Literature review report

Immunological Surveillance Mandate: Final report

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Highlights

- Natural immunity and hybrid immunity wane slower and less rapidly than vaccine immunity.
- Vaccine immunity against severe outcomes is higher than against infection-acquired immunity.
- A second booster dose elicits a significant increase in levels of humoral response; nonetheless, loss in antibody response against Omicron variants and signs of waning continue to appear.
- Levels of binding and neutralization antibodies have been shown to be good correlates of protection.
- Severe infections induce a stronger antibody response against SARS-CoV-2 compared to mild or asymptomatic infections in both non-vaccinated and fully vaccinated individuals.
- Convalescent individuals, particularly those with breakthrough infections, retain a significant amount of T cell and B cell memory up to a year after infection.
- Humoral and cellular responses to Omicron variants are lower than those to older variants in individuals with natural, vaccine-acquired, and hybrid immunity.
- Vaccinated individuals elicit higher cellular immunity responses than nonvaccinated individuals, with 3rd and 4th doses eliciting a diverse repertoire than can neutralize variants of concern including Omicron variants.
- A second booster significantly sustains cellular immunity, in a similar manner to breakthrough infection.

Risk Groups: Elderly (aged >55 years) and immunocompromised persons

- Vaccines offer protection from severe COVID-19 illness and hospitalization which increases by doses in the elderly.
- The vaccine effectiveness of the fourth doses against Omicron infection ranged from 25.8% to 49%, while VE against severe deaths varied from 72% to 89.6% in elderly
- Vaccine effectiveness also wanes over time in elderly groups.
- Humoral and cellular response levels do not correlate with protection from breakthrough infections in the elderly.
- Acquired humoral immunity is weaker in immunocompromised groups compared to healthy groups.
- Third and fourth doses of mRNA vaccines generate a stronger and more durable humoral and cellular response in immunocompromised and elderly groups.
- A stronger and more durable immune response is generated by hybrid immunity in healthy and immunocompromised groups.

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) (2). 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 (3). 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 (4). In addition to all of this, it also elicits a complex immune response (3). The adaptive immune response, composed of humoral and cellular responses, can be measured by analyzing the antibody levels, neutralizing antibodies, T cell, and memory B cell responses. The humoral response is mediated by antibodies, while the cellular response is mediated by specialized cells such as the B cells and T cells. Antibodies that recognize RBDs have been considered the most important component of immunity against SARS-CoV-2 in humans due to their neutralizing activity (3). Nonetheless, the induction of SARS-CoV-2-specific memory T cells and B cells (as opposed to circulating antibodies) is also important due to its long-term protection (5). T follicular helper (TFH) cells, in particular, 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 (5). 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 (5).

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) (6, 7). Studies have shown that these RBDs and NTDs are vital targets for the adaptive immune system, particularly neutralizing antibodies (8). 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 (9). However, mutations in the SARS-CoV-2 spike protein 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 (10). 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, including its multiple subvariants (11). Out of the five VOCs, Omicron has accumulated the highest level of mutations and has mediated the greatest level of immune escape (12). 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 (6, 12). More specifically, the Omicron RBD contains 15 mutations and the NTD contains 11 mutations, which has

compromised neutralization antibody activity in previously vaccinated or infected individuals (13). With its enhanced transmissibility and immune escape, Omicron, and the multiple subvariants that have emerged from it, has become the most dominant COVID-19 variant circulating today. Omicron was initially comprised of three sister lineages, BA.1, BA.2, and BA.3 (14). In mid-December 2021, however, two new Omicron lineages were identified, BA.4 and BA.5. These two lineages have identical spike proteins and are most comparable to BA.2 (14). Relative to BA.2, BA.4 and BA.5 have the additional spike mutations 69-70del, L452R, F486V and wild type amino acid at position Q493, but also individually contain unique mutations (14). These new mutations cause BA.4 and BA.5 to escape neutralization to a higher degree than the original Omicron variant (B.1.1.529) and the three previous sister lineages (15).

Vaccination against SARS-CoV-2 has shown a high preventive effect worldwide, especially for reducing severe illness and death (16). However, with newly emerging variants, especially Omicron, a high reduction in levels of humoral immunity and cellular immunity have been observed with vaccine effectiveness (VE) also being impacted. Several of the studies included in this review have established the waning properties of the Omicron variant and its subvariants, in both humoral and cellular immunity. It has been 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 is lower than the previous one (17). Lyke et al. also found that neutralization of BA.2.12.1 and BA.4/BA.5 were 1.5 and 2.5 times lower, respectively, compared to BA.1 (15). Consequently, these new subvariants influence vaccine effectiveness. Collie et al. also showed that vaccine effectiveness and durability both declined during the BA.4 and BA.5 Omicron waves compared to the BA.1 and BA.2 Omicron waves (18). Therefore, studying and analyzing the effects Omicron and its subvariants have on the levels and duration of protection elicited by adaptive immunity is crucial to appropriately and evidently implement public health decisions. Scientists are now testing the efficacy of variant-modified vaccines that include the Beta, Delta, and Omicron BA.1 spike proteins either alone, or in combination with each other or the ancestral variant spike protein. They also predict that use of a variant-modified vaccine can provide a modest increase in protection, which may be slightly greater in cases where the vaccine immunogen is more antigenically related to the circulating variant or if immunity has waned, (19). They predict that use of a variant-modified vaccine can provide a modest increase in protection, which may be slightly greater in cases where the vaccine immunogen is more antigenically related to the circulating variant or if immunity has waned (19).

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. 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 (which publish articles before they appear in search engines) were screened, and hand searched. To avoid missing the most recent articles, journals such as The Lancet and Nature were independently screened due to the few days gap between their date of publication (latest date of search 30 September 2022) and addition to public databases such as Medline and Embase.

2.1.1 Search Strategy

A search strategy composed of text words (e.g., coronavirus disease), MeSH terms (e.g., covid-19 immunity), Boolean terms (e.g., AND, OR) and truncations (e.g., immune*) to electronically identify studies related to SARS-CoV-2 immunity 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 strategies for Medline, Embase, and medRxiv & bioRxiv can be found in Supplementary Material 1.

2.1.2 Software

Identified literature was imported into a library in EndNote for storage, detection, and deletion of duplicated articles. Screening and full-text review was completed using the Rayyan systematic review software (20).

