 (Beta) respectively. • Using the live-virus assay, all sera at Day 209 neutralized WA1 and D614G, 88% of sera neutralized B.1.1.7 (Alpha), and 58% neutralized B.1.351 (Beta). • The ACE2 competition assay showed reduced activity against B.1.351 (Beta) at Day 209. While many individuals in the oldest age group retained neutralizing activity against the variants at Day 209, lower titers were observed compared to the other age groups with marginally statistically significant differences in some assays for some variants.
Liao (2021) [87] LTE Prospective cohort China May 2020- Mar 2021	Serum samples of 158 adults aged 18-59 were evaluated for immune persistence 180 days after a 2nd dose of inactivated SARS-CoV-2 Vaccine (clinical trial NCT04412538)	• The geometric mean titre ranges of neutralizing antibodies and ELISA-identified antibodies, specific for S and N proteins showed a decreasing trend over time (14, 28, and 180 days post vaccine). Data shown in graphs. • The positive rates of neutralizing antibodies decreased from 92% at day 28 to less than 35.6% and 51.7% in schedules 0/14 days for

Study	Method	Key outcomes
		1st and 2nd dose vs 0/28 days, respectively, at 6 months. • ELISA-identified antibodies showed a similar trend with the anti-S antibody positivity rate decreasing from 100% at day 28 to 52.1% with the 0/14 schedule and 52.4% with the 0/28 schedule and the anti-N antibody positivity rate decreasing to 50.7% and 45.3%, respectively, at 6 months.
Li (2021) [89] Preprint Randomized controlled trail China May 2020 – Apr 2021	In phase 1 of this trial, 68 healthy adults aged 60+ were randomly allocated (1:1:1) to either a 3 µg, 6 µg, or placebo group. Neutralizing antibody titers were evaluated at 6 months or more after the second dose of CoronaVac in all participants. The impact of a 3rd dose of CoronaVac on immune responses was evaluated up to 28 days post booster given at 8 months after the 2nd dose. 303 participants were randomly assigned (2:2:2:1) to either a 1.5 µg, 3 µg, 6 µg, or placebo group. The positive cutoff titer for neutralizing antibodies to live SARS-CoV-2 virus was 1/8.	• Neutralizing antibody titres dropped below the seropositive cutoff in 70% of individuals at 6 months post vaccination across all vaccine groups at the end of the phase 1 trial. • Geometric mean titres (GMTs) were 3.1 (95% CI: 2.7-3.6), 3.4 (95% CI: 2.9-4.1), and 4.1 (95% CI: 3.3-5.1) in the 1.5 µg, 3 µg, and 6 µg vaccine groups, which corresponds to a decrease in seropositivity from over 90% on day 28 post 2nd dose to 11.76% (95% CI: 5.79-20.57%),17.78% (95% CI: 10.52-27.26%], and 21.52% (95% CI: 13.06-32.20%] at six months. • A 3rd dose given at 8 months or more after the second dose resulted in seropositivity rates across all groups returning to 97.5% - 100%.

Study	Method	Key outcomes
Herishanu (2021) [42] **new** Prospective cohort Israel NR	This report follows up with a cohort of naïve adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who were immunized with two doses of Comirnaty. This report covered antibody responses for 61 CLL/SLL patients and 39 healthy controls 6 months (IQR: 168.0 - 178.5 days) measured the Elecsys® Anti-SARS-CoV-2 S assay.	• 90.2% of CLL/SLL patients had positive antibodies at 6 months (100% of healthy controls). • Seropostivity was significantly lower for those currently receiving treatment with lower levels for treatment naïve and previously treated patients. • 9.8 % (6/61) of CLL/SLL patients lost antibody positivity as 6 months, which may have been related to either starting or continuing treatment. • LL/SLL patients started with lower antibody responses and had lower antibodies at 6 months compared to healthy controls however CLL/SLL patients had slower decrease in titers (median decrease of 58.2% vs 77.1% in controls).
Levin (2021) [40] **new** Prospective cohort Israel Dec 2020 – Jul 2021	HCWs from the Sheba Medical Center were recruited before administration of the Comirnaty vaccine then sampled monthly after the second dose for up to 6 months. Of the 12603 elibible HCWs, 4868 were recruited for study participation. At 6 month follow-up 1370 HCWs were tested for antibodies and 517 for NAbs. RBD-IgG was assessed with the commercially available Beckman Coulter SARS-CoV-2 IgG assay in addition to pseudovirus neutralization assays.	Antibodies at 6 months: • IgG decreased each month with an 18.3 factor decrease in the 6 months of follow-up. • Peak IgG levels were weakly and positively correlated with the slope decrease. • Mixed modelling of IgG titers at 6 months found lower titers at 6 months was significantly associated with ≥45 years or male sex, the presense of 2+ coexisting conditions, the presence of an autoimmune disease, or recieving an immunosuppressive drug. • RBD IgG and NAbs were correlated at 6 months.

