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# Long-term levels of protection of different types of immunity against the Omicron variant: a rapid literature review

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## Summary

INTRODUCTION: With the emergence of newer SARS-CoV-2 variants and their substantial effects on the levels and duration of protection against infection, an understanding of these characteristics of the protection conferred by humoral and cellular immunity can aid in the proper development and implementation of vaccine and safety guidelines.

METHODS: We conducted a rapid literature review and searched five electronic databases weekly from 1 November 2021 to 30 September 2022. Studies that assessed the humoral or cellular immunity conferred by infection, vaccination or a hybrid (combination of both) in adults and risk groups (immunocompromised and older populations) were identified. Studies were eligible when they reported data on immunological assays of COVID-19 (related to vaccination and/or infection) or the effectiveness of protection (related to the effectiveness of vaccination and/or infection).

RESULTS: We screened 5103 studies and included 205 studies, of which 70 provided data on the duration of protection against SARS-CoV-2 infection. The duration of protection of adaptive immunity was greatly impacted by Omicron and its subvariants: levels of protection were low by 3–6 months from exposure to infection/vaccination. Although more durable, cellular immunity also showed signs of waning by 6 months. First and second mRNA vaccine booster doses increased the levels of protection against infection and severe disease from Omicron and its subvariants but continued to demonstrate a high degree of waning over time.

CONCLUSION: All humoral immunities (infection-acquired, vaccine-acquired and hybrid) waned by 3–6 months. Cellular immunity was more durable but showed signs of waning by 6 months. Hybrid immunity had the highest magnitude of protection against SARS-CoV-2 infection. Boosting may be recommended as early as 3–4 months after the last dose, especially in risk groups.

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## Introduction

As the fight against COVID-19 persists globally and the emergence of several SARS-CoV-2 variants continues to change the clinical and epidemiological course of the pandemic, an understanding of the duration of long-term protection against SARS-CoV-2 infection conferred by humoral and cellular immunity can aid in the rapid implementation of vaccine and safety guidelines. The adaptive immune response, composed of the humoral and cellular responses, can be measured by analysing antibody levels, neutralising antibodies and T cell and memory B cell responses. Antibodies that recognise receptor-binding domains (RBDs) have been considered the most important component of immunity against SARS-CoV-2 in humans due to their neutralising activity [1]. Nonetheless, the induction of SARS-CoV-2-specific memory T cells and B cells is also important because it provides long-term protection against infection [2].

Many COVID-19 vaccines have been designed to target the SARS-CoV-2 spike protein, with a focus on the receptor-binding domain as it mediates viral entry into cells [3]. However, mutations in the SARS-CoV-2 spike protein have resulted in the emergence of SARS-CoV-2 variants of concern. These variants of concern have demonstrated decreased sensitivity to convalescent sera and threaten the effectiveness and duration of protection of available COVID-19 vaccines [4]. As of December 2022, five variants of concern had been identified: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529), including its multiple subvariants [5]. Of the five variants of concern, Omicron has accumulated the highest number of mutations and has mediated the greatest level of immune escape [6]. With its enhanced transmissibility and immune escape, Omicron, and the multiple subvariants that have emerged from it, has become the most dominant COVID-19 variant circulating by the time of writing. Omicron is comprised of various sister lineages, of which BA.4 and BA.5 have been shown to escape neutrali-

sation to a higher degree than the original Omicron variant (B.1.1.529) and the three previous sister lineages [7].

Vaccination against SARS-CoV-2 has shown a high preventive effect worldwide, especially for reducing severe illness and death [8]. However, with newly emerging variants, especially Omicron, a high reduction in levels of humoral and cellular immunity has been observed, and vaccine effectiveness has also been affected. Several of the studies included in this review have demonstrated waning protection against the SARS-CoV-2 virus and its Omicron variant and subvariants of both humoral and cellular immunity. With each new Omicron subvariant, the ability of the antibodies elicited through vaccination to neutralise the variants is lower than that of the previous variant [9]. Consequently, these new subvariants influence vaccine effectiveness and the durability of the established protection against SARS-CoV-2 infection [10]. Therefore, analysing the effects that Omicron and its subvariants have on the levels and duration of protection against SARS-CoV-2 infection elicited by adaptive immunity is crucial to appropriately implement public health decisions. Due to the considerable number of publications shared daily, a rapid literature review was performed to assess evidence of the levels and duration of long-term protection against SARS-CoV-2 infection in adults and risk groups (immunocompromised and older individuals).

## Methods

### Literature and information search

A search for literature published each week was completed using the following electronic databases: MEDLINE (PubMed), Embase, medRxiv and bioRxiv, Cochrane Library and Social Science Research Network (SSRN). Grey literature, such as information produced by government agencies and academic institutions and press releases, and journals such as the *New England Journal of Medicine*, *The Lancet* and *Nature* (which publish articles before they appear in search engines) were hand-searched.

We employed a search strategy composed of text words (e.g. coronavirus disease), MeSH terms (e.g. COVID-19 immunity), Boolean terms (e.g. AND, OR) and truncations (e.g. immune*) to electronically identify studies related to SARS-CoV-2 immunity in the MEDLINE, Embase and medRxiv/bioRxiv databases. The literature search was performed weekly by one of the researchers. The search strategies for MEDLINE, Embase and medRxiv/bioRxiv can be found in the appendix.

Identified literature was imported into a library in EndNote for storage and detection and deletion of duplicated articles. Screening and full-text review were completed using Rayyan systematic review software [11].

### Literature screening

Search-identified literature was imported into Rayyan, and titles and abstracts were screened for articles related to COVID-19 immunology. At least two reviewers screened the literature and agreed on its inclusion in the full-text review. If a conflict arose during the title and abstract screening, a third, more experienced reviewer screened the study and made a final decision. Full-text reviews were performed to assess the relevancy of each selected article. Relevancy was decided based on the inclusion and exclusion criteria and topics of interest. Studies selected for full-text review were further screened in Rayyan for literature assessment and selection by two reviewers. If a conflict arose during the full-text review, then a third, more experienced reviewer reviewed the study and made a final decision.

### Eligibility of studies

Eligible studies were those reporting any data on immunological assays of COVID-19 (related to vaccination and/or infection) or the effectiveness of protection against SARS-CoV-2 infection (related to the effectiveness of vaccination and/or infection). The population of interest was healthy and immunocompromised people in any geographic setting. Three main exposure groups were eligible for inclusion: individuals fully vaccinated or boosted for COVID-19 (restricted to vaccines approved in Switzerland), individuals with previously confirmed infection and individuals with previously confirmed infection and documented vaccination. The outcome of interest was vaccine effectiveness or immunogenicity against SARS-CoV-2 Omicron infection, hospitalisation, severe disease and death. Test-negative case-control, cross-sectional, cohort, non-randomised controlled trial and randomised controlled trial studies were eligible for inclusion. Due to the focus on the duration of long-term protection, studies evaluating immunology over a long time period (n = 70) were categorised as "duration of protection" and emphasised in this report. No language restriction was imposed (though the search queries were in English), and we limited the search to studies published between 1 November 2021 and 30 September 2022 to capture studies covering the emergence of the Omicron variant. Underage individuals (infants, children and adolescents) and pregnant women were excluded from our search. Additionally, studies of new and second-generation vaccines and other vaccine platforms not approved in Switzerland were not included.

### Risk of bias (quality) assessment

Our study focused on frequent screening to keep up with the rapidly growing body of COVID-19 literature and provide updates for researchers and public health experts. We acknowledge the absence of a quality assessment in our rapid review, and we understand the importance of assessing the strength of evidence in future research.

### Data extraction and analysis

Data were extracted and imported into a common Excel table for studies that included, but were not limited to, data on the immunological surveillance of COVID-19 immunity after vaccination and/or infection. The findings were grouped and summarised by topic (e.g. humoral immunity, cellular immunity, vaccine effectiveness and risk groups).

### Ethical approval

No ethical approval was required.

## Results

A total of 9536 studies were found using the search queries; 5103 studies remained after the removal of duplicates. After title and abstract screening by two authors, 1409 studies were included for full-text review. After full-text review, 205 articles were included in this review. Of the 205 articles, 70 addressed the duration of protection against SARS-CoV-2 infection and were highlighted in the review (figure 1). Further details on the characteristics of the included studies can be found in table S1 in the appendix. The review was mandated by the Federal Office of Public Health, and detailed reports can be found on their website (https://www.bag.admin.ch/bag/en/home/das-bag/publikationen/forschungsberichte/forschungsberichte-uebertragbare-krankheiten/forschung-wissenschaft-covid-19.html) (under the "Literature searches" section and "Monitoring COVID-19 immunity" subsection).