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 further screened in 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 30 September 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 for studies that included, but were not limited to, data on the immunological surveillance of COVID19 immunity after vaccination and/or infection. The findings were grouped and summarized by topic (e.g. humoral immunity, cellular immunity, vaccines effectiveness, and risk groups).

3. Results

3.1 Study Selection and Characteristics

This report includes research published between 01 November 2021 and 30 September 2022. A total of 9536 studies were found using the search queries, including 5,103 after removal of duplicates. After title and abstract screening by two authors, 1,409 studies were included for full-text review. After full-text review, 206 articles were included in this report (Figure 1).

Further details on the characteristics of the included studies can be found in Supplementary Material 2.

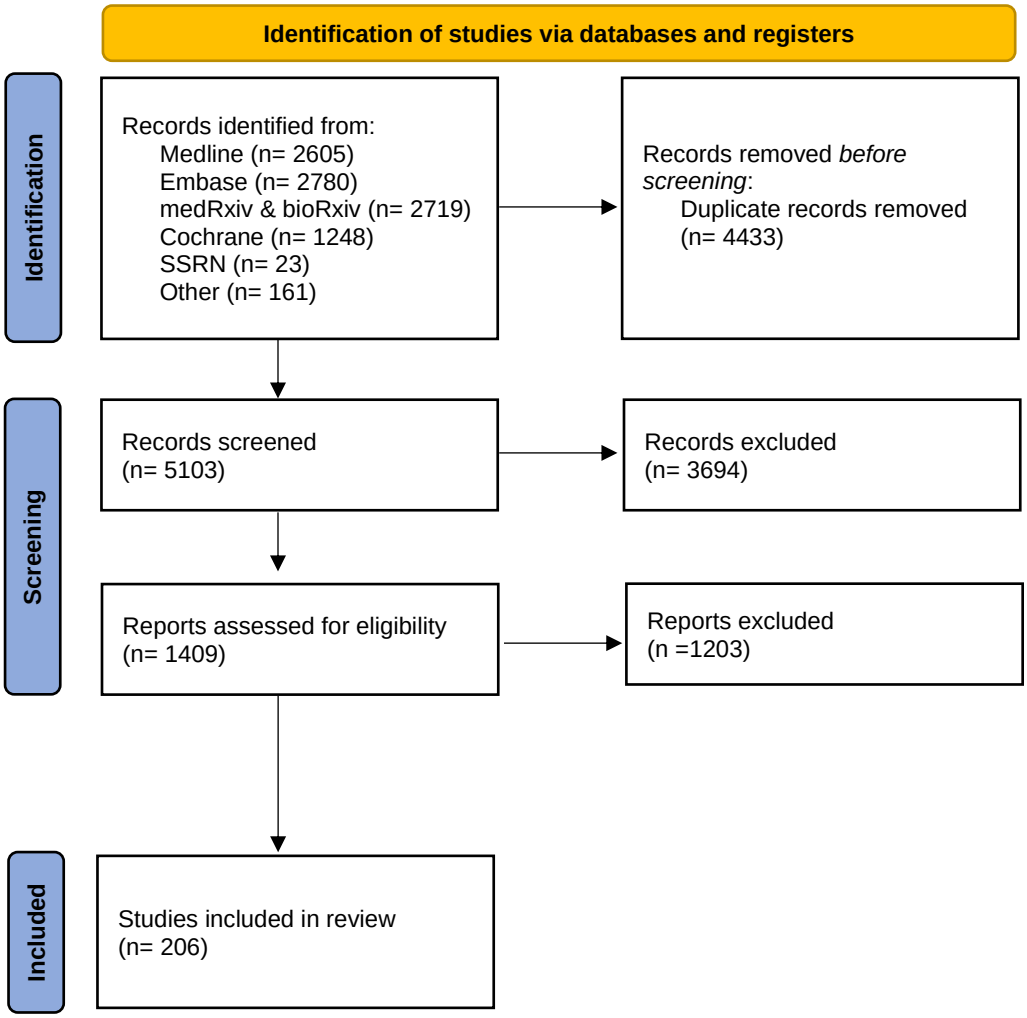

Figure 1. PRISMA flow chart of study identification and selection

3.2 Quantification of Adaptive Immunity

3.2.1 Humoral Immunity

3.2.1.1 Natural immunity

Seven studies analyzed the antibody levels of protection acquired from natural immunity through the measurement of binding and neutralizing antibody responses against the wild-type, previous variants, Omicron (B.1.1.529), or its subvariants BA.1 and BA.2 (3, 21-27). In two studies, the clinical severity of antibody responses was evaluated in infected participants (3, 21, 22), while in all studies the neutralizing or binding capacity of the elicited antibody response acquired from prior infection was tested against the variant Omicron (B.1.1.529) (3, 21-27). The longevity and durability of protection conferred by prior infection against Omicron was assessed in two studies (3, 22, 26), where in Wang et al., the estimated decay rate and half-live of antibodies was assessed to better understand the waning of naturally acquired antibodies (26). In addition, the study analyzed the possible correlation between humoral and cellular immunity (26).

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

Based on the results from Chen et al. and Brazer et al., it was demonstrated that the clinical severity of infected patients plays a role in the level of antibody response against SARS-CoV-2 (3, 21, 22). 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 milder illness (3, 21, 22). This statement also applied to Omicron's subvariants BA.1 and BA.2 where one of the studies found that the titers against BA.1 and BA.2 were significantly higher in unvaccinated patients with severe Delta infections than those with mild or asymptomatic infections (21).

Naturally acquired immunity wanes over time (after 10 to 12 months from infection) where neutralizing antibodies decay slower than binding antibodies.

When looking at the duration of naturally acquired humoral immunity, a clear decrease in the elicited antibodies was observed after 10 to 12 months in three of the included studies (3, 22, 23, 26). In Garcia-Valtanen et al., the longitudinal humoral response in mild-COVID-19 convalescents was analyzed 12 months post-infection and was found to be significantly reduced and completely abrogated for the Omicron variant (B.1.1.529) (23). In another study, Wang et al. evaluated the kinetics and durability of SARS-CoV-2 specific antibodies by measuring and comparing the collective levels of anti-RBD IgG, anti-N IgG, and total neutralizing antibodies from the blood sample of participants infected 2 to 12 months after disease onset (26). Their results also showed a significant reduction in all levels of binding and neutralizing antibodies observed over 12 months, where the half-life of IgG RBD was estimated at 2.79 months, and the half-life of IgG N was estimated at 1.98 months. Nonetheless, neutralizing antibodies were shown to decay at a slower rate than biding antibodies with an estimated half-live of 5.13 months; a longer half-live than all the other binding antibodies (26).