Study	Method	Key outcomes
		NAb: • NAbs decreased steeply within the first month (3.9 factor decrease), but the decline was slower towards 6 months (1.2 factor decrease). • Mixed modelling of NAb titers at 6 months found that lower titers were significantly associated with ≥45 years, males, having an immune condition and higher titers were associated with having a BMI over 30 rather than those with BMI under 30. • Peak NAbs were negatively and strongly correlated to the decay rate of NAbs. The decay rate was faster within 70 days and evened out towards 6 months. • Six months after receipt of the second dose, neutralizing antibody titers were substantially lower among men than among women (ratio of means, 0.64; 95%CI, 0.55 to 0.75), lower among persons 65 years of age or older than among those 18 to less than 45 years of age (ratio of means, 0.58; 95%CI, 0.48 to 0.70), and lower among participants with immunosuppression than among those without immunosuppression (ratio of means, 0.30; 95%CI, 0.20 to 0.46).

Study	Method	Key outcomes
Kertes (2021) [48] Preprint **new** Retrospective cohort Israel Jan 2021-Jul 2021	This study extracted data from a large health centre database which carried out serology testing (Abbot Quant II IgG anti-Spike CoV2-SARS kit) for employees and geriatric residents of medical and retirement facilities. All health center members that received both Comirnaty vaccine doses and had a subsequent IgG test were included. Serology results were available for 1,820 at the 6-month mark (>150 days post vaccination).	At 6 months: • Mean S-IgG levels (AU/ml) were 1411, this was preceded by a sharp decrease between months 1-3 and a slower decrease between 3-6 months. This study reports a higher rate of breakthrough infections in those vaccinated 6-8 months ago (0.19%) comparted to those vaccinated 3-5 months ago (0.11%), p<0.01. • Significant decreases in mean antibody levels were seen for all age groups, genders, socio-economic status, comorbidities, and disease severity. There was <10% difference in IgG levels of those >60 vs. <60 at 6 months.
Yue (2021) [88] LTE **new** Prospective cohort China 2020- Jun 2021 (est)	Three hundred and fifty-five volunteers involved in the development of inactivated vaccines received two doses of vaccine (0 and 14 days or 0 and 28 days). Neutralizing antibody titers were then measured at 1 and 8 months after the second dose.	• 48.5% of participants had a positive seroconversion rate at month 8 down from 88.5% at one month. • There were no statistically significant differences in neutralizing antibody titers due to sex, vaccine dose schedule, or age (under and over 30).