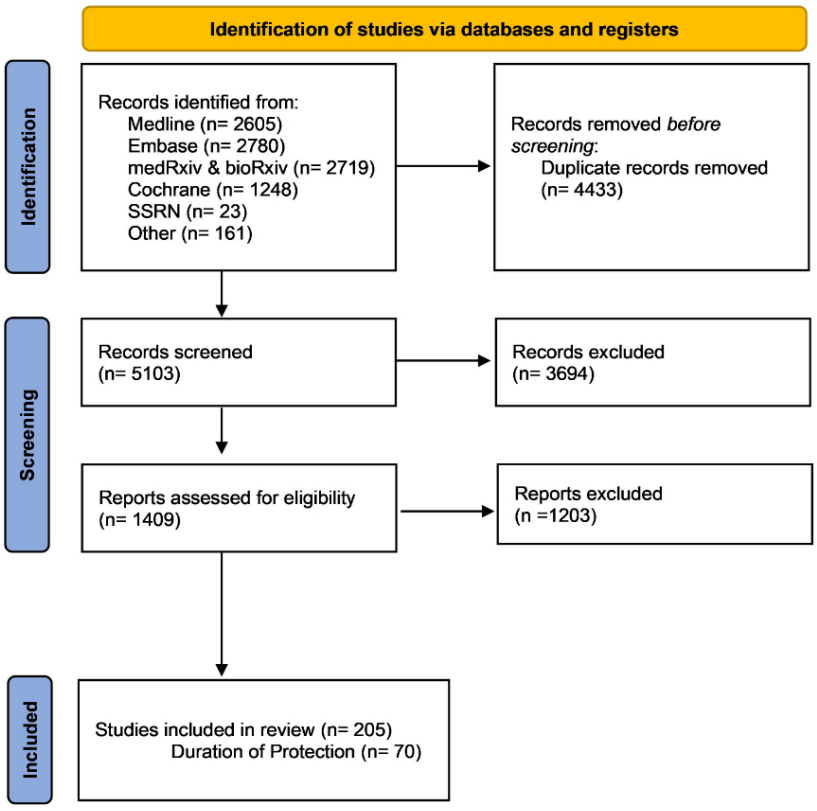
A visual summary of the general results of the levels of protection of SARS-CoV-2 infection over time for the different types of immunity is presented in figure 2.

### Duration of infection-acquired immunity

The longevity and durability of protection against Omicron conferred by prior infection were assessed in three studies, in which a clear decrease in the elicited antibodies was observed after 10–12 months [1, 12, 13]. Twelve months post-infection, the humoral response in mild COVID-19 convalescents was significantly reduced and completely abrogated for the Omicron variant (B.1.1.529) [13]. In terms of the kinetics and durability of SARS-CoV-2-specific antibodies, a significant reduction in all levels of binding and neutralising antibodies was observed over 12 months; the half-life of IgG receptor-binding domain was estimated at 2.79 months, and the half-life of IgG N was estimated at 1.98 months [12]. Neutralising antibodies were shown to decay at a slower rate than binding antibodies, with an estimated half-life of 5.13 months [12]. Levels of humoral response were directly correlated with cellular response; high levels of virus-specific $CD4^+$ T cells during the early convalescent phase were correlated with long-term neutralising antibody levels [12]. Additionally, the binding and neutralising antibodies in the low $CD4^+$ group had a faster estimated decay rate and shorter half-life than those in the high $CD4^+$ group [12].

Multiple studies analysed T cell and memory B cell responses in convalescent individuals [12–15]. In two of the studies, cellular immunity was conserved up to 1 year after infection, with T cells showing a slightly stronger memory than B cells [13, 15]. Both studies also observed a higher frequency of $CD4^+$ T cells than $CD8^+$ T cells, although a majority of $CD8^+$ T cell epitopes of SARS-CoV-2 were reportedly conserved in Omicron [13, 15]. In the study by Wang et al., high percentages of virus-specific $CD4^+$ T cells and cTfh1 cells were associated with a slower decline in humoral immunity, highlighting the importance of coordinating T cell and humoral immunity to achieve long-term protective immunity [12].

**Figure 1:** PRISMA flowchart of study identification and selection.



The effectiveness of previous infection waned more slowly than that of two and three doses of mRNA-1273 and BNT162b2 vaccines. Altarawneh et al. showed that the protection against SARS-CoV-2 infection after vaccination was negligible 6 months after the first and second booster doses (mRNA, 41.2%, vs BNT162b2, 44.7%, after 1 month) [16], while infection-acquired effectiveness ranged from 65–75% at 4–6 months and 32–53% at 10–12 months [16–19].

### Duration of vaccine-acquired immunity

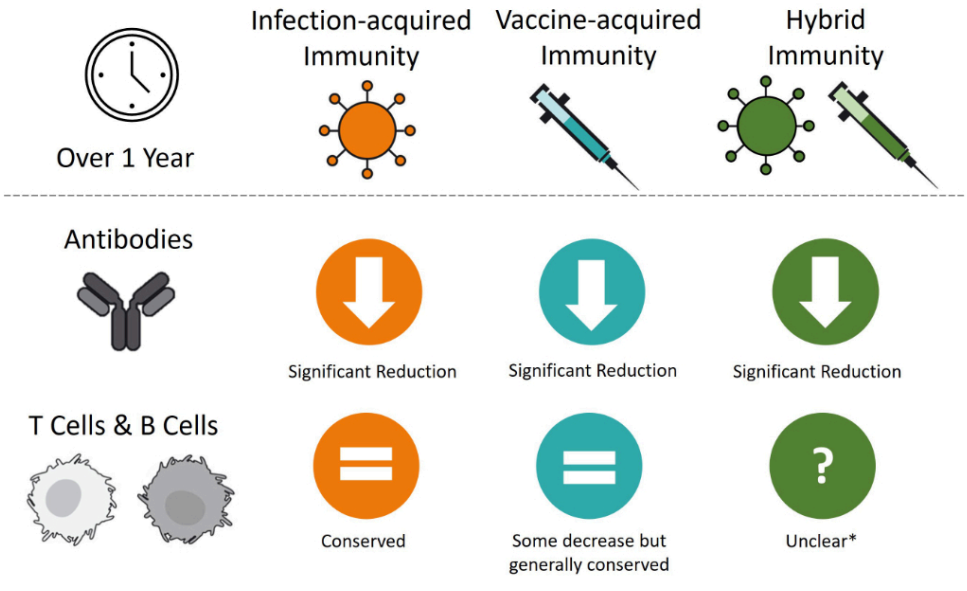
The level of neutralising antibodies against the Omicron variant B.1.1529 3–6 months after receiving the second dose of any mRNA vaccine (BNT162b2 or mRNA-1273) was lower than those against previous variants, such as the original wild strain or the Delta variant, irrespective of the recipient's age [9, 20–25]. In addition, antibody levels after the second dose gradually decreased over time, leading fully vaccinated individuals, those receiving one dose of the Janssen vaccine or two doses of the mRNA vaccines, more vulnerable to breakthrough infections [20]. These low levels of antibody titres were observed 6 months after full administration of the primary scheduled mRNA vaccines mRNA-1273 and BNT162b2 and were not demonstrated to be sufficient for preventing breakthrough infections of the Omicron variant [26]. Nevertheless, binding antibodies against vaccine strain spike proteins and the receptor-binding domain have been shown to be significantly higher in boosted individuals compared with individuals who did not receive a booster dose, demonstrating that a booster dose increases antibody levels and inhibition against the Omicron variant [26–28].

Various studies demonstrated that, a few months after receiving a first booster dose, the neutralisation geometric mean titres (GMTs), along with the levels of binding antibodies, decreased significantly [7, 25, 27, 29]. Within 4 months after the administration of a booster dose, a 3- to 4-fold decrease in protection against SARS-CoV-2 infection was observed for all strains, including Omicron (B.1.1.529) [29], while Omicron BA.1 neutralising antibodies substantially waned by 3 months after homologous mRNA boosting and heterologous boosting with mRNA or Ad26.COV2.S vaccines [7]. Furthermore, the waning of Omicron-binding antibodies was observed as soon as 14 days after booster administration; the titres for IgA and IgG peaked on day 9 but significantly decreased by day 14 after immunisation to 66.6% for IgA (42.3% decrease) and to 30.6% for IgG antibodies (15.7% decrease) [27].

For third doses, a slower waning of the humoral response after a third BNT162b2 dose versus a second dose was reported [29]. Similar kinetics were observed in neutralising antibodies, for which a slower rate of decrease after the third vaccine dose than after the second dose was demonstrated [29]. The mean avidity – the overall strength in binding between an antibody and antigen – observed was 65.7% one month after the second vaccine dose, with no significant change 6 months after the second dose. However, avidity increased to 97.4% 1 month after the third vaccine dose and 98.04% 4 months after the third dose of BNT162b2 [29]. In other words, the binding strength between the antibody and antigen was stronger in individuals who received a third vaccine dose than in individuals who received only two doses, highlighting the stronger humoral response obtained after receiving a booster dose. Studies comparing different types of immunity revealed that the levels of neutralising antibodies in mRNA-vaccinated individuals were elevated up to 1 year after infection, while the anti-N titres amounted to only approximately 66 AU 1 year and approximately 21 AU 2 months after infection-acquired immunity [30].