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 or Delta strain (3, 22-24, 26, 27). According to the results, the neutralizing sensitivity of the Omicron variant (B.1.1.529) compared to the wild-type SARS-CoV-2 demonstrates significant immune escape to Omicron where patients who recovered from wild-type infection had geometric mean titers that were 3.7-fold lower against B.1.1.529 (26). Subsequently, a significant drop in serum neutralization was also observed with 0% of the convalescent exhibiting positive neutralizing activity (23).

Humoral response from naïve Omicron BA.2 infected patients demonstrates limited cross-variant response.

When overseeing the humoral response from naïve Omicron BA.2 infected patients, Lee et al. concluded that the immunological response of naïve Omicron BA.2 convalescent individuals was limited in its cross-variant response and was lower than previous variants of concerns (25). According to the study, individuals infected with BA.2 variant had significantly lower antibody titers against all variants of concern where anti-Omicron BA.1 spike IgG titers were approximately 40-fold lower following a BA.2 infection than BA.1 infection (25). Additionally, IgG titers against the ancestral spike were almost 70-fold lower following BA.2 than BA.1 infection (25). Similar conclusions were made regarding the neutralizing capacity of the BA.2 elicited humoral response. In this case, the neutralizing activity was higher in previously infected participants than in naïve individuals where IgG antibody titers in individuals previously infected with earlier SARS-CoV-2 variants were at least 5-fold higher than those infected with BA.1 or BA.2 (25).

High levels of CD4+ T cells are associated with long-term persistence of neutralizing antibodies.

One of the included studies aimed to directly correlate the levels of humoral response to cellular response (26). Based on the study, high levels of virus specific CD4+ T cells during the early convalescent phase correlated with long-term neutralizing antibody levels (26). In the study, Wang et al. grouped patients with low CD4+ T cell response in one group and patients with high CD4+ T cell response in another one. The investigators then proceeded to compare the estimated decay rates for 10 months. The estimated decay rates of binding and neutralizing antibodies in the low CD4+ group were higher than in those from the high CD4+ group where the low group had a faster decay rate and shorter half-life than the high group (26).

3.2.1.2 Vaccine-acquired immunity

A total of 20 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 (15, 17, 28-45). Of the included studies, 13 reported on the neutralization of antibodies against the Omicron variant

(B.1.1.529) (15, 17, 30, 33, 34, 36-43, 45), while six studies reported on antibody levels (28, 29, 31, 32, 35, 44) in vaccinated participants.

3.2.1.2.1 Primary-scheduled vaccination[1]

Primary-scheduled vaccination does not elicit robust neutralizing antibodies against the Omicron variants, and they wane 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 (17, 30, 33, 38, 40, 41, 45). 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 (17, 30, 33, 38, 40, 41, 45). 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 (17). 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, to be more vulnerable to breakthrough infections (30).

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

When comparing the level of protection provided by different vaccines, the included studies reported that mRNA vaccines induced higher antibody levels and were able to better neutralize the Omicron variant than the Janssen vaccine (39). 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 (30). Overall, mRNA vaccines demonstrated to provide a higher and more robust level of protection compared to the viral vector vaccine of Janssen.

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

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 with 2 doses (29). This loss was more pronounced in antibodies targeting the Omicron RBD than antibodies targeting the Omicron Spike protein (29). 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 (29). Additionally, a difference between vaccine types was observed with

[1] Primary-scheduled vaccination refers to individuals who receive the initial doses from Janssen (1 dose) and from Pfizer-BioNTech and Moderna (2 doses). Might also be referred as 'fully vaccinated'.

respect to 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 (29).

3.2.1.2.2 First booster doses[2]

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 primary scheduled mRNA vaccines mRNA-1273 and BNT162b2 (28). 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 have been shown to be significantly higher in boosted individuals compared with individuals who did not receive a booster dose (28, 35). A study analyzing the kinetic parameters of antibody responses within 14 days after a third homologous vaccination in Pfizer and BioNTech vaccine recipients found that the absolute titers of all Ig antibody subtypes increased within two weeks of receiving the third vaccination (35). By quantifying the Omicron-RBD-binding antibodies and comparing them to unboosted individuals, the researchers showed that a third BNT162b2 vaccine led to a 4.7-fold and 2.5-fold increase in Omicron-RBD IgG and Omicron-RBD IgA binding antibodies, respectively (35). Subsequently, a total of 50% of the maximum antibody titer was achieved for Omicron IgG after 5.4 days and 5.1 days for Omicron IgA (35). Overall, these results demonstrate that vaccination with a booster dose increases the antibody levels and inhibition against the Omicron variant (28, 35, 44).

mRNA vaccines continue to demonstrate higher neutralizing antibodies against Omicron when compared with homologous or heterologous booster 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 (30). As for the difference between homologous and heterologous booster vaccinations, a distinct difference was seen between the homologous prime-boost Ad26.COV2.S and any other heterologous booster combinations (39). 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.COV2.S, or Ad26.COV2.S booster combination had higher neutralizing antibodies against both variants (39). In Tan et al., BNT162b2 boosting in individuals primed with Pfizer and BioNTech was associated with a rapid increase of Omicron neutralizing antibodies with peak median titers of 1018 at week two, while Ad26.COV2.S (Janssen) boosting was associated with increased Omicron neutralizing titers that peaked at a median of 859 by week four (42). Similar results were seen in Lyke et al. in which a booster dose increased the neutralization titers to above 200 GMTs for Omicron in all homologous and heterologous

[2] First booster dose refers to individuals who received, in the case of Janssen, 2 doses and, in the case of Pfizer-BioNTech and Moderna, 3 doses.

groups (BNT162b2, mRNA-1273, Ad26.COV2.S), except the homologous prime-boost Ad26.COV2.S group (42). In this group, the geometric meant titers for Omicron were only 27. In synthesis, the homologous Ad26.COV2.S booster vaccination schedule produces the lowest neutralizing antibodies against Omicron (B.1.1.529) when compared to other homologous and heterologous combinations.

