

Literature review report

Immunological Surveillance: Intermediate report

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Highlights

- Prior infection with non-Omicron variants and primary-scheduled vaccination leads to low and reduced cross-neutralization and to substantial loss in binding antibodies (IgM, IgG, IgA) against Omicron, with reported waning over time.
- Fever or more severe clinical outcomes induce a stronger antibody response than milder symptoms and illnesses.
- mRNA vaccines, specifically mRNA-1273, in both homologous and heterologous vaccine schedules, confer better neutralization against the Omicron variant than non-mRNA vaccines.

- A booster dose increases the magnitude and breadth of neutralizing antibodies against Omicron but continues to show signs of waning.
- Despite high binding antibody titers elicited by booster doses, breakthrough infection with Omicron still occurred.
- Breakthrough infections caused by Omicron induced a high breadth of neutralizing antibodies in fully vaccinated and boosted individuals, although the response was less pronounced in triple vaccinated breakthrough infections than double vaccinated individuals.
- Antibody levels elicited through hybrid immunity also wane over time with significant decreases after 6 months.
- Vaccinated individuals elicit higher neutralizing titers against variants, including Omicron, than unvaccinated convalescent individuals, three months up to one year after full vaccination.
- Convalescent individuals, including those with breakthrough infections, retain a significant amount of T cell and B cell memory up to a year after infection.
- Vaccinated individuals elicit a higher T cell response for all variants of concern, with 3rd vaccine doses eliciting a diverse memory B cell repertoire capable of clearing even Omicron.
- Immune responses after vaccination are generally stronger compared to those after naturally occurring infection.
- Hybrid immunity and three-dose vaccination elicits stronger cellular immune response to Omicron than only two-dose vaccination.
- Immunocompromised groups often generate a weak binding and neutralizing antibody response after mRNA vaccination with antibody responses waning with time after vaccination.
- Cellular immunity is sustained in immunocompromised groups and is enhanced by a third vaccine dose.
- Hybrid immunity and a third dose sustain binding antibody response and increase neutralizing antibodies significantly in the elderly population.
- Vaccines offer protection from severe COVID-19 illness and hospitalization in elderly groups, with protection increasing with increasing doses but waning over time.

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1. Introduction

As the fight against COVID-19 continues globally, an understanding of the role of humoral and cellular immunity can aid in the rapid implementation of vaccine and safety guidelines. SARS-CoV-2 is an enveloped betacoronavirus with protrusions of large trimeric “spike” (S) proteins (1). Receptor binding domains (RBDs) located at the tip of these spikes enable entry into host cells via interaction with human angiotensin-converting enzyme 2 (ACE2) (1). After entry, the SARS-CoV-2 virus is absorbed into the host cell and uses the host ribosome to produce its own mRNA, which then continuously synthesizes viral proteins in the cell cytoplasm (1). SARS-CoV-2 causes a myriad of clinical symptoms ranging from asymptomatic infection to mild to moderate infection, such as upper and lower respiratory symptoms, to critical illness requiring hospitalization, death, and long-COVID symptoms. In addition to all of this, it also elicits a complex immune response (1). Therefore, fully understanding the immune response against SARS-CoV-2 is indispensable. The immune response can be measured by analyzing antibody levels, neutralizing antibodies, T cell, and memory B cell responses. Antibodies that recognize RBDs have been considered the most important component of immunity against SARS-CoV-2 in humans due to their neutralizing activity (1). Humoral response studies in SARS-CoV-2 infected patients have revealed that infection successfully induces robust responses with detectable IgG, IgM, and IgA antibodies (2). The neutralizing activity of SARS-CoV-2-induced antibodies has also been demonstrated in vivo by observing the improvement in the condition of severely ill COVID-19 patients that received passive transfer of specific antibodies from recovered patients (2). Current vaccines for SARS-CoV-2 infections have also been shown to elicit levels of neutralizing antibodies comparable to those observed in naturally infected persons (2). However, although COVID-19 infections induce antibody response, antibody levels may be dependent upon severity of disease and virus inoculum (3). Upon viral clearance, there will no longer be stimulation and proliferation of new B cells, which could lead to waning of immunity. Induction of SARS-CoV-2-specific memory T cells and B cells (as opposed to circulating antibodies) is therefore, important for long-term protection (3). In particular, T follicular helper (TFH) cells indicate maturation of the humoral immune response and the establishment of a pool of specific memory B cells ready to rapidly respond to possible reinfection (3). SARS-CoV-2-specific T cells are recruited from a randomly formed and pre-constituted T cell pool capable of recognizing specific viral epitopes (3). Specific CD4+ T cells are important for eliciting potent B cell responses that result in antibody affinity maturation, and the levels of spike-specific T cells correlate with serum IgG and IgA titers (3). Robust immune responses with spike-specific neutralizing antibodies, memory B cells and circulating TFH cells have been found in patients who have recovered from COVID-19 infection (3). Although spike-specific CD4+ T cells are found in patients with COVID-19, 30–50% of healthy people with no detectable COVID-19 infection also had SARS-CoV-2-specific CD4+ T cells and 20% had CD8+ cytotoxic T cells (3).

Since the beginning of the COVID-19 pandemic in 2019, the world has witnessed the emergence of several SARS-CoV-2 variants that have changed the clinical and epidemiological course of the pandemic. SARS-CoV-2 uses its spike glycoprotein (S) to infect target cells; this spike protein contains the receptor-binding domain (RBD) and the N-terminal domain (NTD) (4, 5). Studies have shown that these RBDs and NTDs are vital targets for the adaptive immune system, particularly neutralizing antibodies (6). Similarly, many COVID-19 vaccines have also been designed to target the SARS-CoV-2 spike protein, with a focus on the RBD as it mediates viral entry into cells (7). However, mutations in the SARS-CoV-2 spike protein are being

increasingly reported, which have resulted in the emergence of SARS-CoV-2 variants and variants of concern (VOC). These emerging VOCs have demonstrated decreased sensitivity to convalescent sera and threaten the effectiveness of available COVID-19 vaccines (8). Currently, five VOCs have been identified: the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529) variants (9). Out of the five VOCs, Omicron has accumulated the highest level of mutations and has mediated the greatest level of immune escape (10). The original Omicron variant (B.1.1.529) spike glycoprotein contains 37 mutations, compared to the approximately 10 substitutions observed in the Alpha and Delta variants (4, 10). More specifically, the Omicron RBD contains 15 mutations and the NTD contains 11 mutations, which has threatened neutralization antibody activity in previously vaccinated or infected individuals (11). With its enhanced transmissibility and immune escape, Omicron has become the most dominant COVID-19 variant circulating today (12). Evidence from laboratory studies point to significantly reduced neutralizing antibody response to the Omicron variant, compared to the original strain or previous VOCs (13). This suggests that the mutations harbored on the spike glycoprotein of the Omicron variant have altered the epitopes that were previously recognized by neutralizing antibodies (14). Consequently, there is emerging evidence that the level of reduction in a robust neutralization response against Omicron is linked to reduced protection from infection with Omicron in previously infected or vaccinated groups (15).

The process of antibody production during SARS-CoV-2 infection appears to be similar to that against other seasonal coronaviruses. Antibodies of the IgM class may be detected approximately 6 days after infection, and IgG may be detected after 8 days (1). Concentrations of the antibodies may decline over several months, which allows for subsequent infection. It has been reported that the size of RBD-specific memory B cells may remain stable nearly 6 months after natural infection with SARS-CoV-2 and that these memory cells could further display clonal turnover, with the derived antibodies exhibiting resistance to RBD mutations (1, 16, 17). More recent studies have observed anti-RBD antibodies after a positive COVID-19 test result for up to 20 months (18). Concerning the duration of effectiveness of vaccines, various studies found that against severe disease, it remains high and decreases slightly by 6 months after full vaccination, defined as 2 doses of mRNA vaccines or 1 dose of Janssen-Ad26.COV2.S (19). More recent research has found that strong CD4+ T cell responses were present against wildtype and mutant SARS-CoV2 variants, including the delta (B.1.617.2) strain, in fully vaccinated individuals, whereas they were partly weaker one year after natural infection (20). Further research needs to be implemented to examine the duration of immunity after a year to fully comprehend the length of protection provided by infection or vaccination.

As SARS-Cov-2 continues to affect large populations worldwide, many scientific publications become available daily, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Due to the large number of publications shared daily, decision makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the GRAPH Network team at the University of Geneva was mandated by the Swiss School of Public Health plus (SSPH+), upon request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature. This mandate focuses on immunological surveillance, with a particular focus on the Omicron variant and any new variants that arise during the time of the study. It provides a review on the protective correlate through SARS-CoV-2 antibodies and cellular immune response against re-infection, breakthrough infections and severe disease progression and a general overview of the duration of this protection in immunized individuals. With the potential for a seasonal increase of COVID-19 cases, the review will collect evidence-based data for recommendations on the strategic planning of the FOPH for the upcoming fall/winter (2022).

2. Methodology

A rapid literature review was conducted while adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Literature and Information Search

To identify potentially relevant studies, a search for literature published per week was completed using the following electronic databases: Medline (PubMed), Embase, medRxiv & bioRxiv, Cochrane Library, and SSRN. In addition, grey literature such as information produced by government agencies, academic institutions, press releases, and journals such as New England Journal of Medicine, The Lancet, and Nature were screened, and hand searched. To avoid missing the most recent articles, journals were independently screened due to the few days gap between their date of publication and addition to public databases such as Medline and Embase.

2.1.1 Search Strategy

A design 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 was used for the Medline, Embase, and medRxiv/bioRxiv databases. Since the scope of the mandate includes both types of adaptive immunities (vaccine-induced immunity and natural immunity), two separate queries for the different immunities were created and performed in parallel for the Medline and Embase databases. The literature search was performed on a weekly basis by one of the researchers. The search strategy for the Medline, Embase, and medRxiv & bioRxiv can be found in Supplementary Material 1.

2.1.2 Software

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

2.2 Literature Screening

Search-identified literature was imported into Rayyan, and titles and abstracts screened for COVID-19 immunology related articles. At least two reviewers screened the literature and agreed on its inclusion to move to the full text review. 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 added to Rayyan for literature assessment and selection.