A general decrease in the effectiveness of the protection offered by vaccination against SARS-CoV-2 symptomatic

**Figure 2:** Visual summary comparing the levels of antibodies and T and B cells from day 1 to day 365 (over a 1-year period) for infection-acquired, vaccine-acquired and hybrid immunity. This figure provides a generalised summary based on the included studies. The designs, durations and results of the included studies were very heterogenous, allowing for only a very generalised summary. * Few studies with results on the duration of the protection of hybrid immunity were included in the review and used to draw conclusions; nonetheless, it is safe to assume that similar trends in infection-acquired immunity can be expected.



infection was observed, in which two doses of BNT162b2 offered a modest effectiveness of 65.5% 2–4 weeks after vaccination but later dropped to 8.8% at 25 weeks and beyond [31]. A similar decrease in the duration of protection was noted for booster doses; three doses of BNT162b2 had an effectiveness of 67.2% at 2–4 weeks, which then plunged to 45.7% at 10 weeks and beyond [31]. The duration of the protection of vaccine-acquired immunity was stronger against severe outcomes and hospitalisation; the estimated mRNA booster effectiveness (BNT162b2 and mRNA-1273 combined) was 87.4% 15–60 days after boosting and 87.2% 5–6 months after boosting, with no significant differences among various vaccine combinations [32]. With the spread of the more infectious Omicron subvariants BA.1/BA.2 and BA.4/BA.5, the duration of vaccine protection was compromised, and rapid waning of vaccine effectiveness in protecting against hospitalisation due to current sub-lineages of the Omicron variant was observed [10].

Waning of memory T cell responses for both the Delta and Omicron variants was observed 3 months after vaccination [33]. Similar to $CD4^+$ T cell responses, $CD8^+$ T cells were consistently detected in more vaccinees than in non-vaccinated controls, though $CD4^+$ T cell responses were stronger up to 6 months after all vaccination regimens [34]. Both $CD8^+$ and $CD4^+$ T cells were maintained after 8 months with some decline and were restored to initial levels by booster vaccination [8]. Additionally, more than one-third of resting memory B cells bound Beta and Omicron variants and steadily increased the B cell receptor breadth up to 4.9 months after vaccination [35]. T cell responses declined between 28 days and 5 months after booster vaccination towards levels similar to those detected prior to vaccination with the Ad26.COV2.S booster [36]. Furthermore, the durability of cellular immune responses in individuals who received a primary vaccination of Pfizer BNT162b2 and were boosted with either Ad26.COV2.S or BNT162b2 was assessed [37]. At 16 weeks, median Omicron T cell responses generated by the Ad26.COV2.S booster were higher than those generated by the BNT162b2 booster [37].

The cellular immune responses after a fourth vaccine dose compared to those after breakthrough infections reached peak frequencies approximately 60 days after the second dose; a substantial but short-lived booster effect after the third dose was reported [38]. Within 30–60 days after the third dose, the $CD8^+$ T cell response was reduced back to pre-third dose levels. When analysing the $CD8^+$ T cell responses after the fourth antigen contact, either by a fourth vaccine dose or by breakthrough infection with Omicron or Delta after three doses, the T cell response was rapidly and robustly induced at similar frequencies. Furthermore, 1 or 2 months after breakthrough infection and second booster vaccination, a fully functional T cell memory was present with similar reactivation capacities [38]. Additionally, the spike-specific $CD8^+$ T cells elicited by a fourth vaccine had a substantial response towards variants of concern, including Omicron.

## Duration of hybrid immunity

Similar to previous results on the duration of protection conferred by infection-acquired or vaccine-acquired immunity, hybrid immunity showed signs of waning. To evaluate the lifespan of the antibodies elicited against the Omicron variant, Chang et al. [39] divided study participants into two groups: one representing a short interval (6 months after recovery from infection) and one representing a long interval (12 months after recovery from infection). Antibodies elicited against Omicron significantly decreased in neutralisation ability 6 months after recovery from infection, when the GMT ratio was 2.6; the GMT ratio 12 months after recovery was 1.7 [39]. When comparing different immunities (vaccine-acquired and hybrid), a greater decay was found in vaccinated and uninfected individuals than in previously infected and vaccinated individuals, in which the neutralising antibodies waned more than the binding antibodies (11.5- and 10.2-fold decreases in uninfected individuals vs 2.9- and 2.5-fold decreases in previously infected individuals in neutralising and binding antibodies, respectively) [40]. Nonetheless, the neutralising antibody titres against all variants tested, including Omicron, declined 1–6 months after the second mRNA vaccine dose [41]. The sera from naïve vaccinated participants demonstrated no neutralising activity against the Omicron variant, while fully vaccinated individuals who recovered from COVID-19 showed a 22-fold reduction, with most participants retaining their neutralising antibody response [42].

Similar kinetics were found in boosted individuals; booster durability waned more substantially in uninfected individuals than in those who had acquired a breakthrough infection [43]. In contrast, two studies observed that the decay of the humoral response was faster in infected and vaccinated participants than uninfected and vaccinated participants [29, 40].

The effectiveness of hybrid immunity 7–59 days post-vaccination with two doses of an mRNA vaccine was 89% and eventually decreased to 68% at 6–12 months. Similar protection over time was noted in participants who received three doses and had a previous infection [17]. In terms of severe outcomes, multiple studies found that hybrid immunity conferred more durable protection against deaths and hospitalisation than against infections over time [44, 45] (84.5% vs 52.8% at 3–5 months, 89.5% vs 32.7% at 6–12 months, 80.3% vs 14.7% after 1 year [44]). A similar pattern was found for BNT162b2 and Ad26.COV2.S, whose effectiveness after the respective booster dose was higher against severe outcomes than against infection (booster dose BNT162b2 after 2–9 weeks, 95.7% vs 70%; Ad26.COV2.S after 2–9 weeks, 97.5% vs 47.2%) and higher against infection for BNT162b2 than for Ad26.COV2.S [44].

## Duration of immunity in risk groups

### *Immunocompromised groups*

A third or fourth dose of an mRNA vaccine enhanced and sustained the antibody response against the Omicron variant in a high proportion of immunocompromised groups [46–59]. Nonetheless, lower levels of neutralising antibodies against Omicron after three doses of an mRNA vaccine and subsequent breakthrough infections in both immunocompromised and healthy groups were observed compared to the levels against the wild-type and Delta variant [50].

Additionally, a cohort study on solid organ transplant recipients found that, even after four doses of an mRNA vaccine, participants still had poor neutralising antibody responses against Omicron, particularly compared to healthy controls [52], and immunosuppressive treatments such as infliximab in inflammatory bowel disease patients were associated with attenuated and waning antibody responses [53]. Despite booster doses increasing the humoral response against Omicron, neutralisation of Omicron was still substantially weaker than that of earlier variants. Moreover, waning of the neutralising antibody response in immunocompromised individuals with time after vaccination was demonstrated [48, 60–62]. One month after a third dose of an mRNA vaccine, 18.3% of organ transplant recipients had detectable levels of neutralising antibodies against Omicron; this decreased to 15.7% 3 months after vaccination [60]. Similarly, antibody responses waned significantly 6 months after second and third doses of mRNA vaccines in kidney transplant recipients and cancer patients, respectively, in whom neutralisation against the Omicron variant was significantly attenuated or completely missing 6 months after vaccination [61, 62].

Spike-specific $CD4^+$ and $CD8^+$ T cells against all variants, including Omicron, were sustained in 45–60% of multiple sclerosis patients taking B cell depleting drugs 6 months after their second vaccination, albeit at lower median frequencies against the Delta and Omicron variants than against the original SARS-CoV-2 vaccine strain [63]. Furthermore, the spike-specific T cell response up to 3 months after two doses of an mRNA vaccine was comparable between inflammatory bowel disease (IBD) patients and healthy individuals [64]. Similar results were demonstrated in heart transplant and solid tumour patients, in whom a durable T cell response was maintained 6 months after a third dose of BNT162b2 vaccine [61, 65]. Additionally, the T cell response was sustained at a higher magnitude, particularly in those treated with tumour necrosis factor (TNF) inhibitor therapy. The T cell response against mutations present in the Omicron variant was found to be mainly preserved in these patients [64]. Similarly, primary antibody deficiency patients were still able to mount a durable $CD4^+$ T cell response specific to SARS-CoV-2 that was similar to that of healthy groups after mRNA vaccination [66].