Janssen boosting was associated with a prolonged and durable humoral immune response

Although the administration the Janssen COVID-19 vaccine elicited lower levels of humoral response, heterologous Janssen boosting was associated with a durable humoral immune response in individuals primed with Pfizer and BioNTech, including against SARS-CoV-2 variants of concern (42). Based on the study, neutralizing antibodies solicited by BNT162b2 boosting declined by 6.9-fold to a median titer of 148 (IQR; 95-266) by week 16, while Ad26.COV2.S boosting only declined by 2.1-fold to a median titer of 403 (IQR; 208-1130) by week 16 (42). Overall, the utilization of a heterologous boosting approach appears to have a more prolonged duration of protection than homologous booster schedules.

Although a booster dose increases the magnitude and breadth of waning protection against Omicron, a lower binding and neutralizing antibody capacity is seen against Omicron.

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 (15, 29, 33-35, 39-41, 43, 45). A third dose of the BNT162b2 or mRNA-1273 vaccine increased the magnitude and breadth of the waning neutralizing antibodies against the Omicron variant; nevertheless, they provided a lower neutralizing capacity against Omicron compared with previous VOCs. For instance, the breath of Omicron-RBD-binding antibody titers elicited by a third BNT162b2 dose was 6.7-fold lower than against the Wuhan variant (35). As for the neutralizing abilities, one study reported that the Omicron-RBD-binding antibodies only peaked at 111 GMT (95% CI, 75-166) for Omicron (34), and another study approximated that 36% of the sera of third BNT162b2 recipients failed to neutralize the Omicron variant (35). This decreased neutralizing capacity was especially emphasized in Janssen boosted individuals where a booster dose of Ad26.COV2.S elicited Omicron neutralizing titers of 11.7 GMT 29 day after administration, while eliciting 110 GMT against the wild-type (15). Overall, a first booster dose demonstrated lower levels of binding antibodies and lower neutralization of the Omicron variant (B.1.1.529).

Newer emerging variants such as BA.4/BA.5 are less susceptible to vaccine-induced neutralization than BA.1

In addition to demonstrating lower binding and neutralizing capacity against Omicron B.1.1.529 variant, the newer emerging Omicron subvariants BA.2.12.1, BA.4, and BA.5 were found to be even less susceptible to vaccine-induced neutralization than BA.1 (15, 37). According to Lyke et al., the neutralizing antibodies to Omicron sub-lineages BA.2 and BA.3 elicited in triple vaccinated mRNA-1273 individuals were similar to BA.1, whereas subvariants BA.2.12.1, BA.4, and BA.5 were approximately twice as less susceptible to neutralization than BA.1 (15). Additionally, when comparing the decrease in neutralization of subvariants BA.2.12.1 and BA.4/BA.5 to the wild type, the neutralizing titers were 7.5 and 12.4 times lower (15). On the

other hand, Khan et al. found that BA.1, BA.4, and BA.5 showed a similar extensive escape in naïve vaccinated individuals, where neutralization in fold-drops relative to the ancestral virus were 19.8-fold for BA.1, 19.6-fold for BA.4 and 20.9-fold for BA.5 (37).

A first booster dose (third dose in most cases) shows early signs of waning.

Despite the ability of booster doses to reestablish previous neutralizing antibodies prior to the Omicron variant, various studies have demonstrated that a few months after receiving a first booster dose, the neutralization geometric mean titers, along with the levels of binding antibodies, decreased significantly (15, 34, 35, 45). Three studies that exemplified the waning of protection over time are Hein et al., Lyke et al., and Gilboa et al. Within 4 months after the administration of a booster dose, a waning in protection of 3- to 4-fold decrease was observed for all strains including Omicron (B.1.1.529) (34), while another study found that homologous mRNA boosting and heterologous boosting with mRNA or Ad26.COV2.S vaccines substantially waned Omicron BA.1 neutralizing antibodies substantially by three months (15). Furthermore, Hein et al. observed waning of Omicron-binding antibodies as soon as 14 days after boost administration, where the titers for IgA and IgG peaked on day nine but significantly decreased by 66.6% for IgA and by 30.6% for IgG antibodies, two weeks after administration (35).

When evaluating the waning dynamics and kinetics of the duration of protection of third doses, a few observations were made. One of them was the slower waning of humoral response after a third BNT162b2 dose versus the second dose. In Gilboa et al., IgG waned observably slower after the third BNT162b2 dose with an estimated percentage decrease of 1.32% per day (95% CI, 1.29-1.36%/day) than after the administration of the second dose (2.26% per day [95% CI, 2.13-2.38%/day]) (34). Similar kinetics were observed in neutralizing antibodies which also demonstrated to have a slower rate of decrease after the third vaccines dose than after the second dose (1.32% [95% CI, 1.21-1.43%/day] vs. 3.34% [95% CI, 2.13-2.38%/per day]) (34). In addition, the neutralizing antibody kinetics after the third dose were constant throughout the study timeframe, while the kinetics following a second dose substantially continued to decrease beyond 70 days after the second vaccination (34). In terms of avidity – the overall strength in binding between and antibody and antigen – the mean avidity observed by Gilboa et al. was of 65.7% one month after the second vaccine with no significant change found six months after the second dose; but, increasing to 97.4% one month after the third vaccine dose, and 98.04% four months after the third dose of BNT162b2 (34).

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

Although an increase in antibodies was seen after the administration of a booster dose, breakthrough infections were reported in boosted cohorts (44), highlighting the possibility of breakthrough infections to occur despite potent adaptive immune responses in vaccinated and even boosted individuals (44). 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 (28, 32, 44). 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 (32). 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 (28). 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.

3.2.1.2.3 Second booster doses

Second booster elicits binding and neutralizing antibodies against multiple SARS-CoV-2 variants of concern.

Through the administration of a second mRNA vaccine booster dose (fourth dose) in uninfected individuals, a significant increase in the level of binding and neutralizing antibodies against various variants was shown (35, 36). When quantifying the binding antibodies to the Omicron-RBD, the results revealed that the second booster increased by 2.9-fold the GMT compared to the first booster (35). A fourth dose also demonstrated to significantly rise the levels of binding and neutralizing antibodies in low-baseline individuals who failed to develop detectable neutralizing antibodies prior to the second booster. In Hertz et al., 65% of participants in the low-baseline group demonstrated an ability to mount to adequate immune responses at 30 days after the administration of a fourth dose, indicating that a second booster dose induced steeper rises in neutralizing antibody titer in low-baseline groups (36). Additionally, the second administration of an mRNA booster dose was also found to increase the immunogenicity against Omicron subvariants BA.1 and BA.2 by decreasing the amount of individuals with low detectable neutralizing titers at baseline from 79.73% for BA.1 and 75.67% for BA.2 to approximately only 30% after 30 days post-vaccination (36).