Study	Method	Key outcomes
Choi (2021) [83] **new** Randomized controlled trial US May 2020-Apr 2021	In this ongoing phase 2a Spikevax trial, where participants where the 100-µg dose for primary vaccine series group received a booster dose of Spikevax or variant-modified mRNA vaccine including multivalent mRNA-1273.211 (mixed Spikevax and mRNA-1273.351) or mRNA-1273.351 on its own. Only data collected at 6 months post primary series and before booster doses met the inclusion criteria of this review, n= 59 participants. VSV-based PsVN assay	6 months after primary series: • Comparing 6 month and 1 month GMTs after the primary series finds a 6 to 7 fold drop for original variant and a 24 to 69-fold drop for Beta and Gamma, 33-40 fold drop in B.1.617.1 and Delta. • At 6 months most Nab were above the threshold of detection for the original variant, whereas 30%-44% of samples were below the threshold for detection for B.1.351 and P.1 and 45% (5/11) for Delta.
Waldhorn (2021) [43] **new** Prospective cohort Israel Jan-Aug 2021	One hundred and fifty four patients with two doses of Comirnaty undergoing cancer treatment during the whole study were recruited then matched to HCWs of the same age, both had serology done at the same time points. Serum antibodies were measured using the Liaison; DiaSorin SARS-CoV-2 anti-spike (S) S1/S2 IgG assay after the first vaccination, 14 days after the second dose and at 6 months.	At 6 months: • Fewer cancer patients (79%) had positive S IgG results compared to HCWs (84%). • 15% seroreversion rate was reported for the cancer patients, this was similar to the HCWs. • The odds of seronegative status was higher for those receiving chemotherapy compared with other treatment modalities (OR = 0.31; P = 0.02). • No significant differences were found in positive serology by age, sex, or disease stage.

Study	Method	Key outcomes
Sadoff (2021) [37] Preprint **new** Randomized control trial US, Belgium Jul 2020- May 2021	Long-term follow-up of participants in a Phase 1/2a trial for Janssen single dose ($5x10^{10}$ virus particles (vp)). A subset of participants in an ongoing Janssen Phase 1a/ 2a (n=42), phase 2 (n=73) or 3 (n= 22) trials were given a booster dose (Janssen of 5×10^{10} vp or 1.25×10^{10} vp) 6 months after their first dose (data not extracted). Neutralizing and Spike IgG antibodies were assessed during 6 to 9 months after the primary dose.	Post 1 dose Janssen: • NAbs 95%- 100% at 6-8 months in adults 18-65. • S-IgG 93% (n=44) at 6 months in adults 18-65. • NAbs 68%-69% at 6-9 months in older adults >65. • S-IgG 86% (n=29) at 6 months in older adults >65. Booster dose at 6 months: • Strong immunogenicity was elicited at 7-28 day samples following the booster dose.

Israel (2021) [45]
Preprint
new
 	
Retrospective cohort
 	
Israel
Jan 2021-Jul 2021
	IgG antibody kinetics were investigated in a cohort of 2,653 fully vaccinated with Comrinaty (summarized) and 4,361 non-vaccinated previously infected patients (not summarized) drawn from the Leumit Health Services (LHS), a large nation-wide health maintenance organization (HMO).
	Serology results (Abbot Alinity™ i system) target the spike protein IgG antibodies and demographics were extracted from health records.
		Vaccinated individuals up to 6 months:
		• Detectable S-IgG levels (titer >50) vs. previously infected results.
		  ○ 94.2% vs. 86.8% in month 1
		  ○ 94.2% vs. 92.7% in month 2
		  ○ 94.1% vs. 93.7% in month 3
		  ○ 90.8% vs. 90.4% in month 4
		  ○ 90.6% vs. 90.1% in month 5
		  ○ 83.9% vs. 90.6% in month 6
		• Regression analysis finds a 40% decrease in antibody titers every month. This was faster than the previously infected titers which dropped ~4%/month.
		• Mean antibody decay factor was increased with increasing age (>60), chronic renal disease, underweight (BMI <18.5), solid malignancy, chronic obstructive pulmonary disease, diabetes, and hypertension.
		• Decay factors were lower for women and Arab and Jewish Ultra-orthodox subjects.