Cellular immunity increased upon receipt of third and fourth doses of an mRNA vaccine [48, 63, 67, 68]. In addition, a third dose enhanced the number of responders to all variants (55–75% of patients) and significantly increased $CD8^+$ T cell responses [63]. However, even after a third mRNA vaccine dose, SARS-CoV-2-specific interferon(IFN)-γ responses were much lower in kidney transplant recipients, although interleukin(IL)-2 responses remained similar to those of healthy participants [69]. T cell responses deteriorated significantly in immunocompromised groups 6 months after mRNA vaccination. Notably, SARS-CoV-2 T cells became undetectable in a significant proportion of dialysis patients and the majority of kidney transplant recipients 6 months post-vaccination [62].

*Older groups*

Decreasing levels of neutralising antibodies over time were observed in older groups. A 4.9-fold decrease in neutralising antibody titres was detected 3–20 weeks after mRNA vaccination, while a greater decline in Omicron neutralisation was reported among older patients 6 months after a third dose of an mRNA vaccine [70, 71]. In contrast, hybrid immunity resulted in a more sustained humoral response over time in older groups of individuals aged 80 years and older 15 months after COVID-19 infection; they were able to sustain their SARS-CoV-2 spike-specific IgG antibody response [72]. Additionally, vaccination with a single dose of an mRNA vaccine enhanced the antibody response in previously infected individuals more significantly than in naïve individuals receiving two doses [72]. Infected patients were able to sustain high levels of anti-receptor-binding domain antibodies 7 months after their second dose of an mRNA vaccine, and, upon receiving the third dose, both anti-receptor-binding domain and neutralising antibody titres against Omicron increased more notably in previously infected groups than in SARS-CoV-2-naïve individuals [73]. In contrast, Gilboa et al. [29] observed that, in participants aged 65 years and older, IgG and neutralising antibodies declined more rapidly in infected individuals.

Few studies focused on cellular immunity in high-risk groups. Gimenez et al. [73] assessed cellular immunity following a third dose of the Pfizer vaccine in nursing home residents. However, while they found that most of the assessed residents had a detectable T cell response at baseline, changes in SARS-CoV-2 S-specific T cells after a third dose of an mRNA vaccine were negligible [73]. In contrast, another study [74] found that, while baseline CD4 $T_H1$ was substantially lower in an older group pre-vaccination, $T_H1$ response was similar to that of younger groups post-vaccination. Additionally, this same study found that older adults produced more IFN-γ than younger adults post-vaccination [74].

However, studies have demonstrated that vaccine effectiveness wanes over time [75]. As observed with the first booster (third dose), the protection against infection was short lived. However, protection against severe illness did not disappear during the study period (i.e. 6 weeks after receiving the fourth dose) [75, 76]. Baum et al. [77] found that, 91–180 days after a second dose, vaccine effectiveness against hospitalisation had decreased from 91% to 76%. Similar results were observed by Gazit et al. [78] after a fourth dose of an mRNA vaccine. Relative effectiveness of the fourth dose of the Pfizer vaccine waned significantly by the tenth week after peaking 3 weeks post-vaccination. However, in the same study, relative effectiveness of the fourth dose against severe COVID-19 was sustained throughout the study period [78]. This is consistent with the findings of Bar-On et al. [75].

## Discussion

Although quantifying the exact duration of protection against SARS-CoV-2 infection poses a great challenge, numerous articles have found a significant decrease in the levels of protection, especially against the Omicron variant (B.1.1.529) and its subvariants, 3–6 months after primary, first booster and second booster vaccination. A list of all the included studies discussing duration of protection is available in the appendix (Data Protection Sheet). In a systematic review and meta-regression study on the duration of effectiveness of vaccination against COVID-19 caused

by the Omicron variant, similar results were reported [79]. Overall, 6 months after vaccination, the primary vaccine series led to little protection against symptomatic infections and to a more rapid decrease in vaccine effectiveness during the Omicron period (47.6% decrease [95% CI, 36.6–60.2]) than the pre-Omicron period (24.9% decrease [95% CI, 13.4–41.6]), while decreases in vaccine effectiveness for severe diseases remained relatively similar [79]. With the first booster vaccination, the waning of protection against Omicron was generally higher than after the primary vaccine series for all outcomes; the mean decrease in vaccine effectiveness against symptomatic disease from 1–4 months was 24.3% (95% CI, 19.9–29.1) and projected to 6 months was 28.5% (95 CI, 18.3–40.5) [79]. For second booster doses (fourth doses), the durability of protection against Omicron infections remains relatively uncertain, although a study analysing the protection of a fourth dose over time demonstrated that, for confirmed infections, a fourth dose appeared to provide only short-term protection and a modest absolute benefit [75].

When estimating the half-lives and decay rates of humoral responses, neutralising antibodies were found to wane at higher rates than binding antibodies in vaccinated individuals [40], while total neutralising antibodies had longer lifespans in convalescent individuals [12]. A correlation between cellular and humoral immunity has also been found, where increased levels of CD4+ T cells in cellular immunity are associated with prolonged neutralising antibody responses, crucial for long-term defense against SARS-CoV-2 infection. In the study by Wang et al. [12], high levels of virus-specific $CD4^+$ T cells at baseline were correlated with long-term neutralising levels, indicating the possible role of $CD4^+$ T cells in regulating long-term humoral immunity in patients with previous COVID-19 infection. Additional differences in the duration and waning of humoral immunity were also noted among the diverse types of antibodies. For instance, the decay of IgG-binding antibodies against variants 30 days after the third or fourth vaccine dose was more pronounced than the decay of the IgA response, suggesting possible long-term advantages of IgA antibodies [80]. These results provide evidence that next-generation vaccines targeting the mucosal immunity driven by IgA antibodies could be a solution to the continuous waning of protection against newly emerged variants. In fact, the highest levels of humoral and even cellular immunity were observed in cases of hybrid immunity in which infections triggered a strong IgA response and detectable Omicron-neutralising activity [81]. While the current COVID-19 vaccines continue to demonstrate durable protection against severe outcomes and hospitalisation, their performance at reducing mild illness and transmission, especially with Omicron variants, is suboptimal. With the potential use of nasal vaccines, the thin mucous membrane that lines the nose, mouth and lungs could, in theory, prevent even mild cases of illness and block transmission to other people – something the first-generation COVID-19 vaccines have been unable to achieve – while triggering a strong and durable IgA response. As of October 2022, two nasal COVID-19 vaccines have been approved for use as booster doses in India and China [82, 83]. Although evidence of the effectiveness and duration of protection of such vaccines is scarce, a phase II trial of CanSino's inhaled vaccines found that they raised blood-serum antibody levels significantly more than an intramuscular booster dose [83].

### Strengths and limitations

To our knowledge, this is the largest review of humoral and cellular immunity against SARS-CoV-2 in adults and risk groups. The studies presented covered the duration of protection of three types of humoral and cellular immunity: infection-acquired, vaccine-acquired and hybrid. However, due to the high complexity of investigating T cell responses of individuals, there were fewer studies analysing such immune responses than evaluating humoral immunity. Consequently, literature addressing cellular immunity against SARS-CoV-2 was less prevalent than literature on humoral immunity in our review. This was particularly apparent for high-risk groups; this report was able to identify only two relevant studies assessing cellular immunity in older populations. The results of this study do not apply to other important populations, such as underage individuals (infants, children and adolescents) and pregnant women, since those populations were excluded from our search. Additionally, studies of new and second-generation vaccines and other vaccine platforms not approved in Switzerland were not included. In addition to the identified gaps in literature, our report did not assess the risk of bias or quality of the studies included. Although we attempted to ensure that our search was as exhaustive as possible, the current report provides a narrative summary of current data in the literature that was limited by our eligibility criteria. Any specific research questions may require further analysis of data.

### Conclusion

Hybrid immunity was shown to elicit the highest levels of humoral and cellular immunity while lasting longer than infection-acquired and vaccine-acquired immunity. However, with the emergence of new Omicron subvariants, the levels and duration of protection were greatly affected, leaving immunised individuals prone to infection or reinfection. Boosting maintains vaccine effectiveness against severe disease caused by the current Omicron sub-lineages; nonetheless, the evidence of rapid waning of durability may indicate that at best, there is a need for regular boosting as early as 4 months after the last dose and the need for vaccines to incorporate variants of concern to maintain protection. In terms of $CD8^+$ T cell responses, mRNA boosters induced a temporary T effector cell response, while spike-specific $CD8^+$ T cell memory was conserved for targeting variants of concern. Infection with the Omicron variant or Omicron variant-specific vaccination may induce a memory T cell response sufficient for protecting against an Omicron infection. Despite humoral response defects, vaccine-induced T cell responses might still provide a layer of protection for patients undergoing immune-modifying therapies.

## Data availability statement

The data that support the findings of this review were gathered from publicly available databases.