Even with a second booster (fourth dose), a substantial loss in binding antibodies against Omicron variants was observed.

Despite the evident increase in elicited binding and neutralizing antibodies by the administration of a second booster dose, a substantial loss against the Omicron variant was observed, compared to the original strain and previous variants of concern (35, 36). In the study conducted by Hertz et al., the GMT of Omicron-RBD-specific antibodies was up to 4.4-fold lower than the original-RBD-specific titers and 2.4-fold lower than the Delta-RBD-specific titers (35). This significant reduction in neutralization to the Omicron variant was also observed in the subvariant BA.1 and BA.2, where, compared to the original SARS-CoV-2 strain, a decrease in baseline neutralizing titers was found 30 days after the fourth dose for the BA.1 and BA.2 subvariants (36).

3.2.1.2.4 Correlates of protection

Baseline binding IgA and IgG responses are correlates of protection for Pfizer-BioNTech mRNA vaccination.

While identifying correlates of protection might pose a challenge, four studies observed an association between the levels of binding antibodies and susceptibility to COVID-19 infections (34, 36, 46, 47). The risk of developing an Omicron breakthrough infection was independent of vaccination scheme, sex, body mass index, smoking status or pre-existing conditions, where participants with low anti-Spike antibodies (≤ 2641.0 BAU/ml) and weaker neutralization capacity (≤ 65.9%) had higher risks of developing an Omicron infection (47). In individuals triple vaccinated, infections with COVID-19, at the time of the Omicron (B.1.1.529) variant surge, mainly occurred in individuals with lower IgG peaks (mean BAU: 2659 [95% CI, 2528-2797]) than those with higher binding antibody levels (mean BAU 3107 [95% CI, 2983-3236]) (ratio of means between those infected and not infected, 0.86 [95% CI, 0.80-0.91]) (34). Similar observations were made in Hertz et al. where infection rates in the low-response group were significantly higher than in the high-response group for both third and fourth dose recipients (36). Thirty days after the administration of a fourth mRNA vaccine, IgA magnitude to the original and previous and current variants of concerns was associated with infection risk (HR for original strain: 3.19 [p=0.019]; HR for VOCs: 4.45 [p=0.006]) (36). In addition, an association between binding antibodies and neutralizing titers was observed in a study conducted by Hertz et al. According to the results, individuals with low-baseline binding antibodies had significantly lower neutralizing antibody titers than individuals with the high-baseline group, and where following a fourth BNT162b2 dose, the number of infected participants in the low-baseline group was significantly higher than in the high-baseline group (36).

3.2.1.3 Hybrid

Nine 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 (36, 43, 44, 48-53).

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 boosted (including first and second booster) 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. 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 (49). 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 (52). Moreover, Omicron breakthrough infections not only increased the geometric mean titers observed in fully vaccinated individuals, but among boosted individuals as well. In addition, Omicron breakthrough infections were found to lead to an overall enhancement of vaccine-induced humoral

immunity against multiple SARS-CoV-2 variants and faster viral clearance that those of the ancestral variant (50).

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 (49). Additionally, 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 (44). A significant rise in antibody levels, regardless of administration of a fourth BNT162b2 vaccine dose, was also observed in a study comparing the IgG and IgA antibody responses of breakthrough infections in individuals infected within the first 30 days from enrollment (36). Moreover, no significant difference was found in binding antibody titers at day 30 in infected individuals with three doses and four doses (36).

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 (43, 48, 53). Subsequently, 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 (51). 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 (51).

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 (48). Nonetheless, the Janssen vaccine reported 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 (48).

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 recover from infection). Based on the results, antibodies elicited against Omicron demonstrated to have significantly

decreased in neutralization 6 months after recovery from infection (48). 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 (48).

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 (21, 26, 34, 37, 46, 49, 51, 54-97). 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 and its subvariants, compared with unvaccinated convalescent individuals.

From all of the included studies, only five articles directly compared the levels and neutralizing capabilities of antibodies between convalescent individuals and naïve individuals fully vaccinated with a COVID-19 vaccine (72, 75, 77, 83, 91). As previously reported, unvaccinated convalescent individuals did not effectively neutralize variants of concern such as the Delta variant and the currently predominant Omicron variant and subvariants. 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 (72). 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 (83, 91). 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 (91). Similar results can be observed with the first booster doses, where three BNT162b2 dose recipients elicited higher neutralizing mean titers against multiple variants of concern such as Omicron BA.1, BA.2, BA.4/BA.5, and Deltacron (Delta and Omicron hybrid) than unvaccinated BA.1 infected individuals (75).

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 (83). 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 (83).

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 (77). 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 (72).

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 subvariants of concern.

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, indicating that hybrid immunity was associated with an enhancement in humoral immunity (74, 84, 85, 90). Post Omicron infection, neutralization against BA.1 increased by 13.6-fold in vaccinated individuals and 6.0-fold in unvaccinated individuals (74). 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 (90). Subsequently, breakthrough infections demonstrated to induce higher neutralizing antibodies than in unvaccinated and infected participants. In Brazer et al., Delta and BA.1 infections in vaccinated participants led to titers 5.2 times higher against BA.1 (p=0.087) and 19.8 times higher against BA.2 (p=0.0081) than titers in unvaccinated participants (21). Additionally, BA.4 breakthrough infections were also found to elicit higher levels of BA.4 titers (GMT 1984) than levels elicited by a BA.4 infection in unvaccinated individuals (GMT 1047) (85). In some cases, critically ill COVID-19 patients showed to elicit higher levels of anti-Spike and anti-Nucleocapsid antibodies compared to vaccinated healthcare workers (58).

Infections with prior variants and Omicron (BA.1) did not mount high cross-neutralizing antibodies against variants and subvariants of concern.

Despite the moderate increase in binding and neutralizing antibodies observed post infection, unvaccinated individuals infected with BA.1 still had limited cross-protection against Omicron, its subvariants and previous variants, (74, 84, 90, 93). 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 (74). Similarly, Seaman et al. showed that neutralizing activity was lower in unvaccinated individuals at the time of infection, compared to previously vaccinated groups (90). These results were also highlighted in Brazer et al., where the neutralizing antibody response against BA.2 and BA.1 from Delta and Omicron BA.1 infections in unvaccinated participants was weak and lacked cross-variant neutralization (21). The low cross-neutralization elicited by infections with prior variants and Omicron

BA.1 against variants of concern was also noted in previously vaccinated individuals (21, 76). In both Liderman et al. and Brazer et al., Delta and even Omicron BA.1 breakthrough infections resulted in low to moderate neutralizing responses against BA.1, BA.2, and BA.5 (21, 76).