2.3 Eligibility of Studies

Eligible studies were those reporting any data about immunological assays of Covid-19 (related to vaccination and/or infection) or effectiveness of protection (related to the effectiveness of vaccination and/or

infection). No language restriction was used (though the search queries were in English), and, for relevance, studies were limited by publication date of 01 November 2021 to 27 May 2022.

2.4 Risk of Bias (Quality) Assessment

Due to the nature of the methodology and the overwhelming new COVID-19 information released on a daily-basis, the risk of bias and quality of included studies was not evaluated.

2.5 Data Extraction and Analysis

Data was extracted to a common Excel table from studies that included, but were not limited to, data on the immunological surveillance of COVID19 immunity after vaccination and/or infection.

3. Results

3.1 Study Selection and Characteristics

This report includes research published between 01 November 2021 and 27 May 2022. The final report in October will include research up until mid-October 2022 and will provide an updated version of this report. A total of 4,487 studies were found using the search queries, including 3,108 after deletion of duplicates. After title and abstract screening by two authors, 957 studies were included for full text review. After full text review 103 articles were included in this review, (Figure 1).

Out of the 103 studies included in this report, 51 focused on humoral responses, 10 on cellular responses, 12 on both cellular and humoral responses and 17 on vaccine effectiveness. The remaining 13 studies compared protection provided by vaccines, natural immunity, or hybrid immunity, while one study assessed the correlate of protection provided by a humoral and cellular immune response. Sixteen studies included in this report assessed healthy or immunocompetent participants while 15 studies included immunocompromised or immunosuppressed individuals. Another 12 studies included subjects that had chronic diseases or co-morbidities while no information was available on the immune status of individuals for 60 of the studies. Further details on the characteristics of the included studies can be found in Supplementary Material 2.

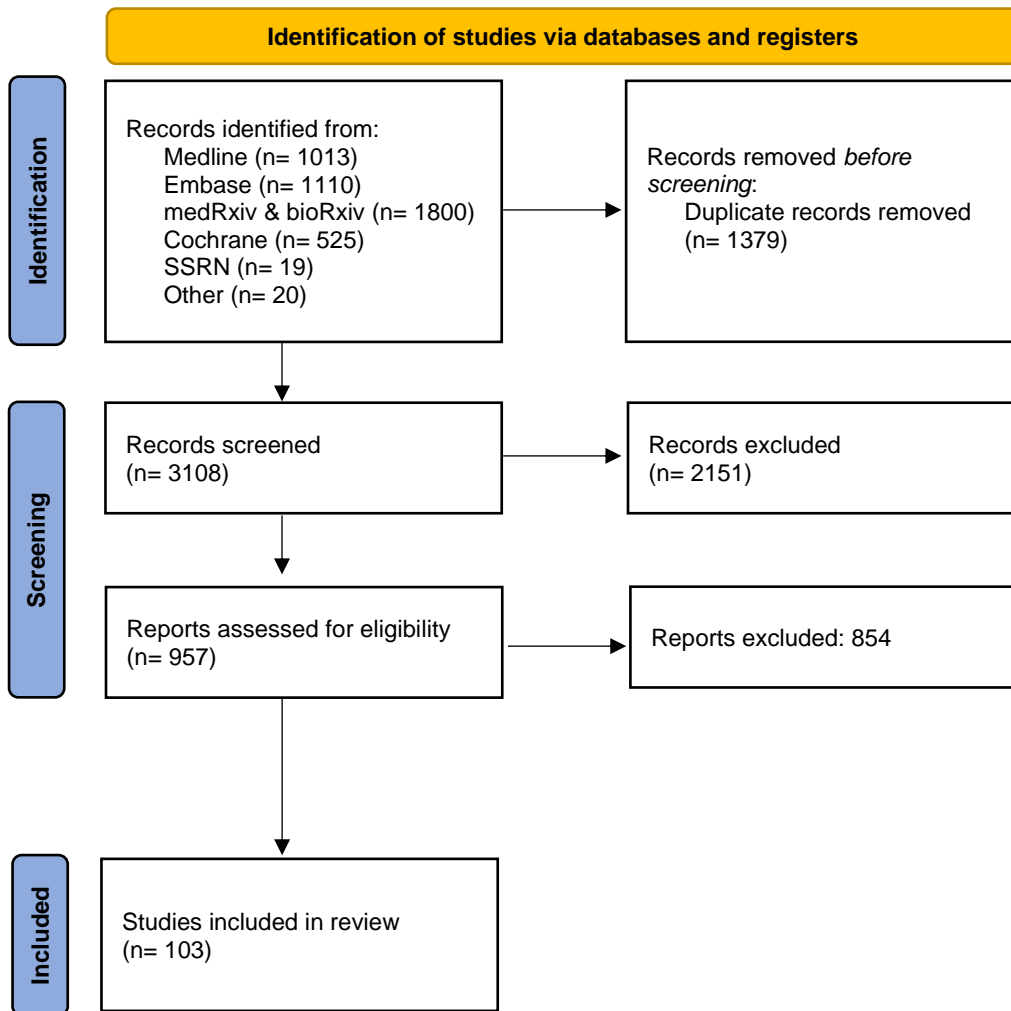


Figure 1. PRISMA flow chart of study identification and selection

3.2 Prevalence of Adaptive Immunity

3.2.1 Humoral Immunity

3.2.1.1 Natural immunity

Two studies analyzed the antibody levels of protection acquired from natural immunity through the measurement of the neutralizing antibodies response against the wild-type and Omicron variant ([1](#), [21](#)). In one study, the clinical severity and longevity of the antibody response was evaluated in infected participants ([1](#)), while in both studies the neutralizing capacity of the elicited antibody response acquired from prior infection was tested against the predominant variant Omicron ([1](#), [21](#)).

Fever or more severe clinical outcomes induce a stronger antibody response than milder symptoms and illnesses.

Based on the results from Chen et al, the clinical severity of infected patients demonstrated to play a role in the level of antibody response against SARS-CoV-2. Participants who experienced symptoms such as fever or more severe clinical outcomes such as pneumonia induced a stronger antibody response than patients who experienced milder symptoms and a milder illness ([1](#)).

Naturally acquired immunity wanes over time (after 11 months from injection).

When looking at the duration of the naturally acquired antibody response, a clear decrease in the elicited antibodies was observed after 11 months ([1](#)).

Prior infection with non-Omicron variant leads to low and reduced cross-neutralization against Omicron.

Regarding the ability of the elicited antibody response to neutralize the Omicron variant, a prior infection with a non-Omicron variant demonstrated to lead to low and reduced cross-neutralization against Omicron (B.1.1.529) where a large fold-decrease in neutralization was observed when compared to the neutralization capacity against the original SARS-CoV-2 strain ([1](#), [21](#)).

3.2.1.2 Vaccine-acquired immunity

A total of 13 studies included in the review analyzed the humoral immunity induced by vaccination through the measurement of antibody levels and neutralizing antibodies against the Omicron variant ([22-34](#)). Of the included studies, eight, including vaccinated participants, reported on the neutralization of antibodies against the Omicron variant (B.1.1.529) ([24](#), [27-32](#), [34](#)), while five studies reported on antibody levels ([22](#), [23](#), [25](#), [26](#), [33](#)).

Primary-scheduled vaccination does not elicit robust neutralizing antibodies against the Omicron variant B.1.1.529 and its subvariants and wanes over time.

Based on the included studies, the level of neutralizing antibodies against the Omicron variant B.1.1529, three to six months after receiving the second dose of any mRNA vaccine (BNT162b2 or mRNA-1273), was lower than previous variants such as the original wild strain or Delta variant (24, 27-29, 31, 32, 34). Overall, two doses of an mRNA COVID-19 vaccine did not elicit robust neutralizing antibodies against the Omicron variant (B.1.1.529), irrespective of the recipient's age (24, 27-29, 31, 32, 34). One study analyzing the neutralizing antibodies of vaccinated participants found that with each new Omicron subvariant (BA.1 vs. BA.2 vs. BA.3), the ability of the antibodies elicited through vaccination to neutralize the variants was lower than the previous one (28). For instance, the BA.1-, BA.2-, and BA.3-spike antibodies were 3.6-, 4.0-, and 6.4-fold less efficiently neutralized than the original, wild strain. In addition to not adequately neutralizing the Omicron variant, the antibody levels after the second dose were shown to gradually decrease with 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 (24).

mRNA vaccines, specifically mRNA-1273, confer better neutralization against the Omicron variant.

When comparing the level of protection different vaccines provide, the included studies reported that mRNA vaccines induced higher antibody levels and were able to better neutralize the Omicron variant than the Janssen vaccine (30). Among mRNA vaccines, the mRNA-1273 vaccine had a higher geometric mean titer than the BNT162b2 vaccine (158 EIA vs. 128 EIA) within 3 weeks after receiving the second dose, showing a somewhat higher neutralizing antibody level in individuals who were vaccinated with Moderna compared to those who received the Pfizer and BioNTech vaccine (24). Overall, mRNA vaccines demonstrated to provide a higher and more robust level of protection compared to the viral vector vaccine Janssen.

A booster dose increases the magnitude and breadth of neutralizing antibodies against Omicron but continues to show signs of waning.

Although antibody levels elicited by the primary vaccination schedule (two doses of mRNA vaccines) were shown to gradually wane over time, the administration of a third dose induced a strong immune response, allowing boosted individuals to regain similar or sometimes higher antibody levels than the initial vaccination schedule (24, 27, 30-32, 34). A third dose of the BNT162b2 or mRNA-1273 vaccine increased the magnitude and breadth of the otherwise waning neutralizing antibodies against the Omicron variant; nevertheless, they provided a lower neutralizing capacity against Omicron compared with previous VOCs. Despite the ability of booster doses to reestablish previous neutralizing antibodies prior to the Omicron variant, one study demonstrated that 4 months after receiving a third booster dose, the neutralization geometric mean titers decreased significantly (34).

mRNA vaccines continue to demonstrate higher neutralizing antibodies against Omicron when compared with homologous or heterologous vaccination schedules including the viral vector vaccine.

Between the two mRNA vaccines, no significant difference in the antibody levels elicited after the third dose was reported (24). As for the difference between homologous and heterologous booster vaccinations, a

distinct difference was seen between the homologous prime-boost Ad26.COVS and any other heterologous booster combinations (30). For instance, participants vaccinated with two doses of the Janssen vaccine elicited the lowest neutralizing antibodies against the wild type and Omicron variant while participants vaccinated with the homologous mRNA-1273, homologous BNT162b2, heterologous BNT162b2/Ad26.COVS, or Ad26. COVS booster combination had higher neutralizing antibodies against both variants (30).