Study	Method	Key outcomes
Achiron (2021) [41] **new** Cross-sectional study Israel Dec 2020 – Feb 2021	Multiple sclerosis (MS) patients (n=414) and healthy controls (n=89) had blood drawn at least 28 days (2.3 to 6.3 months) after the administration of Comirnaty vaccine. Samples were assessed for levels of S-IgG (Euroimmun) and for a subset were assessed for B and T-cell responses* 2 to 4 months after vaccination (Mabtech RBD ELISpotPlus and IFNg and IL2 FluoroSpot assays).	Antibodies: • MS patients receiving treatment (n=74) had lower S-IgG than MS patients not receiving treatment (n=21) or healthy controls 6 months (n=25). After adjusting for age and sex, MS patients on fingolimod, ocrelizumab, and rituximab had significantly lower IgG levels at 6 months.
Chu (2021) [84] Preprint **new** Randomized controlled trial US Jun 2020 – Oct 2021	In this ongoing Phase 2 trial 600 individuals were randomized to placebo, 50 µg Spikevax or 100 µg Spikevax boosters. Pseudo virus neutralizing antibody titers were assessed before the booster was administered 6 to 8 months after the primary series.	• NAbs were not different from 27 days after the second dose to at least 6 months the primary series.
Pan (2021) [85] Preprint **new** Surveillance program NR Jun – Aug 2021	As part of a surveillance testing program using the NIDS® COVID-19 Neutralizing Antibody (NAb) Rapid Test, 93 Spikevax and 122 Cominarty vaccinated individuals had neutralizing antibody titers tested up to 7 months after full vaccination.	5 and 7 months after the full vaccine series: • 40% for Spikevax recipients were non-responders against Wildtype virus and above 60% for Cominarty recipients. Data shown in graphs. • Levels of non-response was higher for Kappa (more than 70% for both vaccines) and for Delta (more than 50% for Spikevax and more than 70% for Comirnarty). Data shown in graphs.

Abbreviations: LTE= letter to the editor, est= estimated date based on publication submission, RBD= Receptor binding domain, S = Spike, HCW = Healthcare worker

Table 3: Immune responses in ≥6 months after primary series of COVID-19 vaccination in individuals with a history of COVID-19 (n=10)

Study	Method	Key outcomes
Circulating antibody, B-cell and T-cell immune responses (n=3)		
Goel (2021) [29] **new** Prospective cohort US Jan-Aug 2021	Longitudinal antibody (1, 3, 6 months after second dose) and memory B and T cell responses including against VOCs (Alpha, Beta, Delta) after mRNA vaccination (Comirnaty or Spikevax) were measured in 45 naïve and 16 recovered individuals. RBD and Spike IgG were measured by ELISA, NAbs were determined against pseudo typed variants, T-cell were detected with activation induced marker assay (AIM) and B-cells through using biotinylated proteins in combination with different streptavidin (SA)-fluorophore conjugates from peripheral blood mononuclear cell (PBMC) samples.	B-cells at 6 months: • In previously infected individuals the number of memory B-cells had started to decline from peak values, however, there was no difference in the frequency of these B-cells between naïve and previously infected individuals perhaps reflecting a long-term level of B-cells that can be maintained. • T-cells at 6 months: Prior infection transiently boosted T-cell responses but had limited impact on long-term T-cell responses. Antibodies at 6 months: • S and RBD IgG two-phase decay rates were not different between previously infected or naïve vacinees. NAbs at 6 months: • 100% (8/8) previously infected and vaccinated individuals had detectable NAbs at 6 months.
Haverall (2021) [39] Preprint **new** Prospective cohort Sweden Apr 2020 – Feb 2021	HCWs binding antibodies (IgG) and neutralizing antibodies against wild-type and VOC were assessed using longitudinally collected blood samples from the COMMUNITY (COVID-19 Immunity) study for up to 7 months. At the last time measurement data was available for 246 naïve individuals (66	T-cells at 7 months: • IFN-γ T-cell titers were 6-fold higher in recovered individuals than naïve vaccinated individuals. Antibodies at 7 months: • Comparing 7 month to 6 week S-IgG binding titers had a 3.6-fold decrease (compared to 1.5-fold