Infection with BA.5 led to better and more cross-neutralizing antibodies against Omicron subvariants in both vaccinated and unvaccinated individuals.

Although infections with prior variants and BA.1 did not mount high and cross-neutralizing antibodies, BA.5 infections demonstrated to lead to better and more cross-neutralizing antibodies against Omicron subvariants in both vaccinated and unvaccinated individual (76). In this study, BA.5 infected patients exhibited a more balanced ratio of Omicron virus neutralization, while Omicron patients infected with BA.1 or BA.2 had detectable neutralizing antibody titers to BA.5, but with lower levels than the ones against BA.1 and BA.2 (76).

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 (61, 62). 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 (60).

A higher neutralization capacity against the SARS-CoV-2 variants, including Omicron, was observed in individuals infected and vaccinated than in naïve vaccinated individuals.

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 (51, 61, 64, 69, 79). 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 (69). An even higher increase in neutralizing antibodies was seen in individuals with Omicron breakthrough after only 2 vaccine doses (69).

Multiple studies have found that breakthrough infections in boosted individuals led to increases in the magnitude, potency, and breadth of antibodies that neutralize the recently circulating Omicron variant and

its subvariants (49, 51, 65, 69, 70, 80, 94, 95). 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) (65). 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 (69). Moreover, when examining the neutralizing capacity against Omicron's subvariants BA.1, BA.2, and BA.4/BA.5 the effects of Omicron 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 (49, 69, 70, 94, 98).

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. Additionally, critically ill COVID-19 patients showed to elicit higher levels of anti-Spike and anti-Nucleocapsid antibodies compared to vaccinated healthcare workers (58) suggesting that the severity of the clinical outcomes from infections played a role in the levels of elicited antibodies (51, 58).

Humoral responses in individuals with vaccine-acquired immunity wanes at a higher rate over time than in those with hybrid 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 (62, 66, 67, 82). 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) (67). 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 (67). 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 (66). Similar kinetics where found in boosted individuals, where the booster durability waned more substantially in uninfected individuals than in those who had experienced a breakthrough infection (82).

Conversely, two studies observed that the decay of the humoral response was faster in infected and vaccinated participants than non-infected and vaccinated ones (34, 46). For instance, Favresse et al. found that the estimated half-life of binding antibodies for participants with and without history of SARS-CoV-2

infection was 42 (95% CI, 25-137) and 36 days (95% CI, 25-65), respectively and the estimated half-life for binding antibodies was 168 (95% CI, 116-303) and 139 days (95% CI, 113-180), respectively (46). Similarly, Gilboa et al. reported a decreasing rate of IgG antibodies of 1.39% per day among infected participant compared to a decreasing rate of 0.99% per day among those not infected, with a mean ratio of 1.40 (34).

Neutralizing antibodies wane at higher levels over time than binding antibodies in individuals with hybrid and vaccine-acquired immunity.

When comparing vaccine-acquired and hybrid neutralizing and binding antibodies, a higher decay can be found in COVID-19 naïve individuals than in previously infected subjects, in which the neutralizing antibodies waned at higher levels than the binding antibodies (11.5- and 10.2-fold decrease in uninfected individuals vs. 2.9- and 2.5-fold decrease in previously infected individuals for neutralizing and binding antibodies, respectively) (46). In addition, when estimating the half-life of neutralizing and binding antibodies in previously infected and naïve vaccinates individuals, the estimations were longer for binding antibodies in both groups (46).

One booster dose and a breakthrough infection with subvariant BA.1 resulted in a higher and more cross-neutralizing humoral immunity than a second booster dose.

In two studies observing the binding and neutralizing antibody levels elicited by second boosters and comparing them to the levels from Omicron BA.1 breakthrough infections in triple vaccinated participants (one booster plus infection), vaccinated individuals with BA.1 breakthrough infections developed greater humoral immunity (71, 97). This observation is clearly explained in the study conducted by Xie et al., where four mRNA vaccine doses showed the lowest geometric mean titers against Omicron sub lineages such as BA.5 compared to two vaccine doses plus BA.1 infection or three vaccine doses plus BA.1 infection (97). In the study, four dose vaccine sera neutralized the original strain, Omicron BA.1, BA.2, BA.212.1, BA.3, and BA.4/5 viruses with geometric mean titers (GMTs) of 1554, 357, 236, 236, 165, and 95, respectively; two dose vaccine plus BA.1 infection sera exhibited GMTs of 2114, 1705, 730, 961, 813, and 274, respectively; and, three dose vaccine plus BA.1 infection sera showed GMTs of 2962, 2038, 983, 1190, 1019, and 297, respectively (97). Overall, one booster breakthrough infection with Omicron BA.1 induced a stronger increase in neutralizing antibodies against the different variants of concern than a second mRNA vaccine booster.

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 (26, 37, 54-57, 59, 63, 68, 73, 78, 86-89, 92, 96).

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 (55). 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 (56, 57, 59, 68, 73, 87-89, 92, 96). 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 (96). In accordance with Wratil et al., 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 (59). 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.

Omicron subvariant cross-neutralization improved with repeated exposure of hybrid immunity.

Eight studies compared the different sort of acquired immunity in participants infected with Omicron's subvariants' BA.1, BA.2, BA.2.12.1, and BA.4/BA.5 (26, 37, 54, 56, 63, 68, 78, 86). Based on the findings, unvaccinated individuals and previously uninfected individuals who acquired a BA.1 or BA.2 SARS-CoV-2 infection had limited cross-neutralizing antibodies to pre-omicron and Omicron subvariants, particularly BA.4 and BA.5 (26, 37, 54, 56, 63, 78, 86). For instance, the study conducted by Khan et al., neutralization relative to BA.1 declined 7.6-fold for BA.4 and 7.5-fold for BA.5 in BA.1-infected unvaccinated individuals, while a decrease of 3.2-fold for BA.4 and 2.6-fold for BA.5 was observed in vaccinated individuals with subsequent BA.1 infections (37). 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.