Substantial loss in binding antibodies (IgM, IgA, and IgG) to Omicron variant.

When looking at the different Omicron binding antibodies elicited through vaccination, a substantial loss in the levels of IgM, IgA, and even IgG antibodies was noted in individuals fully vaccinated (23). This loss was more pronounced in antibodies targeting the Omicron RBD than antibodies targeting the Omicron Spike protein (23). Despite the antibodies' reduction in Omicron RBD recognition and neutralization, a robust and stable IgG response across variants of concern was observed for individuals vaccinated with mRNA vaccines (23). Additionally, a difference between vaccine types was observed in respects of the IgA RBD-specific cross-reactive response. Compared to BNT162b2, the mRNA-1273 vaccine reportedly maintained a stable binding against the full-length Omicron Spike protein, although compromised but not completely lost (23).

Antibodies elicited by primary vaccination wane over time, but a booster dose increases the antibody levels and inhibition against Omicron.

Regarding the duration of antibody levels, low levels of antibody titers were observed six months after full administration of the mRNA-1273 vaccine (22). These levels were not proven to provide sufficient antibodies to prevent breakthrough infections with the Omicron variant as primary-schedule vaccinated individuals experienced breakthrough infections. Nevertheless, binding antibodies against vaccine strain spike and the receptor binding domain were significantly higher in boosted individuals compared with individuals who did not receive a booster dose. These results demonstrate that vaccination with a booster dose increases the antibody levels and inhibition against the Omicron variant (33). Although an increase in antibodies was seen after the administration of a booster dose, breakthrough infections were reported in the study's cohort (33), highlighting the possibility of breakthrough infections to occur despite potent adaptive immune responses in vaccinated and even boosted individuals (33).

Despite high binding antibody titers elicited by booster doses, breakthrough infection with Omicron still occurred.

Various studies including Adachi et al. analyzed the total antibody concentration of individuals vaccinated with 2 doses (fully vaccinated) or boosted individuals at the time of breakthrough infection (22, 26, 33). The majority of the Omicron breakthrough infections occurred in individuals with relatively high total antibody concentrations where 90% of the Omicron infections occurred in people whose total antibody concentrations was less than or equal to 6967 BAU/mL (26). When comparing the median antibody titer at breakthrough infection, between the two mRNA vaccines, a median of 633 AU/mL (IQR 400-994) for the BNT162b2 vaccine and 9416 AU/mL for the mRNA-1273 vaccine was reported. An aggregated and overall median antibody titer at breakthrough infection of 776 AU/mL (IQR: 411-1805) was calculated (22). Despite the high binding antibody concentration, breakthrough infections with the Omicron variant were reported even with concentrations 2.4 times higher than infections with the Delta variant.

3.2.1.3 Hybrid

Four included studies analyzed the humoral immunity through the measurement of neutralizing antibodies and levels of antibodies against various SARS-CoV-2 strains, including the wild type, Delta, and Omicron variants (33, 35-37).

Breakthrough infections caused by Omicron induced a high breadth of neutralizing antibodies in fully vaccinated and boosted individuals, although the response was less pronounced in triple vaccinated breakthrough infections.

After analyzing the results from the included studies, breakthrough infections caused by the Omicron variant induced a profound breadth of neutralizing antibodies in previously fully vaccinated subjects. Nevertheless, this response was not always persistent. For instance, in individuals previously vaccinated with the two doses of the BNT162b2 vaccine, a breakthrough infection with the Omicron variant resulted in a strong cross-neutralizing activity against the Omicron variant as well as against previous SARS-CoV-2 variants of concern (36). As seen in Quandt et al., the geometric mean titers of neutralizing antibodies against Omicron BA.1 and BA.2 was more than 100-fold and 35-fold higher than the geometric mean titers of individuals fully vaccinated and without prior infection. Additionally, in Soraas et al. an infection with the Omicron or even the Delta variant demonstrated to modestly increase the levels of anti-RBD titers (37). Moreover, Omicron breakthrough infections not only increased the geometric mean titers observed in fully vaccinated individuals, but among boosted individuals as well. Conversely, the effects of Omicron breakthrough infections was less pronounced in boosted individuals where the hybrid immunity only conferred an approximate 7- to 4-fold increase in neutralizing ability compared to triple vaccinated individuals with no prior infection (36). Opposingly, one study found that at one to three weeks after the onset of symptoms, breakthrough infections in vaccinated individuals led to comparable antibodies levels against the variant's spike protein seen in non-convalescent boosted individuals (33).

Lower titers of Omicron cross-reactive antibodies were elicited in individuals with hybrid immunity than with other variants.

Despite the non-persistent increase in antibody levels conferred by hybrid immunity, statistically significant lower titers of Omicron cross-reactive antibodies were elicited in vaccinated COVID-19 convalescent individuals compared with other variants (35). These results continue to emphasize that Omicron evades elicited antibodies more effectively than other variants, regardless of the super-immunity induced by vaccination and infection.

mRNA vaccines (BNT162b2/mRNA-1273) confer higher antibody levels and response than Janssen vaccine.

When comparing the antibody level response a previous infection and different vaccines confer, mRNA vaccines were shown to lead to higher levels of anti-Spike antibody response than the Janssen vaccine (35). Nonetheless, the Janssen vaccine demonstrated to induce greater RBD antibodies for all variants, including Omicron. In addition, the antibody level maintained a stable response even after 8 months post vaccination (35).

Antibody levels elicited through hybrid immunity also wane over time with significant decreases after 6 months.

Similar to previous results on the duration of protection conferred by natural or vaccine-acquired immunity, hybrid immunity showed signs of waning protection. To evaluate the duration of the antibodies elicited against the Omicron variant, Chang et al. divided the study participants into two groups: one representing the short-interval (6 months after recovery from infection) and the long-interval (12 months after recovery from infection). Based on the results, antibodies elicited against Omicron demonstrated to have significantly decreased in neutralization 6 months after recovery from infection (35). For example, the geometric mean titer ratio for individuals in the short-interval group was 2.6, whereas the geometric mean titer ratio for individuals in the long-interval was 1.7 (35).

3.2.1.4 Comparing different immunities

Various studies included in this review compared different adaptive immunities (e.g.: natural, vaccine-acquired, hybrid) through the measurement of humoral immunity (13, 20, 36, 38-64). The studies were organized by the comparison of the different type of immunities (e.g.: natural vs. vaccinated; natural vs. hybrid; vaccine vs. hybrid; natural vs. vaccine vs. hybrid).

3.2.1.4.1 Natural vs. vaccination

Vaccinated individuals elicit higher neutralizing titers against variants, including Omicron, compared with unvaccinated convalescent individuals three months after full vaccination.

From all of the included studies, only four articles directly compared the levels and neutralizing capabilities of antibodies between convalescent individuals and naïve individuals fully vaccinated with a COVID-19 vaccine (20, 49, 52, 60). As previously reported, unvaccinated convalescent individuals did not effectively neutralize variants of concern such as the Delta variant and the currently predominant Omicron variant. For instance, one study identified a near-complete lack of neutralizing activity against Omicron in individuals vaccinated with two doses of the BNT162b2 COVID-19 vaccine as well as in convalescent individuals (49). When drawing a direct comparison between unvaccinated convalescent individuals and naïve vaccinated individuals, the neutralizing titers against the wild type, Delta, and Omicron variant were significantly higher in vaccinated individuals compared to the unvaccinated convalescent individuals (20, 60). Consequently, the immune response elicited in vaccinated individuals was higher and stronger than in naturally occurring infections. An illustration of this example can be seen in the article from Seidel et al. where a 11- to 60-fold higher geometric mean neutralizing titers was observed in vaccinated participants compared to convalescent participants, especially in the first three months following the administration of the primary series vaccine (60).

One year after vaccination or infection, mRNA vaccinated individuals had higher neutralizing antibodies than convalescent ones.

One study examined the levels of neutralizing antibodies in convalescent and vaccinated individuals up to one year after the initially reported infection (20). Based on the reported results, the levels of neutralizing

antibodies in mRNA vaccinated individuals were up to one year after infection, where the anti-N titers only amounted to around 66 AU one year and around 21 AU two months after natural infection (20).

Booster doses improve the humoral immune response against Omicron in both previously vaccinated and convalescent individuals.

When performing an antigenic cartography to explore how the different immunities distinguish the different spike antigens, the convalescent samples were more heterogeneous than the vaccinated samples. These results demonstrate that vaccinated samples were able to decrease the antigenic distance between Omicron and other variants such as the wild type and Delta. This decrease in the antigenic distance was even more emphasized in triple vaccinated individuals compared to convalescent and double vaccinated individuals (52). Similar results where double vaccinated and convalescent individuals received a booster dose were seen in Gruell et al. In the study, mRNA booster immunization in vaccinated and convalescent individuals resulted in a significant increase of serum neutralizing activity against Omicron. Overall, demonstrating that booster immunization can critically improve the humoral immune response against the Omicron variant in both previously vaccinated and convalescent individuals (49).

3.2.1.4.2 *Natural vs. hybrid*

Infection with Omicron increased the neutralizing antibodies in both vaccinated and unvaccinated individuals, despite lower and moderate increase in absolute levels of neutralization against BA.1, BA.2 in unvaccinated individuals compared to vaccinated ones.

Studies by Khan et al., Richardson et al., and Seaman et al. showed that Omicron infection increased the geometric mean of neutralizing antibodies in both vaccinated and unvaccinated individuals (51, 54, 59). Post Omicron infection, neutralization against BA.1 Omicron increased by 13.6-fold in vaccinated individuals and 6.0-fold in unvaccinated individuals (51). Infection with the BA.1 variant alone was also found to induce stronger neutralization against Delta, BA.1 and BA.2, when compared to infection with the Delta variant alone (59). Nevertheless, unvaccinated individuals infected with BA.1 still had limited cross-protection against Omicron, its subvariants and previous variants, despite the moderate increase in neutralizing antibodies observed post infection (51, 54, 59, 63). Khan et al, found that unvaccinated individuals had low absolute levels of neutralization, 2.2-fold lower for the BA.1 variant and 4.8 fold lower for BA.2 relative to vaccinated individuals infected with BA.1 (51). Similarly, Seaman et al. showed that neutralizing activity was lower in unvaccinated individuals at the time of infection, compared to previously vaccinated groups (59).