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**Author contributions:** SRV and SBM conceived and designed the study. MA, and OK made substantial contributions in reviewing the design of the study. SRV, LEB, and SMH conducted the literature search. SRV, LEB, and SMH conducted the title and abstract screening. SRV, LEB, SMH, IT, and JD conducted the full-text review. SRV, LEB, SMH, IT, and JD conducted the data extraction. SRV, LEB, SMH, IT, and JD drafted the manuscript. MA, SBM, CBGV, and OK contributed by revising the manuscript critically for important intellectual content. MA and OK critically reviewed the manuscript. All authors contributed to final approval of the version to be submitted.

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**Potential competing interests**
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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# Appendix

## Search strategy – final report

**Medline (PubMed):**

Vaccine-induced Immunity:

**Query:** (((((("Coronavirus Infections"[MeSH] OR SARS-CoV-2[tiab] OR coronavirus[tiab] OR "coronavirus disease"[tiab] OR "COVID-19"[MeSH] OR "COVID-19"[tiab] OR SARS Virus [MeSH] OR SARS-CoV[MeSH] OR "coronavirus"[MeSH] OR severe acute respiratory syndrome coronavirus 2[MeSH] OR "SARS-CoV-2"[MeSH]) AND ("SARS-CoV-2 variants" [Supplementary Concept])) AND ("Immunity"[MeSH] OR "Antibodies"[MeSH] OR "Serology"[MeSH] OR "Immunology"[All Fields] OR "Immunogenicity"[Title/Abstract] OR "Protection"[Title/Abstract])) AND (covid-19 vaccine [MeSH] OR "viral vaccine"[tiab] OR vaccine*[tiab] OR vaccination*[tiab] OR inoculate*[tiab] or inoculation*[tiab] OR "market-authori*"[tiab] AND vaccine*[tiab])) AND (hasabstract[text])) AND ("2021/11/01"[Date - Publication]: "3000"[Date - Publication])

Infection Immunity:

**Query:** (((((("Coronavirus Infections"[MeSH] OR SARS-CoV-2[tiab] OR coronavirus[tiab] OR "coronavirus disease"[tiab] OR "COVID-19"[MeSH] OR "COVID-19"[tiab] OR SARS Virus [MeSH] OR SARS-CoV[MeSH] OR "coronavirus"[MeSH] OR severe acute respiratory syndrome coronavirus 2[MeSH] OR "SARS-CoV-2"[MeSH]) AND ("SARS-CoV-2 variants" [Supplementary Concept])) AND ("Immunity"[MeSH] OR "Antibodies"[MeSH] OR "Serology"[MeSH] OR "Immunology"[All Fields] OR "Immunogenicity"[Title/Abstract] OR "Protection"[Title/Abstract])) AND ("breakthrough infection"[Title/Abstract] OR "reinfection"[Title/Abstract] OR "re-infection"[Title/Abstract])) AND (hasabstract[text])) AND ("2021/11/01"[Date - Publication]: "3000"[Date - Publication])

**Embase:**

Vaccine-induced Immunity:

**Query:** ('severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome'/exp OR 'coronavirus infection' OR 'coronavirus disease 2019') AND ('variant of concern' OR 'variant of interest' OR 'sars-cov-2 delta' OR 'sars-cov-2 lineage b.1.1.529') AND ('immunity' OR 'immunogenicity' OR 'immunology' OR 'antibody' OR 'protection') AND ('sars-cov-2 vaccine'/exp OR 'vaccin*':ti,ab OR 'immunization':ti,ab OR 'immunisation':ti,ab) AND [humans]/lim AND [01-11-2021]/sd AND [2021-2022]/py

Infection Immunity:

**Query:** ('severe acute respiratory syndrome coronavirus 2'/exp OR 'severe acute respiratory syndrome'/exp OR 'coronavirus infection' OR 'coronavirus disease 2019') AND ('variant of concern' OR 'variant of interest' OR 'sars-cov-2 delta' OR 'sars-cov-2 lineage b.1.1.529') AND ('immunity' OR 'immunogenicity' OR 'immunology' OR 'antibody' OR 'protection') AND ('breakthrough infection' OR 'reinfection' OR 'infection') AND [humans]/lim AND [01-11-2021]/sd AND [2021-2022]/py

**MedRxiv:**

Limited by word term "(Coronavirus Infection OR SARS-CoV-2 OR COVID-19 OR coronavirus) AND (immunity OR immunology OR antibodies) AND (variant)" – search term or keyword – and date of publication starts from 01.11.2021

| Author, year | Country | Study Timeframe | Study Design | Total Sample Size | Population | Age | Gender | Immune Status | Immunity | Measurement of protection |
|---|---|---|---|---|---|---|---|---|---|---|
| Adachi et al, 2022 | Japan | Individuals diagnosed with COVID-19 in January 2022 | Retrospective cohort | 32 | Patients infected with SARS-CoV-2 omicron after 2 doses of mRNA vaccine | Median 54 (16-94) | 77% male | Healthy | Hybrid | Anti-spike protein antibodies |
| Arashiro, 2022 | Japan | Delta-dominant period (August-September 2021) and the Omicron-dominant period (January-March 2022) | Test-negative case-control | 5795 | symptomatic adults enrolled in 16 medical facilities during the study period | 20–29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+ | Female 2893 (50.0%) | some participants reported comorbidities including hypertension, heart disease, diabetes mellitus, obesity, kidney disease, asthma, chronic obstructive pulmonary disease, cancer, immunodeficiency, and immunosuppressant use | Vaccine acquired | Effectiveness |
| Becker 2022 | Germany | na | Longitudinal cohort | 88 (50 dyalisis; 22 controls) | Haemodialysis patients | ≥18 years | Female (n, %): 9 (38·0); 23 (69·7) | Immunocompetent, comorbidity, chronic diseases | Vaccine acquired | Anti-SARS-CoV-2 RBD IgG and ACE2 binding inhibition |
| Belik, 2022 | Finland | December 2020 to December 2021 | Prospective longi- | 328 | Health care workers | Median 44, (range 22-66) | 13% male | NA | Vaccine-acquired | Neutralizing antibodies |

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| | | | tudinal cohort | | | | | | | |
| Bellusci, 2022 | United States | NA | Cohort | 81: naïve (N = 50) or SARS-CoV-2 convalescent (infection before vaccination; N = 31) individuals | General population | Mean age: Coivalence: 46 (22–65); Naïve 53 (30–81) | Female: Coivalence 21(68); Naïve 33 (65) | healthy | Vaccine acquired and hybrid | Neutralizing antibodies, spike binding antibody and antibody affinity |
| Brlic, 2022 | Croatia | Samples collected in 3 periods: November–December of 2020, April 2021, November–December 2021 | Cohort | HCWs cohort: prior to vaccination n= 937; +3 weeks after 1st dose n=651; +6 months after 2nd dose n=380; +14-16 months n= 20 Hospitalized cohort: n=102 | HCWs & hospitalized patients | HCWs cohort (mean ± SD): prior to vaccination 46 ± 11; +3 weeks after 1st dose 45 ± 11; +6 months after 2nd dose 46 ± 11; +14-16 months 49 ± 13 Hospitalized cohort: median 68 (40-89) | HCWs cohort: prior to vaccination 77.2% female; +3 weeks after 1st dose 75.3% female; +6 months after 2nd dose 78.4% female; +14-16 months 70.0% female Hospitalized cohort: 28% female | Hospital cohort included critically ill (requiring invasive ventilator support) patients | Vaccine acquired and hybrid | RDB binding antibody and Nucleocapsid-specific IgG antibodies |
| Brosh-Nissimov, 2022 | Israel | from 15 to 31 January 2022 | Cohort | 1049 patients | hospitalized adults with severe COVID-19 | median age 80 years stratified by number of | 535 (51%) were males | hospitalized adults with severe COVID-19, | Vaccine acquired | Effectiveness |

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| | | | | | | vaccinations received | | some were immuno-compromised because of other comorbidities | | |
| Carazo, 2022 | Canada | Between March 27 and June 4, 2022 | Test-negative case-control | Cases = 37 732; Controls = 73 507 | Health-care workers | 94.1% of participants were aged 18-59yrs | 82.6% female | NA | Natural, vaccine acquired, and hybrid | Effectiveness (duration) |
| Carazo, 2022 | Canada | between December 26 (epi-week 52), 2021 and March 12 (epi-week 10), 2022 | Test-negative case-control | 696439 | Community-dwelling ≥12-year-olds tested for SARS-CoV-2 | ≥12 | Cases group: prior primary infection, 70.3% females; no infection, 61.9% females; Controls group: prior primary infection, 69.6% females; no infection, 63.5% females | NA | Natural, vaccine-acquired | Protection conferred by prior SARS-CoV-2 infection against Omicron re-infection, and the added value of vaccination |
| Chang, 2022 | United States | June 2020 to December 2021 | Cohort | 48 | Patients and public around DFCI medical campus | Median 50 years (range 22-73) | 71% female | NA | Hybrid | Neutralizing antibodies |
| Chang, 2022 | USA | NA | Longitudinal cohort | 121 patients | Patients with non-Hodgkin lymphoma & chronic lymphocytic leukemia & healthy controls | Median 63.8 | 59% male | Immunosuppressed | Vaccine-acquired | Neutralizing antibodies |