Multiple studies analyzed T cell and memory B cell responses in convalescent individuals (23, 24, 26, 99). Li et al. and Garcia-Valtanen et al. found that cellular immunity was conserved up to a year after infection, with T cells showing a slightly stronger memory than B cells (23, 99). Both of these studies also observed that CD4+ T cells had a higher frequency than CD8+ T cells, although Li et al. saw that a majority of CD8+ T cell epitopes of SARS-CoV-2 were conserved in Omicron (23, 99). In their study, Wang et al. also noted that a high percentage of virus specific CD4+ T cells and cTfh1 were associated with a slower decline in humoral immunity which could highlight the importance of coordinating T-cell and humoral immunity to achieve long-term protective immunity (26).

T cell responses to Omicron variants are lower than responses to wild type and Delta variants.

Garcia-Valtanen et al. and Guo et al. evaluated T cell responses against Omicron compared to WT and other earlier variants in convalescents (23, 24). They found that responses against Omicron were significantly impaired. Guo et al. assessed T cell responses to wild type and Omicron variants in individuals recovered from COVID-19 infection and found that, from 41 participants, there was a 78.0% positive rate of T cell responses to the Wuhan strain compared to a 70.7% response rate to the Omicron variant (24). For IFN- γ responses, overall, they found no significant differences between the two strains (23, 24).

3.2.2.2 Vaccine-acquired immunity

A total of thirteen studies analyzed the cellular immunity initiated by vaccination through the measurement of T cell and memory B cell responses (16, 42, 44, 100-109).

Vaccinated individuals elicit a higher T cell response for all variants of concern than nonvaccinated individuals, with mRNA vaccines eliciting a higher response than vector vaccines.

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 (104). 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 (100, 107). 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 (107). There was a slight non-significant decrease in IFN-γ secreting cells responding to Omicron spike (100) and three months after vaccination, there was waning of memory T cell responses for both Delta and Omicron variants (107). 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 (101). Woldemeskel et al. also found that boosted vaccine recipients had significantly stronger T cell responses to both vaccine strains and Omicron variant spike proteins at times of breakthrough infection compared to boosted COVID-19 negative individuals (44).

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

Mise-Omata et al. assessed T cell responses among volunteers at 3 time points between the 2nd dose and 3 dose vaccination and found that both CD8+ and CD4+ T cells were maintained after 8 months with some decline and were recovered to initial levels by booster vaccination (16). Additionally, they found that T cell memory responded equally to both the Wuhan and Omicron-variant spike peptide pools whereas memory B cells had a lower affinity for the Omicron variant (16). With these results, Mise-Omata et al. inferred that because the T cell response was normal against Omicron, infection with the Omicron variant or Omicron variant-specific vaccination may induce a memory T cell response that is high enough to protect against an Omicron infection (16). Kotaki et al., Mise-Omata et al., and Muecksch et al. investigated memory B cell responses in vaccinated cohorts (16, 102, 106). Kotaki et al. profiled the memory B cell responses of 40 health care workers vaccinated with two doses of the Pfizer BNT162b2 mRNA vaccine and found that they were still able to produce a strong neutralizing antibody response against Omicron (102). They also found that more than one-third of resting memory B cells bound Beta and Omicron variants and steadily increased the B cell receptor breadth up to 4.9 months after vaccination. Muecksch et al. and Mise-Omata et al. measured memory B cell repertoire in healthy individuals after two or three vaccine doses and found that the 3rd dose further increased the cells that were present after the 2nd dose (16, 106). 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 (106).

Heterologous vaccination regimens with mRNA primary and Ad26.COV2.S booster seem to elicit higher cellular immune response than homologous regimens.

In a study that followed Ad26.COV2.S-primed health care workers as they received various booster vaccines, (109) found that T cell responses declined between 28 days and 5 months after booster vaccination, toward similar levels as detected pre-booster vaccination with Ad26.COV2.S vaccine. They also found that T cell responses were higher 28 days after mRNA-based booster vaccination compared to Ad26.COV2.S booster vaccination. However, this difference was not apparent 5 months later. Furthermore, a study by Tan et al. examined the durability of cellular immune responses in individuals who received a primary vaccination of Pfizer BNT162b2 and were boosted with either Ad26.COV2.S or BNT162b2 (42). In contrast to Sablerolles et al. they found that at 16 weeks, median Omicron T cell responses generated by the Ad26.COV2.S booster were higher than those generated by the BNT162b2 booster (109). Additionally, CD8+ and CD4+ T-cell responses generated by Omicron BA.1 and WA1/20200 were comparable, which is consistent with prior studies (42). Tan, 2022 also assessed Omicron BA.1 RBD-specific memory B-cell responses was also assessed where the levels after Ad26.COV2.S booster were found to be higher than those after BNT162b2 booster (42). These data suggest potential benefits of heterologous prime-boost vaccine regimens for SARS-CoV-2.

3.2.2.3 Hybrid

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

Three studies examined hybrid cellular immunity (26, 49, 52). 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 (49). 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. Wang et al. investigated the development of memory B cell antibodies after a 3rd or 4th antigenic exposure by Delta and Omicron BA.1 infection among individuals that had been vaccinated with 2 or 3 doses of an mRNA vaccine (26). They found that the number of memory B cells after Delta breakthrough was significantly higher compared to after the 2nd or 3rd vaccine dose. Like Quandt et al., Wang et al. observed that Omicron BA.1 breakthrough infection induced a 1.7-fold increase in memory B cell responses compared to 3rd dose vaccination (26). Wang et al. also examined the specificity and neutralizing activity of the antibodies produced by memory B cells post breakthrough infection and found that a 3rd antigenic exposure by Delta infection elicits strain-specific memory responses and increases in the overall potency and breadth of the memory B cells (26). In contrast, the effects of a 4th antigenic exposure with Omicron BA.1 is limited to increased strain specific memory with little effect on the potency or breadth of memory B cell antibodies. These results suggest that the effect of strain-specific boosting on memory B cell response may be insufficient. Soraas e al. investigated spike peptide-induced release of interferon gamma (IFN-γ) in vaccinated individuals infected with the Omicron and Delta variants (52). 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 (52). 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

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

Several studies investigated naturally acquired and vaccine-acquired cellular immunities (16, 83, 110-114). Mazzoni et al., Keeton et al., Richardson et al., Gao et al., and Mise-Omata et al. 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 (83, 110-112). 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 the wild-type or mutant SARS-CoV-2 spikes were significantly weaker after natural occurring infections compared to those in vaccinated individuals (83). 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 (83). Four studies found that T-cell responses, both after natural infection and vaccination, were conserved against the Omicron variant despite Omicron harboring considerably more mutations (111-114). 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 (112). Unexpectedly however, Emmelot et al. found that frequencies of IFN-ɣ+ T cells reactive to the Omicron BA.1 spike protein were significantly lower in the vaccinated cohort than in the convalescent cohort (113).