Even with Omicron infection, high cross-neutralizing antibodies against variants of concern were not mounted.

Although neutralization triggered by the Omicron BA.1 infection could not mount highly cross-reactive neutralization against variants of concern (54), hybrid immunity after an Omicron breakthrough infection was associated with enhanced cross neutralization across various variants of concern including Delta and Omicron (51, 54, 59). Tada et al. found that viruses with the Omicron spike protein were 26-fold more resistant to neutralization by sera from recovered donors (63). Similarly, these viruses were 26-34-fold resistant to mRNA vaccine induced neutralization following two doses. Furthermore, Seaman et al. found

that the BA.2 variant exhibited the highest resistance to neutralization by convalescent serum from previously infected individuals (59). However, a booster dose combined with a history of prior SARS-CoV-2 infection did increase neutralizing titers against Omicron (63).

3.2.1.4.3 Vaccination vs. hybrid

Drop in elicited neutralization against the Omicron variant was seen in individuals infected and vaccinated as well as in naïve individuals who received a full vaccination schedule.

A general trend in individuals with vaccine-acquired and hybrid immunity was observed when analyzing the neutralizing antibody titers against the Omicron variant. Based on two studies, both infected-vaccinated and naïve-vaccinated individuals showed a similar fold drop in elicited neutralization against the predominant Omicron variant (41, 42). These results demonstrate that Omicron decreased the overall neutralizing capacity of induced antibodies in both groups, regardless of super immunity. In Cele et al., both participants who were infected and vaccinated and vaccinated with no prior infection showed a 22-fold reduction in neutralization against Omicron. In previously infected and vaccinated participants a 95% confidence interval of 16 to 34 was reported while naïve vaccinated participants had an interval of 15 to 32 (13).

A higher neutralization capacity against the Omicron and previous variants was observed in individuals previously infected and vaccinated than in only vaccinated individuals.

Once again, hybrid immunity demonstrated to elicit higher humoral immunity when compared to vaccinated individuals. Overall, Individuals who were vaccinated and had previously been infected exhibited higher neutralization capacity for the ancestral virus and the Omicron variant relative to only individuals vaccinated with two doses of the BNT162b2 vaccine (41, 44, 48, 53, 61). As seen in one of the articles, participants with pre-Omicron breakthrough infections had a median plasma neutralization titer 2.8-, 4.9-, and 26.4-times greater against ancestral strain, Delta, and Omicron variants than uninfected two-doses vaccines recipients (48). An even higher increase in neutralizing antibodies was seen in individuals with Omicron breakthrough after only 2 vaccine doses. Median neutralizing titers of 4.2-, 7.4-, and 161.5-times greater against the ancestral strain, Delta, and Omicron variants was observed in breakthrough infections in fully vaccinated breakthrough infection compared to uninfected vaccinated ones (48). Additionally, the Omicron virus neutralization from individuals with super immunity (previously infected and fully vaccinated) restored the waning levels of neutralization elicited in naïve double BNT162b2 vaccinated individuals against the ancestral virus (41).

A booster dose and breakthrough infection induced higher breadths of neutralizing activity against Omicron, although Omicron breakthroughs provided limited variant-specific cross-neutralizing immunity.

Multiple studies have found that breakthrough infections in boosted individuals led to dramatic increases in the magnitude, potency, and breadth of antibodies that neutralize the recently circulating Omicron variant (36, 45, 48, 61). When comparing the response after two doses of mRNA vaccines, the humoral response three months after a third vaccine dose and one month after breakthrough infection due to prior variants showed increasing levels of antibodies (cellular phagocytosis dependent and neutralizing) (45). Even when comparing the neutralizing titers of three dose recipients, participants with Omicron

breakthrough infection continued to demonstrate greater levels against Omicron and previous variants (48). Based on the article, Omicron breakthrough infection had neutralizing titers 2.9-times greater against Omicron and 1.4-times greater against Delta than triple vaccinated individuals; nonetheless, titers from breakthrough infections did not elicit a higher response against the ancestral strain than in boosted individuals (48). Moreover, when examining the neutralizing capacity against Omicron's subvariants BA.1 and BA.2, the effects of Omicron a breakthrough infection in triple vaccinated individuals was less pronounced, nonetheless greater, than in Omicron-naïve triple vaccinated individuals, where an approximate increase of 7- to 4-fold and a geometric mean titer of 1029 and 836 versus 160 and 211 was seen observed, respectively (36, 48). Although, Omicron breakthrough infections elicited the greatest increase in neutralizing titers against the same variant (Omicron), when compared to vaccine-acquired humoral immunity, Delta or even Omicron breakthrough infections were found to have limited variant-specific cross-neutralizing immunity. According to Servellita et al., Delta breakthrough infections elicited 57- and 3,1-higher titers compared to uninfected three dose and two dose individuals, respectively, while Omicron breakthrough infections only led to a 5.8- and 3.1-fold increase (61). These results suggest that Omicron breakthrough infections were less immunogenic than Delta and would, therefore, provide reduced protection against reinfection or infection from new possible emerging variants (61).

Longer interval between vaccination and breakthrough infection led to better antibody response against Omicron.

Miyamoto et al. evaluated the relationship between neutralizing activity against each variant and the time between vaccine completion and breakthrough infection in each of the included cases, in order to understand possible factors contributing to high heterogeneity of cross-neutralizing titers against variants (53). Based on the findings, the neutralizing activity against the ancestral virus and each variant, including Omicron, positively increased with the increase in the time between vaccination and breakthrough infection. In addition, the degree of correlation between neutralizing activity and vaccination-to-infection interval was stronger for the Beta and Omicron variants (53). Overall, a longer interval between vaccination and breakthrough infection was significantly correlated to a more favorable and better antibody response against the Omicron variant in individuals who had non-Omicron-variant breakthrough infections, as these results were not tested in Omicron-breakthroughs (53).

Over time, hybrid immunity continued to exhibit higher neutralizing abilities against all variants, including Omicron than vaccine-acquired immunity.

When taking into consideration the duration of the humoral immunity in individuals with a hybrid or vaccine-acquired immunity, vaccinated and infected individuals continued to exhibit higher neutralizing abilities against Omicron than only vaccinated individuals (42, 46, 47). With the passing of time, vaccinated individuals who experienced an infection with SARS-CoV-2 continued to demonstrate a higher fold-neutralizing capacity against variants than only vaccinated individuals. For instance, 6 months after vaccination, healthcare workers with anti-N proteins (convalescent individuals), exhibited 5.9-fold higher neutralizing values for all variants than healthcare workers with no anti-N protein (no prior infection) (47). Nonetheless, the neutralizing antibody titers against all variants tested, including Omicron, declined from one to six months after the second mRNA vaccine dose; however, an infection boosted the vaccine response (47). Another study found similar results where six months after the initial primary vaccine doses, the sera from naïve vaccinated participants demonstrated no neutralizing activity against the Omicron variant, while fully vaccinated individuals who recovered from COVID-19 only showed a 22-fold reduction

with most participants retaining their neutralizing antibody response (46). When looking at the Spike protein antibodies, from 3 weeks to 25 weeks after the administration of a second dose, the levels of plasma binding against Omicron in previously infected individuals were similar to those against Delta in naïve individuals (42). Additionally, Spike recognition declined more rapidly in naïve vaccinated individuals compared to the previously infected vaccinated individuals (42).

Milder clinical outcomes after breakthrough infections lead to lower titers against Omicron and previous variants than more severe infections.

In one specific study, the antibody response in Omicron asymptomatic or mild breakthrough infections exhibited 12.3-fold lower titers against the wild type virus compared with moderate to severe breakthrough infections, suggesting that the severity of the clinical outcomes from infections played a role in the levels of elicited antibodies (61).

3.2.1.4.4 Natural vs. vaccination vs. hybrid

Multiple studies included participants with various and diverse immunities such as convalescent, fully vaccinated, boosted, super-immune, and individuals with a combination of multiple re-infections with vaccination (38-40, 43, 50, 55-58, 62, 64).

Hybrid immunity elicited the most robust humoral immunity with the highest levels of neutralizing titers against Omicron, compared to naturally and vaccine-acquired immunity.

After comparing the humoral immunity conferred from natural, vaccine-acquired, or hybrid immunity, the largest drop in neutralizing antibodies against Omicron was observed in individuals who only experienced an infection and did not receive any sort of COVID-19 vaccination. These results were observed in Arien et al. where a significant larger reduction against the Omicron variant, more specifically a 22 to higher fold reduction in convalescent individuals, a 13.1-fold reduction in triple vaccinated individuals without prior infection, and a 20.5-fold reduction in triple vaccinated individuals with previous infection, was reported (38). To a similar extent, multiple studies reported similar results where participants with a hybrid immunity, especially boosted individuals, generated the most robust humoral immunity against the Omicron variants, when compared to natural and vaccine-acquired immunity (39, 40, 50, 56-58, 62, 64). These results were mainly highlighted in Wratil et al., wherein the article demonstrated that superior neutralization capacity against all variants of concerns, including Omicron, was obtained after two or three vaccinations in convalescents or a breakthrough infection in fully vaccinated individuals (64). In accordance with Wratil et al. results, Carreno et al. concluded that neutralizing activity from only infected and fully vaccinated individuals was undetectable against Omicron to some extent, whereas, among individuals who had been exposed three or four times through infection and vaccination, the neutralizing capacity against the Omicron variant was maintained, although at significantly reduced levels (40). Overall, high-quality antibodies with an increased neutralizing capacity against Omicron were elicited through three or more consecutive antigen exposures (through vaccination or infection). Nonetheless, other individuals with full vaccination or booster doses and with or without infections still showed a pronounced decrease in neutralizing antibody titers compared to previous variants of concerns such as Delta, as demonstrated in most of the previously mentioned studies.

BA.1 and BA.2 cross-neutralization improved with repeated exposure of hybrid immunity.