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| Chemaitelly, 2022 | Qatar | February 28, 2020 and June 5, 2022 | Cohort | cohort 1 (pre-omicron reinfection): 290,638; cohort 2 (omicron reinfection): 120,483; cohort 3 (primary infection with any variant reinfection with any variant): 407,214 | Total population of Qatar | Predominantly young | Predominantly male | NA | Natural | Effectiveness (duration) |
| Chemaitelly, 2022 | Qatar | December 2021 to February 2022 | Test-negative case-control | BNT162b2 effectiveness study: 88,321; mRNA-1273 effectiveness study: 49,861 | General population | BNT162b2: median age 32 for all cohorts but one- median age 31); mRNA-1273: median age 28-30 for all cohorts | BNT162b2 effectiveness against symptomatic SARS-CoV-2 BA.1 Omicron infection, cases: 49.0% male, 51.1% female; effectiveness against symptomatic SARS-CoV-2 BA.1 Omicron infection, controls: 51.6% male, 48.4% | NA | Natural, vaccine-acquired | VE against symptomatic infection |

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| | | | | | | | female; effectiveness against symptomatic SARS-CoV-2 BA.2 Omicron infection, cases and controls: 55.6% male, 44.4% female; effectiveness against any symptomatic SARS-CoV-2 Omicron infection, cases: 55.1% male, 44.9% female; effectiveness against any symptomatic SARS-CoV-2 Omicron infection, controls: 55.7% male, 44.3% female; mRNA-1273; effectiveness against symptomatic SARS-CoV-2 BA.1 Omicron infection, cases: 49.5% male, 50.5% female; effectiveness | | | |

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| | | | | | | | against symptomatic SARS-CoV-2 BA.1 Omicron infection, controls: 52.3% male, 47.7% female; effectiveness against symptomatic SARS-CoV-2 BA.2 Omicron infection, cases and controls: 57.0% male, 43.0% female; effectiveness against any symptomatic SARS-CoV-2 Omicron infection, cases: 58.2% male, 41.9% female; effectiveness against any symptomatic SARS-CoV-2 Omicron infection, controls: 58.3% male, 41.7% female | | | |

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| Chemaitelly, 2022 | Qatar | December 2021 to February 2022 | Test-negative case-control | 133’327 | General population | all ages (heavily young adult population) | 1 month after 2nd dose BNT162b2 cases: 52.4% male, 47.7% female; 1 month after 2nd dose BNT162b2 controls:; 52.7% male, 47.3% female; 4-5 weeks after 3rd dose BNT162b2 cases:; 52.8% male, 47.2% female; 4-5 weeks after 3rd dose BNT162b2 controls:; 53.3% male, 46.7% female; 1-3 months after 2nd dose mRNA-1273 cases: 52.6% male, 47.5% female; 1-3 months after 2nd dose mRNA-1273 controls: 53.0% male, 47.0% female; | NA | Vaccine-acquired | VE against symptomatic infection |

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| | | | | | | | 4-5 weeks after 3rd dose mRNA-1273 cases:; 52.8% male, 47.2% female; 4-5 weeks after 3rd dose mRNA-1273 controls: 53.2% male, 46.8% female | | | |
| Chen, 2022 | Taiwan | Enrollment between January and September 2020 | Cohort | 25 | Adults | Range: 20-63 (mean 38.68) | 12 females, 13 males | NA | Natural | Anti-spike antibodies and memory B cell responses |
| Collie, 2022 | South Africa | November 15, 2021, to June 24, 2022 | Cohort | 32883 | General population | 18 to ≥80 | 51.9% male | NA | Vaccine acquired | Effectiveness/durability |
| Edara, 2022 | United States | Convalescent samples were collected March-August 2020 and vaccinated sera was collected up to 6 months after | Cross-sectional | 138 | Adults | ≥18 | NA | NA | Vaccine-acquired, hybrid | Neutralizing antibodies |

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| | | primary vaccination and booster dose | | | | | | | | |
| Evans, 2022 | United States | Received 2nd dose between January and February 2021 | Cohort | 48 | Health care workers | Median 37 (IQR 31.75-43.25) | 54% male | NA | Vaccine-acquired, hybrid | Neutralizing Antibodies |
| Favresse, 2022 | Belgium | booster was administered between 8 November 2021 and 31 January 2022 and blood collected 2 days before and after 7, 14, 28, 56, 90, and 180 days | Cohort | 155 | HCWs | 18 to 65 yrs, median 45 | 72.3% female | NA | Vaccine acquired and hybrid | Neutralizing and binding antibodies |
| Gilboa, 2022 | Israel | December 15, 2021 and February 27, 2022 | Cohort | 3972 | HCWs older than age 18 years | (mean [SD] age, 48.5 [14.1] years | (mean [SD]: 996 [74.9%] women | NA | vaccine acquired | neutralizing antibodies (durability) |
| Goel, 2022 | United States | 9–10 months after primary 2-dose SARS-CoV-2 mRNA vaccination and 3 months after a 3rd dose | Longitudinal cohort | 61 | general pop receiving mRNA vaccines | Age: 36.9 [22-67] and Age: 38.3 [23-59], for two groups - SARS infected and SARS recovered | Sex: 21M 24F and Sex: 10M 6F, for two groups - SARS infected and SARS recovered | NA | Vaccine acquired and hybrid | Neutralizing antibodies and RBD-specific memory B cells |

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| Gray, 2022 | South Africa | November 15, 2021, to January 14, 2022 | Test-negative case-control | 162,637 PCR test | Healthcare workers | NA | NA | NA | Vaccine acquired | Effectiveness |
| Grikscheit, 2022 | Germany | January to March 2022 | Cohort | 43 | Adults | 2nd booster mean age: 49.6 years (28-79); 1st booster and infection mean age: 41.6 years (22-63) | 53.5% male | Healthy | Vaccine acquired and hybrid | Antibodies, neutralizing antibodies, T-cells |
| Hein, 2022 | Germany | NA | Prospective cohort | 112 | Healthcare workers | 20 to 66 | Varies by cohort | Healthy | Vaccine acquired | Omicron RBD IgG, Omicron RBD IgA, Neutralizing antibodies |
| Hertz, 2022 | Israel | January 6 to February 9, 2022 | Cohort | 608 | Healthcare providers | Over 18 yrs of age | NA | healthy | Vaccine acquired | Effectiveness (hazard ratios) and neutralizing antibodies |
| Ioannou, 2022 | United States | December 1, 2021 to March 31, 2022 | Cohort | n=490,838 in both matched groups | Veterans Affairs enrollees aged 18 years or older | both groups had mean age 63.0 ±14 yrs | Group 1: Male 87.4% Group 2: Male 87.7% | Some reported comorbidities | Vaccine acquired | Effectiveness |
| Jung, 2022 | Korea | NA | Cohort | 60 | HCWs with 2 doses (no previous infection): n = 20;; HCWs | Mean age: 41,7; 39,3; 49,3 | male:female = 12:8; male:female = | na | Vaccine | Neutralizing antibodies |

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| | | | | | with 3 doses (no previous infection): n=20;; Individuals (with previous infection): n=20 | | 13:7; male:female = 0:20 | | acquired and hybrid | and T-cells |
| Kaku, 2022 | United States | between 30 December 2021 and 19 January 2022 | Cohort | Breakthrough infection donors (n = 7) and uninfected, two-dose vaccinated donors (n = 12) | participants were previously immunized with two or three doses of an mRNA vaccine (BNT162b2 or mRNA-1273) and had no documented history of SARS-CoV-2 infection before vaccination | 19 to 45 years | Predominantly females | healthy | Vaccine acquired and hybrid | B cell response and antibodies titres |
| Kared, 2022 | Norway | June to August 2020, Delta and Omicron predominant periods | Cohort | 56 | Breakthrough patients and health care workers | Delta breakthrough: mean 27 (range 21-30) ; Omicron breakthrough: mean 37.3 (range 28-50) ; Noninfected: mean 31.9 (range 25-44) | Delta breakthrough: 61.6% female ; Omicron breakthrough: 69.2% female ; Noninfected: 71.4% female | NA | Vaccine-acquired, hybrid | T cells (CD4+ and CD8+) and memory B cells |
| Kotaki, 2022 | Japan | NA | Cohort | 40 | Healthcare workers | Median age: 46.5 years | 40% male | NA | Vaccine acquired | Antibodies and Memory B-cells |
| Kumar, 2022 | Canada | NA | Cohort | 60 | transplant recepients | median 66.9 years (IQR 64.0–71.8) | Male: 62% | immunocompromised | Vaccine acquired | neutralization |