Study	Method	Key outcomes
	previously infected) who received the Comirnaty vaccine. S-IgG binding antibodies were determined by multiplex antigen bead array, IFN-γ T-cells through IGRA assay as well as T-SPOT® Discovery SARS-CoV-2 kit, and neutralizing antibodies were through pseudotyped virus assays and for a subset of 17 naïve vaccinated live virus micro-neutralization.	between 6 weeks and 12 weeks). • Pseudo typed virus neutralization assay had 5.1-fold decrease from week 6 to month 7 (compared to a 2.3-fold decrease between 6 and 12 weeks). VOC at 7 months: • Delta NAbs had 3.6-fold decrease from week 6 to month 7 (compared to 2.1-fold between 6 and 12 weeks). • Recovered individuals neutralization capacity for variants Alpha, Beta, Gamma, and Delta) were at least 2-fold higher than naïve vaccinated.
Giménez (2021) [30] LTE **new** Prospective cohort Spain Feb – Sept 2021	Forty-six (10 previously infected) nursing home residents from a prior study that captured both B and T cell responses after Comirnaty vaccination were reassessed between 179 to 195 days for total RBD and N antibodies (IgG and IgM) (n=45) using the Roche Elecsys® electrochemiluminescence assay as well as IFNγ-producing-CD8+ and CD4+ T cells measured through flow cytometry.	Antibodies: • 10% (1/10) of infected-vaccinated individuals had decreasing RBD antibodies from baseline to 6 months. T-cell: • 80% (8/10) of previously infected individuals had detectable SARS-CoV-2 IFN-γ CD8+ and 70% (7/10) had CD4+ T-cell, higher than naïve vaccinated at 6 months.

Study	Method	Key outcomes
Circulating antibody immune responses (n=7)		
Salvagno (2021) [46] Preprint **new** Prospective cohort Italy Jan- Aug 2021	787 HCWs who received the Comirnaty vaccine 3 weeks apart, had blood samples drawn before the first and second dose as well as 1, 3, and 6 months after the second dose to follow the kinetics of total antibodies as measured through the Roche Elecsys Anti-SARS-CoV-2 S chemiluminescent Immunoassay.	• Declines from peak titers were higher in previously infected than naïve vaccinated (74% vs 52%). • 98.1% (160/163) of previously infected individuals had declines in antibody titers.
Eyran (2021) [50] Preprint **new** Prospective cohort Israel Jun 2020- Sep 2021	A subset of 20 COVID-19 recovered patients and 17 COVID-19 naïve individuals who received the Comirnaty vaccine and were followed for samples 8, 35, 91, and 182 days (6 months) after the second dose to measure RBD Ig levels.	Recovered individuals received a single dose: • The decay rate for RBD IgG, IgA, and IgM was slower for recovered individuals compared to naïve-vaccinated individuals.
Kontopoulou (2021) [47] Preprint **new** Prospective cohort Greece Feb-Sep 2021	RBD IgG responses after Comirnaty were investigated longitudinally from 2 weeks up to 6 months in a cohort of 252 HCWs (217 no prior infection). IgG antibodies were assessed SARS-CoV-2 IgG II Quant assay.	• At 6 months RBD IgG was higher in those with prior COVID-19 infection. • Decreases in titers were less rapid in those with prior infection but the difference was limited when comparing 6 months to 3 months. • Estimated trajectories of antibody titers indicated high levels of protection beyond a year for those with prior infection.

Study	Method	Key outcomes
Zhong (2021) [49] Preprint **new** Prospective cohort US Jun 2020-Sep 2021	1960 HCWs, 1887 HCWs with no prior infection (1530 Comirnaty/357 Spikevax), before vaccination, and 73 with prior infection (62 Comirnaty/11 Spikevax) were analyzed to determine IgG responses 1, 3, 6 months after vaccination other vaccines not specified). Anti spike (S) IgG was measured through the Euroimmun ELISA assay. Linear regression adjusted median IgG for time since vaccination, prior infection, vaccine, age and sex.	At 6 months: • Adjusted median S-IgG was higher among the previously infected 7.12 (95%CI 6.29, 8.64).
Remy (2021) [34] Preprint **new** Prospective cohort US Aug 2020-Sept 2021	A convenience sample of medical research company employees and household members (n=261) was used. Voluntary self-collected blood samples were measured for Spike IgG once per month up to 13 months. Persons who completed their primary series of vaccination (n= 21 Janssen, n= 78 Moderna, n=152 Pfizer) and 9 were unvaccinated. Forty-three participants reported prior positive PCR before vaccination, 9 reported a breakthrough infection and 24 reported a booster vaccination.	• Up to 300 days post infection there was no pattern of S-IgG titers decreasing.
Canaday (2021) [38] LTE Preprint **new** Prospective cohort US Jan-Jul 2021	Circulating antibodies and NAbs were measured in 120 nursing home residents and 92 healthcare workers (HCWs) 2 weeks and 6 months after a full primary series of Comirnaty vaccination. S and RBD-IgG were measured through ELISA and NAbs through pseudovirus neutralization assay.	At 6 months: • Among those with prior COVID-19 and vaccination 65% (28/43) had NAbs compared to 81% (21/26) of HCWs. The seroreversion rate was 35% among residents. • NAbs, anti-spike and anti-RBD IgG levels decreased more than 84% between 2 weeks and 6 months post