Two studies compared the different sort of acquired immunity in participants infected with Omicron's subvariants' BA.1 and BA.2 (43, 55). Based on the findings, unvaccinated individuals and previously uninfected individuals who acquired a BA.2 SARS-CoV-2 infection had limited cross-neutralizing antibodies to pre-omicron and BA.1 variants (43, 55). Nevertheless, vaccinated individuals with BA.2 breakthrough infections or individuals with a repeated exposure of at least two times, including both vaccination and infection, had broad neutralizing responses to the wild type, BA.1, BA.2, and even Delta. In other words, cross-neutralization improved with repeated exposure and increase in absolute titers of antibodies.

3.2.2 Cellular Immunity

3.2.2.1 Natural immunity

Convalescent individuals retain a significant amount of T cell and B cell memory up to a year after infection.

One study analyzed circulating memory B cells, and T cells against wild type, Delta, and Omicron variants in convalescent individuals (65). Based on the results from this study, CD4+ and CD8+ T cells showed a stronger memory than memory B cells against SARS-CoV-2 at one year after infection (65). A positive SARS-CoV-2-specific memory CD4+ T cells response was determined using different kinds of peptide pools. 92% of individuals responded to at least one peptide pool at 1-year after infection and 77% of convalescents responded to more than 3 peptide pools, showing a strong CD4+ T memory. When looking at CD8+ T cell response, 90% of the individuals responded to at least one peptide pool (65). However, only 56% of individuals responded to more than 3 peptide pools, a ratio that is lower than CD4+ T cell responses. In terms of memory B cells, only 38% of the convalescents maintained a prominent amount of memory responses after one-year post-infection with no difference in responses between mild and severe groups (65). The study also found that convalescents should still be able to induce effective T cell immunity against the Omicron variant as a majority of CD8+ T cell epitopes of SARS-CoV-2 are conserved in Omicron (65).

3.2.2.2 Vaccine-acquired immunity

A total of nine studies analyzed the cellular immunity initiated by vaccination through the measurement of T cell and memory B cell responses against wild type, Delta, and Omicron variants (33, 66-73).

Vaccinated individuals elicit a higher T cell response for all variants of concern than nonvaccinated individuals.

The study by Liu et al. found that individuals who received the Ad26.COV2.S or BNT162b2 vaccines demonstrated durable spike-specific CD8+ and CD4+ T cell responses, which showed extensive cross-reactivity against both the Delta and the Omicron variants, including in central and effector memory cellular subpopulations (69). Median Omicron spike-specific CD8+ T cell responses were 82–84% of the WA1/2020 spike-specific CD8+ T cell responses. Studies by Cohen et al. and Peng et al. analyzed CD4+ T cell response in the form of IFN- γ presence after vaccination (66, 72). One study found that the frequencies of spike-specific IFN- γ +CD4+T cells in the vaccinated group were significantly higher than those of the non-vaccinated controls (72). There was a slight non-significant decrease in IFN- γ secreting cells responding to

Omicron spike (66) and three months after vaccination, there was waning of memory T cell responses for both Delta and Omicron variants (72). 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 are stronger up to 6 months after all vaccination regimens (67). Woldemeskel et al. also found that boosted vaccine recipients had significantly stronger T cell responses to both vaccine strain and Omicron variant spike proteins at times of breakthrough infection compared to boosted COVID-19 negative individuals (33).

3rd vaccine dose can elicit a diverse memory B cell repertoire capable of clearing variants of concern including Omicron.

Muecksch et al. measured memory B cell repertoire in healthy individuals after two or three doses of Pfizer (BNT162b2) or Moderna (mRNA-1273) vaccines (71). The study found that after the 3rd vaccine dose, all individuals showed expanded clones of memory B cells which accounted for 33% of memory B cell repertoire 5 months after the 2nd dose and 47% of the repertoire 1 month after the 3rd dose. They found that the 3rd dose was accompanied by an increase in, and evolution of, anti-receptor binding domain specific memory B cells due to expansion of memory B cell clones that were present after the 2nd dose as well as the emergence of new clones. This diverse memory B cell repertoire induced by the 3rd dose can respond rapidly and produce antibodies capable of clearing even diversified variants such as Omicron (71).

3.2.2.3 Hybrid

Breakthrough infections induce a robust memory B cell and T cell response when compared to healthy vaccinated individuals.

Two studies examined hybrid cellular immunity (36, 37). Quandt et al. analyzed memory B cell responses induced by Omicron breakthrough infections in BNT162b2 vaccinated individuals and found that breakthrough infections mediated a robust B cell recall response (36). They also found that breakthrough infections expanded pre-formed memory B cells that recognized epitopes shared broadly by different variants, rather than inducing new B cells against strictly Omicron-specific epitopes. The other study investigated spike peptide-induced release of interferon gamma (IFN-γ) in vaccinated individuals infected with the Omicron and Delta variants (37). They found that infection with Omicron and Delta led to a rapid increase in spike peptide-induced IFN-γ. Levels of secreted IFN-γ were similar in individuals infected with Omicron and Delta, and were higher than observed in healthy vaccinated controls (37). These results suggest that memory T-cells were expanded at a very early stage during infection.

3.2.2.4 Comparing different immunities

3.2.2.4.1 Natural vs. Vaccination

Various studies compared differently acquired cellular immunities (20, 74-82).

Immune responses after vaccination are stronger compared to those after naturally occurring infection.

Naturally-acquired and vaccine-acquired cellular immunities were compared by Mazzoni et al., Keeton et al., Richardson et al., and Gao et al. who collectively found that immune responses after vaccination are stronger compared to those after naturally occurring infection, pointing out the need of the vaccine to

overcome the pandemic (20, 75, 78, 79). SARS-CoV-2 spike-specific CD4+ and CD8+ T cells induced by prior infection or BNT162b2 vaccination provided extensive immune coverage against Omicron B.1.1.529 (75). The study by Gao et al. also found that SARS-CoV-2 spike-reactive CD4+ and CD8+ T cells were functionally and phenotypically similar in response to the ancestral strain or Omicron B.1.1.529. Similarly, Richardson et al. found that T-cell responses to wt or mutant SARS-CoV-2 spikes were significantly weaker after natural occurring infections compared to those in vaccinated individuals (20). Strong CD4 T cell responses were present against wt and mutant SARS-CoV2 variants, including the delta (B.1.617.2) strain, in fully vaccinated individuals, whereas they were partly weaker 1 year after natural infection (20). Two studies found that T-cell responses, both after natural infection and vaccination, were conserved against the Omicron variant despite Omicron harboring considerably more mutations (78, 79). These observations suggest that T-cell responses induced by vaccination or infection are able to provide an efficacious line of defense that can protect from the development of severe forms of COVID-19 (79).

3.2.2.4.2 Vaccination vs. Hybrid

There is no significant difference between the immunity acquired through vaccination or vaccination and breakthrough infection.

Vaccine-acquired and hybrid-acquired cellular immunity were compared by Kared et al., Sokal et al., and De Marco et al. (74, 77, 81). Two studies analyzed anti-RBD memory B cells (77, 81). One study found a sizable fraction of MBCs encoding antibodies with affinity and neutralizing potential against all the tested VOCs, suggesting that MBCs elicited by prior infection or vaccination would be able to provide an efficient secondary layer of protection (81). When testing whether such a conclusion held true in the context of the Omicron variant, Sokal et al. found, as previously reported, that monoclonal antibodies encoded by MBCs isolated from vaccinated COVID-19-recovered patients and vaccinated naive patients contained a vast majority of high-affinity binders against the ancestral Hu-1 RBD, among which ~50% retained high affinity against the Beta and Delta RBD, but this proportion further decreased against the Omicron RBD to 33% (81). Similarly, Kared et al. found that in contrast to the Delta breakthrough cases, the frequencies of anti-RBD spike B cells were not increased in Omicron breakthrough cases (77). De Marco et al. investigated T-cell reactivity to the Omicron variant in individuals with established vaccine-acquired or hybrid immunity to SARS-CoV-2 (74). They found that the median frequency of CD4+ T cells reactive to peptides covering the mutated regions in the Omicron variant was 0.039%, a decrease of 64% compared with the frequency of CD4+ cells specific for the same regions of the ancestral strain (0.109%) (74). Within CD8+ T cells, a median of 0.02% cells recognized the mutated spike regions, while 0.039% of cells were reactive to the equivalent unmutated regions, a reduction of 49% (74). However, overall reactivity to the peptide library of the full-length protein was largely maintained (estimated 87%) and no significant differences in loss of immune recognition were identified between groups of participants with different vaccination or infection histories (74).

3.2.2.4.3 Natural vs. Vaccination vs. Hybrid

Infection, infection and vaccination, and three-dose vaccination elicits stronger cellular immune response to Omicron than two-dose vaccination.

Three studies focused on comparing naturally-acquired, vaccine-acquired, and hybrid-acquired cellular immunity (76, 80, 82). One study found that three-dose vaccinated participants had similar T-cell responses to Omicron relative to convalescent or convalescent plus two-dose vaccinated groups and exhibited responses significantly higher than those receiving two mRNA vaccine doses (76). Stratified analysis of subjects immunized by vaccines or prior infection clearly revealed that participants vaccinated with two doses exhibited inferior responses to both Omicron and the ancestral strain relative to infected, infected and vaccinated, and in particular, participants vaccinated with three doses, that trended, or were significantly higher, by most measures of immunity (76). Similarly, the study by Naranbhai et al. found that T-cell responses in individuals with prior infection, vaccination without prior infection, both prior infection and vaccination, and boosted vaccinations were largely preserved to Omicron spike and non-spike proteins, with a reduced recognition to Omicron spike being primarily observed within the CD8+ T-cell compartment (80). In terms of memory B cells, Tarke et al. found that there was an overall decrease in Omicron recognition compared to other variants (82).

3.3 Effectiveness of Adaptive Immunity (RR, OR, HR, VE)

Various studies have been conducted to assess the effectiveness of booster (third dose) of mRNA vaccines (Pfizer/BioNTech (BNT162b2); Moderna (mRNA-1273) and Janssen (Ad.26.Cov.S) against symptomatic SARS-CoV-2 infection (83-98). Several studies have concluded that the protection against SARS-CoV-2 Omicron variant is lower than that against other variants, and fades more rapidly than against earlier variants (Delta) after the second and booster doses of mRNA vaccines (83, 84, 86, 88, 89). However, the protection against COVID-19 related hospitalization and death has been found to be strong, robust, and durable after both the second and booster doses (83, 88, 89, 93, 94, 97, 98).