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| Lasagna, 2022 | Italy | NA | Cohort | 83 | Solid tumors patients | Median age: 63 years | 36 females and 47 males | Immunocompromised | Vaccine acquired | Antibodies, T-cells |
| Lin 2022 | United States | NA | Prospective cohort | 2 cohorts: 30 Primary antibody deficiency syndromes (PAD) cohort ; Healthly individuals cohort - Immunocompetent healthy donor volunteer blood samples were obtained as previously described | Primary antibody deficiency syndromes (PAD) | ≥18 years | NA | Immunocompromised | Vaccine acquired and hybrid | Antibodies and Memory B-cells |
| Lyke, 2022 | United States | NA | Clinical trial | 696 | healthy adults | ≥18 years | na | Healthy | Vaccine acquired | Neutralizing antibodies |
| Malato 2022 | Portugal | From June 1st 2022 to July 4th 2022. | Prospective Cohort | 4 940 504 individual without a documented infection by 4-7-22; | Portuguese residents | ≥12 years | na | na | Vaccine acquired and hybrid | Effectiveness |

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| | | | | 367 783 ndividual with a documented first infection during a BA.5 dominance; 2 039 118 individual with no BA.5 reinfection; 38 800 individuals with reinfection in the period of BA-5 dominance | | | | | | |
| Mise-Omata, 2022 | Japan | Samples collected: March 2021 - January 2022 (vaccinated healthy) Covalescent patients enrolled between April and December 2020 | Prospective cohort | 43 (vaccinated healthy) 88 COVID-19 recovered | Healthy volunteers and convalescent patients | 28-62 (vaccinated healthy) 23 -74 (covalescent patients) | 55.8% female 44.2% male (vaccinated healthy) 35% female 65% male (covalescent patients) | Healthy and covalescent patients | Natural and vaccine acquired | B cell and T cell response |

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| Mwimanzi, 2022 | Canada | Second-dose interval: December 2020 to July 2021; Third dose interval: 7 month after second dose | Cohort | 69 healthcare workers; 47 older adults | Healthcare workers and elderly | Healthcare workers: median 40 years; Older age: median 78 years | NA | NA | Vaccine acquired and hybrid | Antibodies, neutralizing antibodies |
| Mwimanzi, 2022 | Canada | 6 months after the second dose, and at 1 month after the third dose | Prospective longitudinal cohort | 151 | health care, older adults, and workers individuals with anti-SARS-CoV-2 nucleocapsid (N) antibodies at study entry | Age, y, median (IQR): 41 (35–51) 78 (73–83) 48 (36–87) in Health Care Workers, Older Adults,; COVID-19 Convalescent at Study Entry | Female sex, n (%) 61 (75) 38 (68) 10 (71) in Health Care Workers, Older Adults, COVID-19 Convalescent at Study Entry | healthy except 1 individual | Vaccine acquired | binding and neutralizing antibody |
| Newman, 2021 | United Kingdom | Samples taken 3 to 20-weeks post 2nd immunization | Cohort | 37 | Elderly individuals based in UK | Median: 78 years (IQR 75-80) | NA | NA | Vaccine-acquired | Neutralizing antibodies |
| Ng, 2022 | Singapore | from December 27, 2021, to March 10, 2022 | Cohort | 2’441’581 | Singapore citizens or permanent residents | 846 110 (34.7%) aged 60 years and older), | 52.4% women | Healthy | Vaccine acquired | Effectiveness |
| Patalon, 2022 | Israel | January 1 to January 21, 2022 | Test-negative case-control | 389265 | General population | 16 to ≥60 | 57.8% female | Some have comorbidities | Vaccine-acquired, hybrid | Vaccine effectiveness of third dose |

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| Peled, 2022 | Israel | July 2021 to December 2021 | Longitudinal cohort | 103 | Heart Transplant patients | Mean age: 59.3 (±15.4) years | 45 (75%) male | immunocompromised | Vaccine acquired | Neutralizing antibodies, T-cells |
| Peng, 2022 | Hong Kong | Individuals vaccinated before June 2021 | Prospective longitudinal cohort | 62 vaccinated & 16 unvaccinated controls | Adults | Pfizer BNT162b2 median: 30.5(26.8 - 35.3); CoronaVac median: 29.0(26.0 - 31.0); Non-vaccinated median: 32.5 (24.3-39.8) | Male % -> Pfizer BNT162b2: 47.1%; CoronaVac: 50.0%; Non-vaccinated: 50.0% | Healthy except for 2 participants in BNT162b2 group with mild hypertension and diabetes | Vaccine-acquired | Neutralizing antibodies and T cells (CD4+ and CD8+) |
| Planas, 2022 | France | NA | Longitudinal cohort | 27 | Healthcare workers | 31 to 96 | Female: 48.15% Male: 51.85% | NA | Vaccine acquired and hybrid | neutralizing antibodies |
| Qu, 2022 | United States | Sample collection -> Cohort 1: Oct 2021-Feb 2022; cohort 2: Feb 2022-June 2022; cohort: Feb 2022-June 2022 | Longitudinal cohort | Cohort 1: n= 28; cohort 2: n=37; cohort: n=36 | Health care workers | Cohort 1: median 35 (26-61); cohort 2: median 35 (25-58); cohort: median 36.5 (25-61) | Cohort 1: 28.6% female; cohort 2: 45.9% female; cohort: 41.7% female | NA | Vaccine acquired | Neutralizing antibodies |
| Quandt, 2022 | Germany | Serum was drawn from double-vaccinated individuals (BNT162b22) | Cohort | 66 | Four independent groups: individuals who were (i) double- or (ii) triple-vaccinated with BNT162b2 without a | Cohort 1: median 52; Cohort 2: median 38; Cohort 3: | NA | NA | Vaccine-acquired, hybrid | Neutralizing antibodies & Memory B cells |

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| | | at 22 days after the second dose, from triple-vaccinated individuals (BNT162b23) at 28 days after the third dose, from double-vaccinated individuals with Omicron breakthrough infection (BNT162b22 + Omi) at 46 days post-infection, and from triple-vaccinated individuals and Omicron breakthrough infection (BNT162b23 + Omi) at 44 days post-infection. PBMC samples from double-vaccinated individuals (BNT162b22) | | | prior or breakthrough infection at the time of sample collection (BNT162b22, BNT162b23) and individuals who were (iii) double- or (iv) triple-vaccinated with BNT162b2 and who experienced breakthrough infection with the SARS-CoV-2 Omicron variant after a median of approximately 5 months or 4 weeks, respectively | median 39; Cohort 4: median 32 | | | | |

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| | | at 22 days after the second dose and 5 months after the second dose, from triple-vaccinated individuals (BNT162b23) at 84 days after the third dose, from double-vaccinated individuals with Omicron breakthrough infection (BNT162b22 + Omi) at 46 days post-infection, and from triple-vaccinated individuals with Omicron breakthrough infection (BNT162b23 + Omi) at 44 days post-infection. | | | | | | | | |

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| Qui, 2022 | Singapore | July 2021 to January 2022 | Pro-spec-tive cohort | 83 | Patients undergoing immune modifying therapies | 21-83 media: 39 | Male: 63.8% | Immunosuppressed | Vac-cine-ac-quired | Anti-RBD an-tibody, Spike-specific T cell |
| Reinscheid, 2022 | Germany | three and nine months post 2nd dose & three months after the 3rd dose, 1 month post 4th dose and breakthrough infection | Cohort | 38 (31 with 3 doses, 5 with 4 doses, 13 with break-through infections after 3rd dose) | Adults | Range 23 - 63 | 17 females, 21 males | NA | Vac-cine ac-quired and hybrid | T-cells |
| Renia, 2022 | Singapore | beginning of January 2021–May 2021 | Cohort | 312 | HCWs and older in-dividuals | median age was 50.9 years (range, 22–82) | predomi-nantly female (58.3%) | healthy | Vac-cine ac-quired | specific antibod-ies, B and T cell memory re-sponses |
| Richardson et al, 2022 | Germany | Blood sam-ples from convalescent individuals were col-lected up to one year af-ter infection. Samples for vaccinated individuals | Cohort | 67 | Convalescent indi-viduals and vac-cinated individuals | Vaccinated in-dividuals: mean age 51; convalenscent individuals: mean age 49 | Vaccinated in-dividuals: 10 males & 13 females; con-valescent in-dividuals: 9 males & 8 fe-males | NA | Natu-ral, vac-cine-ac-quired | T cell ( CD4+) and anti-RBD antibody |