Study	Method	Key outcomes
		vaccination regardless of prior COVID-19 infection status.
Hsu (2021) [35] Preprint **new** Retrospective cohort US Jan 2021-Jul 2021	Dialysis patients (1567 with no prior history of COVID-19 and 299 prior COVID-19) who attended a maintenance dialysis center and had both vaccine doses (441 Comirnaty/779 Spikevax/347 Janssen*) were analyzed for their long term Spike (S) -IgG responses. SARS-CoV-2 spike antigen was measured using the chemiluminescent assay ADVIA Centaur® XP/XPT COV2G.	Infected then vaccinated dialysis patients: • >75% of those with prior COVID-19 infection and Spikevax (14/15) and Comirnaty (30/34) maintained S-IgG >20 U/L (max detection limit).

Abbreviations: LTE= letter to the editor, est= estimated date based on publication submission, RBD= Receptor binding domain S = Spike HCW = Healthcare worker

Table 4: Systematic and rapid reviews relevant to vaccinated immunity (n=3)

Study	Method	Key outcomes
Chen (2021)[90] Systematic review NA July 2021 (est)	A systematic review of 6 databases was conducted with a search date of July 8, 2021. PROSPERO registration no. CRD42021256932. 50% neutralization titers were extracted. No risk of bias was conducted. Random-effects meta-analysis of GMTs was conducted.	• Included 106 studies, 65 and 10 were on previously infected with original variant and VOC participants respectively. 15 included vaccinated participants. • Neutralization was conducted in live virus neutralization assays (n=48 studies), lentivirus-vector pseudovirus neutralization assay (n=39) and VSV-vector pseudovirus neutralization assay (n=24). • They provide pooled GMT for original variants and VOCs showing 4.2 and 3.3 fold reductions in neutralization of Beta and Delta respectively. • Vaccine recipient titers are also presented with high

Study	Method	Key outcomes
		heterogeneity across studies and reduced neutralization for Beta and Delta. Potency of immunity depended on the vaccine platform. • For vaccinated individuals that had previously been infected, neutralization was significantly higher than for uninfected vaccinated individuals. • Data is not analysed for changes in neutralization titers over time.
Notarte (2021) [91] preprint Systematic Review NA Jul 2021 (est)	A systematic literature search was conducted to identify studies reporting the factors affecting humoral response of individuals who received the mRNA vaccines. Search date end of July 2021. Outcomes: IgG, IgA and NAbs No risk of bias.	• 32 articles were included. Associations between humoral response and age (n=7), sex (n=3), baseline serostatus (n=12) and comorbidities (n=18) were examined. • Comorbidity classes: hemodialysis or end stage renal disease (5 articles), cancer and autoimmune diseases (6 articles), transplant patients (4 articles), and metabolic derangements (3 articles). • Older individuals, the male sex, seronegativity, and those with more underlying comorbidities mounted less humoral immune response.
Carr (2021) [92] Systematic Review NA July 2021 (est)	A systematic review of immunity after vaccination in chronic kidney disease (CKD) cases including those on dialysis and transplant patients.	• 35 studies were included. 17 had a control group. • Post one dose of vaccine 18-53% of CKD patients had antibodies. • Post 2 doses of vaccine 70-96% of CKD patients had antibodies.

Abbreviations: est= Search date or publication date when search date was not available was used.

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