Chemaitelly et al., observed no significant differences in the effectiveness of mRNA vaccines (BNT162b2 and mRNA-1273) against symptomatic infections (89). Both vaccines provide comparable, moderate, and short-lived protection against symptomatic BA.1- and BA.2 Omicron infections (89). As per a study conducted by McMenamin et al., the booster of BNT162b2 provided substantial additional protection against severe COVID-19 (94). There was a significant decrease in the VE of the BNT162b2 booster (from 53.4% to 16.5%) within 3 months after administration (96). Gray et al. provides the first evidence of VE of Ad26.COV.2 vaccine booster in 69092 HCW, given during a period of 6-9 months after the initial single vaccination series during the Omicron wave in Africa, showing an increment in VE for hospitalization over time since booster dose (91).

Two doses of BNT162b2 offered a modest effectiveness of 65.5% at 2 to 4 weeks after its administration. However, the VE dropped to 8.8% at 25 weeks and over. Three doses of BNT162b2 offered a moderate effectiveness of 67.2% at 2 to 4 weeks after its administration, which plunged to 45.7% at 10 weeks and over. Two doses of BNT162b2 followed by one dose of mRNA-1273 provided an effectiveness of 73.9% at 2 to 4 weeks before declining to 64.4% at 5-9 weeks (86). This study shows the importance of getting a booster (BNT162b2/BNT162b2/BNT162b2 or BNT162b2/BNT162b2/mRNA-1273) as it provides more protection as compared to only two doses (BNT162b2/BNT162b2).

One dose of Janssen/Ad26.COV2.S vaccine offered a low effectiveness of 17.8% at 14 days to 1 month since the last dose. However, the VE dropped to 8.4% in 2-4 months since the last dose. Two doses of

Jensen/Ad26.COVS vaccine offered an effectiveness of 27.9% at 14 days to 1 month since the last dose, which increased to 29.2% in 2-4 months since the last dose. One dose of Jensen/Ad26.COVS followed by one dose of mRNA vaccine offered an effectiveness of 61.3% at 14 days to 1 month since the last dose, which plunged to 54.3% in 2-4 months since the last dose. Three doses of mRNA vaccine offered a moderate effectiveness of 68.9% at 14 days to 1 month since the last dose, which decreased to 62.8% in 2-4 months since the last dose. This study concluded that the VE was highest for the combinations that included a booster dose of mRNA vaccine (either BNT162b2 or mRNA-1273) and was lowest for one dose of Ad26.COVS ([85](#)).

As per the study conducted by Natarajan et al., VE against COVID-19 - was 24% after 1 dose of Jansen, 54% after 2 Janssen doses, 79% after 1 Janssen/1 mRNA dose, and 83% after 3 mRNA doses; suggesting that the adults who received the first dose of Janssen vaccine should receive a heterologous mRNA vaccine booster preferably or a homologous Janssen vaccine booster dose if mRNA vaccine booster is out of stock ([95](#)).

3.3.1 Comparing immunities

Hybrid immunity showed highest protection against Omicron infections.

This section includes six studies overall. The four studies that compared natural, vaccine and hybrid immunities found that hybrid immunity from natural infection (or previous) and booster vaccination showed a highest protection against Omicron infection ([99-101](#)), and, in some studies, against severe outcomes and hospitalization ([99, 102](#)).

Altarawneh et al. reported that the effectiveness of hybrid immunity (three doses of BNT162b2 and previous infection; median time of 43 days between third dose and test) was 77.3%, while the effectiveness of no previous infection was 52.2% ([99](#)). The effectiveness of two doses and previous infection was 55.1%, similar to previous infection with no vaccination (46.1%). These results showed a similar pattern with mRNA vaccines ([99](#)). Carazo et al. further corroborated these findings ([102](#)). mRNA vaccine effectiveness was higher among previous infected than non-infected subjects: 65% vs. 20% for one-dose; 68% vs. 42% for two doses; and 83% vs. 73% for three doses respectively ([102](#)).

Carazo et al., Chemaitelly et al., and Cerqueira-Silva et al. found that the effectiveness of natural infection ranged from 40% to 66%, and the incidence of Omicron re-infection was 50% with BNT162b2 and 40% with mRNA ([100, 102, 103](#)).

The level of protection against severe outcomes increases with hybrid immunity.

Against severe Omicron infections, all forms of immunity showed strong effectiveness with a similar pattern among BNT162b2 and mRNA vaccines ([99, 100, 102, 103](#)). Severe outcomes were defined by Cerquera-Silvia et al. as hospital admission or death occurring within 28 days after a positive test. The level of protection in individuals with natural immunity reached 85.6% against severe outcomes (within 3-5 months after vaccination) ([100](#)), 73% (as a maximum of 6 months after vaccination) ([101](#)), and 81% against hospitalization ([102](#)).

Protection against severe outcomes increases with hybrid immunity (natural immunity and boosters). The effectiveness of BNT162b2 and Ad26.COVS booster dose (within 2-9 weeks) was 95.7% and 97.5%,

respectively ([100](#)). Smid et al. reported a VE of 86% after a recent booster (within 2 months after vaccination) and a lower VE of 45% and 29%, within 2 months and > 2 months after the second dose, respectively ([101](#)). Moreover, Carazo et al. found that the effectiveness of two doses following a natural infection did not vary from the effectiveness of three doses (despite longer follow-up: median 158 and 27 days, respectively) ([102](#)).

Chemaitelly et al. and Cerqueira-Silva et al. concluded that hospitalization was rare for both natural-infection and vaccinated individuals in Qatar and in Brazil, reaching 0.5% of death and 1.7% of hospitalization respectively ([100](#), [103](#)).

Natural immunity and hybrid immunity waned slower and less rapidly than vaccine immunity. The effectiveness of previous infection waned slower and less rapidly than two and three-doses mRNA and BNT162b2 vaccine. Altarawneh et al. showed that the protection after vaccines was negligible by 6 months after the second and booster dose (mRNA 41.2% vs BNT162b2 44.7% after 1 month) ([99](#)), while natural infection effectiveness ranged from 65% to 75% at 4-6 months and 32% to 53% at 10-12 months ([99](#), [101-103](#)). The effectiveness of hybrid immunity after three doses was 80% then it decreases to 67% after two doses and one dose (64%) at 2-5 months post-vaccination, according to Carazo et al. ([102](#)).

Vaccine immunities against severe outcomes is higher than against infection.

In terms of severe outcomes, Cerqueira-Silva et al. found a more durable protection due to previous infection against deaths and hospitalization than infections throughout the time (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 years) ([100](#)). A similar pattern is valid for BNT162b2 and Ad26.COVS.2 where the effectiveness after the respective booster dose is higher against severe outcome than infection (booster dose BNT162b2 after 2-9 week, 95.7 vs 70; Ad26.COVS.2 after 2-9 week, 97.5 vs 47.2) and higher for BNT162b2 than Ad26.COVS.2 against infection ([100](#)).

Effectiveness of vaccines on the BA.1 and BA.2 VOC is unclear and under investigated.

Only two papers compared the vaccine effectiveness against BA.1- BA.2 VOC, showing contrasting results. No different in protection was found against both variants ([99](#)), while a drastic reduction of effectiveness was found after the transition to BA.2 (from 90% to 54%) with two doses ([104](#)). With three doses, the effectiveness remains stable at 80% ([104](#)).

3.4. Risk groups (older & immunocompromised)

3.4.1 Humoral

3.4.1.1 Immunocompromised groups

Eight studies included in this review assessed the humoral response of immunocompromised individuals to Omicron after vaccination through the measure of neutralizing and binding antibody responses ([105-](#)

[112](#)). While 4 of these studies were conducted on transplant recipients ([105](#), [106](#), [109](#), [110](#)), 3 studies assessed cancer patients ([108](#)), and 1 study focused on hemodialysis patients ([107](#), [111](#), [112](#)).

Immunocompromised groups generate a weak binding and neutralizing antibody response after mRNA vaccination.

Generally, studies demonstrated that the humoral response of immunocompromised groups to the Omicron variant, was much weaker compared to wild type (WT) SARS Cov 2 post mRNA vaccination ([110](#), [112](#)). Overall, immunocompromised groups did not generate a robust neutralizing antibody response to the Omicron variant after 2 doses mRNA vaccination especially compared to healthy vaccinees (Pfizer/Moderna) ([105](#), [107](#), [111](#)). However, Al-Juri et al. and Carr et al. demonstrated that a third dose of mRNA vaccination was able to elicit, an albeit weak, neutralizing antibody response against Omicron in kidney transplant recipients and hemodialysis patients respectively, despite the undetectable levels observed in these groups post 2 doses of mRNA vaccination ([105](#), [107](#)). Nonetheless, a cohort study on solid organ transplant recipients found that even after 4 doses of mRNA vaccination, participants still had poor neutralizing antibody response against Omicron, particularly compared to healthy controls ([109](#)). Additionally, Chang et al. observed lower levels of binding antibody response in immunocompromised groups ([108](#)). In this study, Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukaemia patients had lower anti SARS Cov 2 spike IgG titers compared with healthy controls following 2 doses of mRNA vaccine. However, a study by Karaba et al. found that 4 doses of mRNA vaccine in solid organ transplant recipients increased anti spike IgG in solid organ transplant recipients ([109](#)).

Neutralizing antibody response wanes with time after vaccination.

Moreover, waning of the neutralizing antibody response, with time after vaccination, was demonstrated by Kumar et al. ([110](#)). In this study, 18.3% of organ transplant recipients had detectable levels of neutralizing antibodies against Omicron 1 month after their third dose of mRNA vaccine. However, this decreased to 15.7% of the participants 3 months post the third dose ([110](#)).

3.4.1.2 Elderly groups

A third dose of mRNA vaccine increases neutralizing antibodies significantly in the elderly population.

This review includes 5 studies examining the humoral response of elderly groups (>55 years) to the Omicron variant, post vaccination or infection ([24](#), [27](#), [113-115](#)). Belik et al. and Furukawa et al. demonstrated that humoral response to the Omicron variant is significantly stronger after a third dose of mRNA vaccination as opposed to a second dose ([24](#), [27](#)). However, while Belik et al. found a weaker immune response in the older age groups (55-65 years), when compared to the 35-54 year old groups, Furukawa et al. saw that titres of neutralizing antibodies against Omicron post a second dose of mRNA vaccination were low in all age groups ([24](#), [27](#)). Additionally, upon receipt of a third dose of an mRNA vaccine, similar levels of an increase in neutralizing antibody titers were observed across all age groups, although the older age group had the lowest titer ([27](#)).