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| | | were collected from 2 weeks to 3 months after 2nd dose. | | | | | | | | |
| Richterman, 2022 | United States | 1 July 2021 -5 April 2022 (analysis stratified into 2 periods: pre-Omicron and post-Omicron period as beginning on 20 December 2021) | Test-negative case-control | 28 000 employees | HCW | 18–30: 1465 (21) ; 31–40: 2454 (35) ; 41–50: 1362 (19) ; 51–60 :1165 (16) ; >60: 652 (9) | 81% female | NA | Natural, vaccine acquired, and hybrid | Effectiveness |
| Rössler, 2022 | Austria | Sera collected 4-6 months after 2nd dose | Cohort | Convalescent: 25; Vaccinated: 60; Super immune: 10 | General population | Convalescent: range 23-62; Vaccinated: 10-86; Super immune: 28-66 | 47 females, 48 males | NA | Natural, vaccine-acquired, hybrid | Neutralizing antibodies |
| Sablerolles, 2022 | Netherlands | Up to 5 months after booster dose | Cohort | 279 | Individuals vaccinated with Janssen | median age: 43; interquartile range: 32-52 | 106 males (38%) | Some reported comorbidities | Vaccine acquired | Antibodies, neutralizing antibodies, and T-cells |
| Sammartino, 2022 | Italy | sera were collected during the first wave of COVID-19 in- | Cohort | 30 (Convalescent) 30 ( Naïve) 16 (COVID-19 Exposed) 15 | Convalescent individuals, Naïve Healthcare Workers, COVID-19 Exposed Healthcare Workers, Previously Omicron | median age of 67 years (range 35–84) Convalescent, median age of 52 years | 80% male and 20% female Convalescent, 20% male and 80% female Naive, 13% | NA | Natural, vaccine- | Neutralizing antibodies |

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| | | fections between May and July 2020 (for convalescent plasma donors) (time frame unavailable for other cohorts) | | (omicron specific) | infected + vaccinated healthcare workers | (range 30–66) Naive, median age of 42 years (range 25–61) COVID-19 Exposed, median age of 28 (range 26–34) Omicron exposed | male and 87% female COVID-19 Exposed, 54% male and 46% female Omicron exposed | | ac-quired, hybrid | |
| Sanders, 2022 | Netherlands | 28 days and 6 months after the second vaccination | Cohort | 181 controls; 152 patients with chronic kidney disease; 145 dialysis patients; 267 kidney transplant recipients | Patients With Chronic Kidney Disease, on Dialysis, or Living With a Kidney Transplant | controls: 58.4 ± 12.9 patients with chronic kidney disease: 60.6 ± 13.4 dialysis patients: 60.0 ± 13.8 kidney transplant recipients: 55.9 ± 14.1 | controls: female (59.1%) patients with chronic kidney disease: female (34.9%) dialysis patients: female (33.1%) kidney transplant recipients: (46.1%) | Immunocompromised | Vaccine acquired | Spike S1 binding antibodies, neutralizing antibodies, T cell |
| Seki, 2022 | Japan | NA | Cohort | 259 samples | Health care workers | Mean in males: 42.1 years; Mean in females: 40 years | 38% male | NA | Vaccine-acquired | Neutralizing antibodies |
| Sievers, 2022 | United States | Infected individuals (April 25 to July 17 2020) and pregnant vaccinated individuals (March 2020 | Cohort | 224 | Adults previously infected, pregnant, or health care workers | NA | NA | NA | Natural, vaccine-acquired | Neutralizing Antibodies |

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| | | to January 2021) | | | | | | | | |
| Šmíd, 2022 | Czech Republic | from 7 December 2021 to 13 February 2022 | Cohort | NA | the entire population of the Czech Republic | general | NA | NA | Natural, vaccine-acquired | VE against infection and hospitalization |
| Tan, 2022 | United States | Enrolled August 12, 2021, to October 25, 2021 samples analysed November 2021 to February 2022 | Cohort | 68 | Adults | (Ad26.COV2.S) median 36 [23-84] (BNT162b2) median 35 [23-76] | Female: 82% | Healthy | Vaccine acquired | Neutralizing antibodies, binding antibodies, functional antibodies and T-cells |
| Tarke, 2022 | United States | 2 weeks after 2nd immunization and 6 weeks post immunization with Janssen, 1 month post symptom onset | Cross-sectional | 112 | Adults | Early COVID: median 44 (range 27-68); mRNA-1273: median 42 (range 21-78) ; BNT162b2: median 36 (range 24-66); Ad26.COV2.S: median 50 (20-70) ; NVX-CoV2373: median 35 (range 18-60) | Early COVID-19: 44% male; mRNA-1273: 29% male; BNT162b2: 40% male; Ad26.COV2.S: 43% male; NVX-CoV2373: 62% male | NA | Natural, vaccine-acquired, hybrid | T cells ( CD4+ and CD8+) & Memory B cells |

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| Tauzin, 2022 | Canada | December 2021 to May 2022 | Cohort | 45 | Adults | Median age: 51 years (range 24 to 67) | 17 males and 28 females | NA | Natural, vaccine acquired and hybrid | Neutralizing antibodies |
| Thakkar, 2022 | United States | 3rd dose study: 4 weeks after 3rd dose and 4-6 months follow-up; 4th dose study: 4 weeks after 4th dose | Cohort | 106 patients | Cancer patients | median: 68 (IQR 63.25-76.5) | female 55%; male 45% | Immunocompromised | Vaccine acquired | Effectiveness |
| Valanparambil, 2022 | United States | Antibody response measured 1-3 weeks after 1st dose and over six months after 2nd dose in lung cancer patients | Cohort | 82 lung cancer patients & 53 healthy adults control | lung cancer patients | Median 68.0 | 59.8% female | Immunocompromised | Vaccine-acquired | Neutralizing antibodies |
| Vergori 2022 | Italy | na | Cohort | 134 (106 PLWH and 28 HCWs) | vaccinated PLWH | na | na | immunocompromised and healthy | vaccine acquired | Neutralizing antibodies |
| Vietri, 2022 | Italy | October to December 2020 (first | Cohort | 61 | Healthcare workers | 27 to 70 years | 26 males and 35 females | Healthy | Vaccine acquired | Serum IgG antibodies |

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| | | dose); November 2021 (blood sample); 12 months after first dose of vaccine, up to 270 days after second dose, and 90 days after booster dose | | | | | | | and hybrid | |
| Wang, 2022 | China | 2 (M2) and 12 months (M12) after disease onset | Cohort | 46 patients with COVID-19 (antibody-positive and/or nucleic acid test positive, Ab+ and/or NAT+) and 39 previously defined close contacts (Ab- and NAT- ) w | people with COVID-19 and some close contacts | Age: 48.3 (43.50–53.08), 49.2 (45.20–53.10) at M2 and M12 | Female 30.4% and 48.9% at M2 and M12 | NA | Natural | Anti-RBD IgG, Anti-nucleocapsid IgG, neutralizing antibodies, and T cells |
| Wilhelm, 2022 | Germany | Sera obtained 3 months after 3rd dose | Cohort | 165 | Adult serum donors | 2x BNT162b2: mean 51.7 yrs; 2x BNT162b2 + 1x BNT162b2: mean 40.8 yrs; 2x BNT162b2 + 1x BNT162b2: | 115/165 females | NA | Natural and vaccine acquired | Neutralizing antibodies |

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| | | | | | | mean 43.6 yrs; 2x mRNA-1273: mean 34.6 yrs; 2x mRNA-1273 + 1x BNT162b2: mean 31.9 yrs; 1x ChAdOx1 + 1x BNT162b2: 40.5 yrs; 1x ChAdOx1 + 2x BNT162b2: mean 45.9 yrs; 2x BNT162b2 + SARS-CoV-2: mean 85.5 yrs | | | | |
| Wratil, 2022 | Germany | April 2020 onward | Cohort | 202 | Adult health care workers | Naïve individuals: median 36 (IQR 29-53) ; Convalescent: median 40 (IQR 29-54) ; Breakthrough infections (Delta): median 35 (IQR 31-38) ; Breakthrough infection (Omicron): median 41 (IQR 28-49) | Naïve individuals: 65.8% female; Convalescent: 57.6% female; Breakthrough infections (Delta): 56.3% female; Breakthrough infection (Omicron): 40% female | NA | Natural, vaccine-acquired, hybrid | IgG antibodies & neutralizing antibodies |
| Xia, 2022 | United States | After 3rd dose administration | Cohort | 42 | Boosted individuals | Range: 23-74 | 15 females, 9 males | NA | Vaccine-acquired | Neutralizing antibodies |

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| Zou, 2022 | United States | April 2020 to January 2021 (sera collection) | Cohort | 100 | Convalescent individuals | All ages | NA | NA | Natural | Neutralizing antibodies |