Neutralizing antibodies wane with time after vaccination, but hybrid immunity and a third dose sustain binding antibody response.

Furthermore, with increasing time after vaccination, decreasing levels of neutralizing antibodies were observed in elderly groups. In a study by Newman et al., a 4.9-fold drop in neutralizing antibody titers was detected 3 to 20 weeks post mRNA vaccination (115). Alternatively, hybrid immunity results in a more sustained humoral response over time in older age groups. Lee et al. showed that 15 months post COVID-19 infection, the studied octogenarians were able to sustain their SARS-CoV-2 spike-specific IgG antibody response (114). Additionally, vaccination with a single dose of mRNA vaccine enhanced this antibody response 35-fold, significantly higher than naïve individuals receiving 2 doses (114). Gimenez et al. found similar results in which previously infected residents were able to sustain high levels of anti-RBD antibodies 7 months post their second dose of an mRNA vaccine (113). In addition, upon vaccination with the third dose, both anti-RBD and neutralizing antibody titers against Omicron increased more notably in previously infected groups than SARS-CoV-2-naïve subjects.(113)

3.4.2 Cellular

There was a negligible T cell response post mRNA vaccine in elderly groups.

Few studies focused on cellular immunity in high-risk groups. Gimenez et al. assessed cellular immunity following a third dose of the Pfizer vaccine in nursing home residents (113). 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 post third dose of mRNA vaccines were negligible (113).

Cellular response is sustained in immunocompromised groups and is enhanced by a third vaccine dose.

Three studies were included in this report that examined cellular response in immunocompromised groups (68, 70, 73). Spike specific CD4+ and CD8+ T cells against all variants including Omicron were sustained in 45-60% of Multiple Sclerosis (MS) patients taking B-cell depleting drugs 6 months after their 2nd vaccination, albeit at lower median frequencies against the Delta and Omicron variants compared with the vaccine strain (70). Furthermore, Qui et al. demonstrated that spike specific T-cell response up to 3 months post two doses of mRNA vaccine was comparable between inflammatory bowel disease (IBD) patients and healthy individuals (73). They found that a spike-specific T-cell response is induced in treated IBD patients at levels similar to healthy individuals and also sustained at a higher magnitude, particularly in those treated with TNF inhibitor therapy. They also found that the T-cell response in these patients is mainly preserved against mutations present in the Omicron variant, demonstrating that despite humoral response defects, vaccine-induced T-cell responses might still provide a layer of protection to patients under immune-modifying therapies (73).

Moreover, studies conducted by Lasagna et al. and Mandelon et al. both found that cellular immunity increased upon receipt of a third dose of an mRNA vaccine (68, 70). Lasagna et al. found that the median IFN- γ level at 3 weeks post 3rd dose of the BNT162b2 SARS-CoV-2 vaccine was significantly higher than that measured before the booster in cancer patients on active treatment (68). Mandelon et al. also found that a 3rd dose enhanced the number of responders to all variants (55-75% of patients) and significantly increased CD8+ T-cell responses (70).

3.4.3 Vaccine Effectiveness in elderly groups

Vaccines offer protection from severe COVID-19 illness and hospitalization – protection increases with increasing doses.

Six studies included in this report assessed vaccine effectiveness against Omicron in elderly groups ([87](#), [92](#), [116-119](#)). Overall, the studies found that vaccines provided significant protection against severe COVID-19 illness and hospitalization in elderly groups. Baum et al. found that after the second dose of the Pfizer vaccine, vaccine effectiveness against hospitalization with the Omicron variant was 91% and rose to 95% after the administration of the third dose ([116](#)). The effectiveness of a fourth dose of mRNA vaccine in elderly groups was investigated by Grewal et al., Gazit et al., Bar-On et al., and Magen et al. ([87](#), [92](#), [117](#), [118](#)). The findings showed that a fourth dose enhanced protection from asymptomatic and symptomatic infections as well as severe clinical outcomes ([117](#), [118](#)). Furthermore, Grewal et al. found that with each dose of an mRNA vaccine, vaccine effectiveness increased with maximum effectiveness observed in the fourth dose recipients ([118](#)). In addition, Bar-On et al., observed that the fourth dose of BNT162b2 vaccine reduces both the rates of confirmed SARS-CoV-2 infection and severe COVID-19 than after only three doses ([87](#)).

Vaccine effectiveness wanes over time in elderly groups.

However, studies demonstrated that vaccine effectiveness waned over time ([87](#)). As observed with the booster, the protection against infection was short-lived. However, the protection against severe illness did not disappear during the study period (i.e., 6 weeks after receipt of the fourth dose ([87](#), [92](#))). Baum et al. found that 91–180 days post second dose vaccination, vaccine effectiveness against hospitalization had decreased from 91% to 76% ([116](#)). Similar results were observed by Gazit et al., after a fourth dose of mRNA vaccination ([117](#)). Relative effectiveness of the fourth dose of Pfizer waned significantly by the 10th week followed period of the study, having peaked 3 weeks post vaccination. However, in the same study, relative effectiveness of the fourth dose against severe COVID-19 disease was sustained throughout the study time period ([117](#)). This is consistent with what was also found by Bar-On, 2022, et al. ([87](#)).

Humoral and cellular response levels do not correlate with protection from breakthrough infections.

Moreover, Torres et al. aimed to assess the correlate of protection provided by humoral and cellular immune responses post Pfizer vaccination, from breakthrough Omicron infections in elderly groups ([119](#)). Within 4 months after receiving a third dose of the Pfizer vaccine, 33/146 of the study participants had breakthrough Omicron infections. However, binding antibody levels, neutralizing antibody titers and T cell response were similar between infected and uninfected groups ([119](#)). Therefore, humoral, and cellular responses were not seen to correlate with protection from Omicron breakthrough infections.

4. Discussion

Understanding the long-term levels of protection and duration acquired through adaptive immunity is crucial to plan the next measures in COVID-19 vaccination and non-pharmaceutical interventions. In this report, the systematic review of available literature on the levels and duration of humoral and cellular protection in natural, vaccine-acquired, and hybrid immunities, as well as the effectiveness of named protection, dating from November 2021 until May 23, 2022, was reviewed, analyzed, and summarized to provide a complete report on the immunological surveillance of COVID-19.

4.1 Levels of protection

Based on our work, a significant decrease in the levels of protection against Omicron was observed in all types of conferred immunities (natural, vaccine-acquired, and hybrid immunity). This reduction was mainly emphasized in the humoral immunity measured as levels of antibodies and neutralization of the former. Although booster doses or breakthrough infections increased the levels of protection against Omicron, the levels of protection remained relatively lower than against prior variants such as Delta. This observed decrease can be mainly explained by the high number of mutational shifts in the Spike-protein of Omicron causing the emerged variant to be more antigenically heterologous from prior variants, specifically the ancestral strain ([120](#)). Since a vast majority of the mutations observed in the Omicron variant have been identified within the Spike-protein, the principal vaccine-target, antibodies elicited by non-Omicron infections or through approved COVID-19 vaccines have shown a drop in its neutralization. In addition to the structural changes in the newly emerged variant, by the time Omicron started circulating and becoming the predominant variant, a high proportion of the population was already vaccinated with a COVID-19 vaccine to which waning levels of antibodies and effectiveness against infection were already being reported ([121](#), [122](#)). Despite the reported decrease in humoral immunity against Omicron, the levels of cellular immunity against Omicron were found to be maintained in convalescent, vaccinated, and super-immune (infected and vaccinated) individuals, where a booster dose was shown to illicit a diverse memory B cell repertoire against Omicron ([71](#), [75](#)). While the cellular immunity might not play an initial and immediate role in the defense against SARS-CoV-2, T cells such as CD4+ and CD8+ as well as memory B cells part-take in the crucial second line of defense against infection and infected cells. This stable cellular immunity in individuals immunized with prior variants or COVID-19 vaccines might explain the lower risk of hospitalization and severe illnesses associated with B.1.1.529 breakthrough infections ([75](#), [78](#), [123](#)). Furthermore, T cell memory has been shown to encompass broad recognition of viral proteins with an estimate of around 30 epitopes within each individual, while remaining well sustained; suggesting that this breadth of recognition was likely to underpin protection against severe disease from viral variants, including Omicron ([124](#)).

Some studies have demonstrated that the mRNA vaccines, specifically Moderna/mRNA-1273, provide better neutralization against the Omicron variant in vaccine-acquired immunity and even hybrid immunization, as compared to the other vaccines (Pfizer and Janssen) ([24](#), [30](#), [108](#)). In fact, Lyke et al. ([30](#)), and Chang et al. ([108](#)), found that the mRNA vaccine induced higher levels of antibody levels as well as higher anti-Spike response than the Janssen vaccine. Moreover, within the mRNA vaccines, the Moderna vaccine had a higher geometric mean titer than the Pfizer vaccine ([24](#)). Among various homologous vs heterologous booster vaccine schedules, mRNA vaccines continued to demonstrate higher levels of protection against the Omicron variant ([30](#), [85](#), [95](#), [125](#)). Highest neutralizing antibodies were found in

mRNA vaccines while participants with homologous Janssen vaccine had the lowest levels of neutralizing antibodies (30). These levels of protection were translated into vaccine effectiveness against symptomatic infection where various studies demonstrated that the highest vaccine effectiveness was observed in homologous or heterologous vaccine schedules that included an mRNA vaccine combination (85, 95). Despite our results not covering the cellular immunity elicited by heterologous vaccination, Atmar et al. found that the Spike-specific T-cell responses increased in all but the homologous Janssen-boosted subgroup (125). Moreover, CD8+ T-cell levels were more durable in the Janssen -primed recipients, and heterologous boosting with the Janssen vaccine substantially increased spike-specific CD8+ T cells among the people who received mRNA vaccines (125). Although the Janssen booster vaccine did not elicit the highest immunogenicity, its cellular response showed more promising results (125). The conclusions of these studies suggest that the mRNA vaccines booster should be preferred over viral vector (Janssen) (30, 85, 95, 125) vaccines.

All forms of acquired immunity, provided moderate effectiveness against symptomatic infection and stronger effectiveness against the severe outcomes, where hospitalization was less frequent for both natural infections and vaccinated individuals. In fact, the protection against COVID-19 related hospitalization and death was found to be strong, robust, and durable after both the second and booster doses, in several studies (83, 88, 90, 93, 94, 97, 98). Hybrid immunity (natural immunity and boosters) provided the highest level of protection against severe outcomes (60, 90, 99, 100, 102, 103). However, natural immunity provides more durable protection than hybrid immunity and vaccine immunity (99, 102, 103). Cerqueira-Silva et al., illustrated that the vaccine immunities against severe outcomes (deaths and hospitalization) is higher than that against infection (100). Servellita et al. found that individuals with severe infection reported higher antibody titers than individuals with mild infection in breakthrough infection (61). In addition, Chen et al. reported that patients who developed fever and pneumonia showed significantly stronger anti-spike antibody and B cell responses than individuals without these severe symptoms (1). Previous studies analyzing the levels of antibodies in individuals with different clinical outcomes noted that more severe disease (hospitalization) led to higher IgM, IgA, IgG levels, especially IgG, compared to asymptomatic or symptomatic non-hospitalized individuals (126). These antibody binding titers were different early after onset of symptoms, while it reached similar levels after 90 days the level of antibodies in both groups (127). This is confirmed for all three antibody isotypes including IgM (126) and against Omicron.

Our review suggest that immunocompromised individuals develop a weaker humoral response against Omicron compared to wild type SARS-CoV-2 response after 2 doses mRNA vaccination. Organ transplant recipients remain at high risk for infection as neutralization capacity and the binding antibody response remain low despite boosting. There is growing evidence demonstrating that use of mRNA vaccines in combination with immunosuppressants elicit a low humoral response to vaccinations for organ transplants (128). This evidence may be supported by the findings on routine vaccination response of the meta-analysis of Nguyen et al. (129), where the group that received immunosuppressive therapy showed 60% lower probability of reaching adequate protection compared to the group that was not receiving this therapy for inflammatory bowel disorders. The review of Perry et al., found mixed evidence about the association between the level of immunological marker and protection against infection (correlate of protection) and supported the antibody target as a potential correlate (130). Based on this review, low humoral response may suggest that immunocompromised groups are more susceptible to Omicron infection and incur in

severe outcomes. A recent review on the role of cellular immunity in protection against SARS-CoV-2 infection supported the protective role of SARS-CoV-2-specific T cell in the control of infection, indicating that cellular responses underpin protection against infection and death (124). In immunocompromised individuals, cellular response seems to be sustained and it could be providing added protection from severe COVID-19 illness where humoral response is lacking.

While Belik et al. found that elderly groups generated a weaker immune response post vaccination (24), studies assessing vaccine effectiveness have demonstrated that mRNA vaccines have provided elderly groups with protection from severe COVID-19 illness and hospitalization (116-119). However, in the elderly group, a recent observational study found that the humoral and cellular response levels were not associated with the likelihood of subsequent breakthrough infections due to the Omicron variant (119). Third doses and hybrid immunity sustained the antibody response, while the cellular response after the third dose of mRNA was negligible. The vaccine protects from severe outcomes and hospitalization, which increases with boosters. As per the rest of the population, the effectiveness wanes over time. Ultimately, our findings suggest that elderly groups can mount sufficient levels of an immune response post mRNA vaccination in order to have protection from severe COVID-19 infection. Additionally, protection was enhanced with additional doses of the mRNA vaccine (118).

4.2 Duration of protection

Although quantifying the exact duration of protection against SARS-CoV-2 infections poses a great challenge, numerous articles have found a significant decrease in the levels of protection three to six months after primary and booster vaccination. In fact, in a study conducted by Patalon et al., the effectiveness of a third BNT162b2 booster dose against SARS-CoV-2 infection decreased from 53.4% to 16.5%, within 3 months after administration, emphasizing this rapid decrease (96). This short duration of protection may be attributed to the continuous emergence of more transmissible and more antigenically mutated variants that have shown to escape existing and gained humoral immunity (131). This short-lived protection against infection raises the pivotal question about the need for a fourth vaccine dose, especially in risk groups such as immunocompromised individuals and elderly populations. Similar to the levels of protection, cellular immunity granted a longer duration of protection. Although the study covers pre-Omicron variants, Goel et al. demonstrated that SARS-CoV-2 specific memory CD4+ T cells were relatively stable from three to six months after mRNA vaccination, and that the vast majority of vaccinees maintained robust CD4+ T cells responses for at least 6 months (132). These results highlight the role of T cell immunity in shaping response to vaccination. Additionally, an increase in memory B cells between three to six months after mRNA vaccination, even as antibody levels declined in the same individuals, was observed (132). This suggests that prolonged germinal center reactions continue to generate circulating memory B cells for at least several months after vaccination (132).

When comparing the duration of protection with different types of immunities, hybrid immunity showed the most durable protection. For instance, the effectiveness of hybrid immunity after three doses was 80%, and decreased to 67% after two, and one dose (64%) at 2-5 months post-vaccination, (102). Among the elderly population (people aged 60 or more), four doses of vaccines provided significant protection against severe COVID-19 illness and hospitalization (87, 92, 116-119); nonetheless, vaccine effectiveness against the

symptomatic infection continued to wane with time (87, 116, 117). Fortunately, the protection against severe illness was sustained during the study period (87, 117).

Some studies have demonstrated a highly predictive relationship between high levels of neutralizing titers and immune protection (133); nonetheless, recent studies examining breakthrough infections with the Omicron variant found that participants with high binding titers elicited by booster doses still experienced Omicron breakthrough infection. This phenomenon was mainly observed in Dimeglio et al., where the majority of the Omicron breakthrough infections occurred in individuals with relatively high total antibody concentrations (26). Additionally, elicited humoral immunity against the Omicron variant showed signs of waning as soon as six months or less (108). Due to the increase of breakthrough infections in individuals with high antibody titers and their demonstrated waning immunity, the idea that high levels of antibodies might correlate with long-term protection is challenged. Declining antibody titers over time can likely reduce the potential that vaccination will completely prevent infection or provide near-sterilizing immunity. However, the durability of cellular immunity, has demonstrated, for at least 6 months, a rapid recall responses that can limit initial viral replication and dissemination in the host, thereby preventing severe disease (132). Contingent on these results, the levels of cellular immunity might provide a more suitable correlate of long-term protection, as effector T cell responses to Omicron were preserved even in individuals with undetectable neutralization of Omicron (80). Additionally, the SARS-CoV-2 variants of concern were reported to partially escape humoral but not T cell response in convalescent and vaccine recipients (134). Furthermore, cellular immunity demonstrated to be conserved up to, one year where vaccines elicited highly conserved immunity to Omicron (69), and memory T cells responses to the original strain were not disrupted by new variants while neutralizing antibodies were significantly affected (135). In other words, when trying to assess the long-term protection elicited by vaccination or infections, the cellular immunity should carefully be taken into account and also be used as a correlate of protection, especially for infections with the new variants of concern and its subvariants.

4.3 Protection against emerging variants

Another important aspect to consider in addition to the duration of any gained immunity, is its effectiveness to cross-neutralize and protect against possible emerging variants such as the diverse and more recent Omicron subvariants, BA.2, BA.3, BA.4 or BA.5. Although our results do not include studies discussing the levels of protection against the newer subvariants BA.4 or BA.5, our review includes a few studies that go over BA.1, BA.2, and BA.3. According to our review, humoral immunity did not provide robust and long-lived neutralization against Omicron and the BA.1, BA.2, and BA.3 subvariants, where prior infections with non-Omicron variant and even vaccination with mRNA vaccines led to low and reduced cross-neutralization (1, 21, 24). The highest breadths of protection were seen in individuals with hybrid immunity, although this one significantly waned over time (36, 48). Additionally, the breakthrough infections with Omicron were reported to be less immunogenic than the Delta ones. Similar results were seen in studies evaluating the effectiveness of COVID-19 vaccines against BA.1 or BA.2 infections, where moderate and short-lived protection against symptomatic BA.1 and BA.2 Omicron infection, but strong and durable protection against COVID-19 hospitalization and death was observed (89). Despite the rapid decline of the protection against symptomatic illnesses, current COVID-19 vaccines, which are based on the ancestral strain of SARS-CoV-2, continue to exhibit strong protection against severe disease and death across Omicron and its subvariants. Nevertheless, one study found that increased exposure to immunity, through infection or

vaccination, led to higher and broader cross-neutralization of emerged variants such as BA.1 and BA.2 (43, 55).

With the fast-evolving COVID-19 variants and the clear increase in infections, existing vaccines based on the ancestral strain of SARS-CoV-2 have demonstrated to be a poor match against current Omicron strains; therefore, providing short-lived protection. As a result, the scientific community is currently discussing whether COVID-19 vaccines should be updated to provide a greater and hopefully longer protection against Omicron and future emerging variants (136). As the need to assess whether variant-updated COVID-19 vaccines would improve the overall protection against infection, factors such as a more durable protection against severe disease and death, and broader protection against future variants becoming even more antigenically distant to the index virus are crucial to consider (137). At the moment, vaccine-updated vaccines are ongoing clinical development and have yet to be assessed by advisory panels.

4.4 Limitations

Due to the high complexity of T cell response investigation in individuals, the number of studies analyzing such immune response are lower than studies evaluating humoral immunity. Consequently, literature covering the cellular immunity against SARS-CoV-2, is less prevalent than humoral immunity in our report. Additionally, by restricting the timeframe of included studies from November 2021 to end of May 2022 and by solely focusing on Omicron relevant studies, our report is limited in the number of studies on the duration of protection against Omicron and studies on the protection offered from second boosters. Nonetheless, as more literature on the Omicron variant and its subsequent lineages and second boosters becomes available, more studies covering those subjects will be published and added to the updated report. In addition to the identified gaps in literature, our report did not assess the risk of bias or quality of the included studies. Since this report serves as a mid-report or update of the current knowledge in the levels of protection and their duration, a finalized report, submitted later in October 2022, should provide a more inclusive and updated general summary of the literature. In other words, we hope to address the gaps in the literature and updating it in the final October report.

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