3.2.2.4.2 Vaccination vs. Hybrid

Vaccine-acquired and hybrid-acquired cellular immunity were compared by Kared et al., Sokal et al., and De Marco et al. (115-121).

There is no significant difference between memory B cell immunity induced by vaccination or vaccination and breakthrough infection.

Four studies analyzed memory B cells responses (116-118, 120). Two studies 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 (117, 118). When testing whether such a conclusion held true in the context of the Omicron variant, Sokal et al., Kaku et al., and Goel et al., found, as previously reported, that memory B cells in vaccinated COVID-19-recovered patients and vaccinated naive patients bound WT RBD with high-affinity, had slightly reduced affinity against the Beta and Delta RBD, and even more reduced against the Omicron RBD (117, 118, 120). 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 (116). Furthermore, Goel et al. noted that spike- and RBD-specific memory B cell numbers continued to remain highly stable through at least 9 months post primary vaccination in both SARS-CoV-2-naive and previously infected individuals with no evidence of decline and an expansion in number upon receipt of a 3rd vaccine dose (118). Alternatively, Kaku et al. who investigated memory B cell response after Omicron BA.1 breakthrough infection found that breakthrough infections induced significantly higher IgA B cell responses to the BA.1 RBD compared to two and three-dose vaccination but relatively similar IgG B cell responses to vaccination (120).

CD4+ T cells have a relatively higher reactivity to mutated spike regions than CD8+ T cells.

Two studies investigated T cell responses (115, 119). 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 (115).

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%) (115). 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% (115). 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 (115). In addition to this, Jung et al. found that in individuals with prior infection, 2-doses of the BNT162b2 vaccine increased the percentage of IFN-γ+ responses to 100% against both WT and Omicron spike protein and that these responses were maintained for 3 months (119). They observed similar results for TNF- or IL-2-producing CD4+ T cells. In their analysis of CD8+ T cell responses, Jung et al. found that the percentages of positive responses were relatively low compared to the CD4+ T cells, as similarly observed by De Marco et al., but IFN-γ+ or TNF+ producing CD8+ T cell responses did not notably differ against the WT versus Omicron spike protein in the vaccinated cohort or hybrid cohort (119).

A second booster (4th dose) sustains cellular immunity, similarly to breakthrough infection.

One study documented the cellular immune responses after a 4th vaccine dose compared to those after breakthrough infection (121). Reinscheid et al. first analyzed CD8+ T cell responses pre and post 3rd dose and found that frequencies had reached their peak around 60 days after the 2nd dose and there was a substantial but short-lived booster effect after the 3rd dose (121). Within 30 to 60 days after the 3rd dose, the CD8+ T cell response was reduced back to pre-3rd dose levels. Next, they analyzed CD8+ T cell responses after the 4th antigen contact, either by a 4th vaccine dose or by breakthrough infection with Omicron or Delta after 3 doses (121). They found that the T cell response was rapidly and robustly induced at similar frequencies by the 4th dose and breakthrough infection. Furthermore, the authors observed that a month or two after breakthrough infection and second booster vaccination, a fully functional T cell memory was present with similar reactivation capacities (121). They also observed that 4th vaccine-elicited spike-specific CD8+ T cells had a significant response towards variants of concern including Omicron. In terms of CD8+ T cell responses, the authors concluded that mRNA boosters induce a temporary T effector cell response while spike-specific CD8+ T cell memory is conserved for targeting variants of concern.

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 (122-124). 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 (122). 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 (122). 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 none-spike proteins, with a reduced recognition to Omicron spike being primarily observed within the CD8+ T-cell compartment (123). In terms of memory B cells, Tarke et al. found that there was an overall decrease in Omicron recognition compared to other variants (124).

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

3.3.1 Comparing immunities

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 (125-140). 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 (125, 126, 128, 130, 131). 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 (125, 130, 131, 135, 136, 139, 140). There was a significant decrease in the VE of the BNT162b2 booster (from 53.4% to 16.5%) within 3 months after administration (138). 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 (133).

3.3.1.1 Vaccine-acquired immunity

mRNA vaccine-doses were moderately effective at preventing Omicron (B.1.1.529) infection

Ioannou et al. and Monge et al. estimated that booster mRNA vaccine-doses were moderately effective at preventing Omicron (B.1.1.529) infection with the omicron variant (B.1.1.529) (141, 142). Monge et al. conducted a national wide follow-up study in Spain (sample: 3 111 159 individuals) where it was estimated that booster mRNA vaccine-doses were moderately effective up to 34 days after administration (142). Ioannou et al. reported a booster VE of 42.3% (95% CI 40.6-43.9) >10 days after booster (141). Furthermore, the effectiveness against hospitalization and death were 53.3% and 79.1%.

In another study conducted by Tseng et al. in USA, the two-dose VE against Omicron infection at 14–90 days was 44.0% but declined quickly (143). The three-dose VE was 93.7% and 86.0% against Delta infection and 71.6% and 47.4% against Omicron infection at 14–60 days and >60 days, respectively. The three-dose VE was 29.4% against Omicron infection in immunocompromised individuals. The three-dose

VE against hospitalization with Delta or Omicron was >99% across the entire study population. These findings demonstrate high, durable three-dose VE against Delta infection but lower effectiveness against Omicron infection, particularly among immunocompromised people. However, three-dose VE of mRNA-1273 was high against hospitalization with Delta and Omicron variants.

Richterman et al. observed that the effectiveness of 2 vaccine doses was lower during Omicron, with no significant protection against infection (144). Booster doses added significant protection, although they also showed reduced effectiveness during Omicron. However, the protection conferred by a booster dose was higher than the one coffered by two doses. Moreover, after initial waning in BNT162b2 booster protection against infection, it remained largely stable for ≥16 weeks after vaccination.

Effectiveness of booster mRNA vaccine against infection and severe COVID-19

The effectiveness of mRNA booster against confirmed infection 15 to 60 days after boosting was estimated to range from 31.7% to 41.3% for the 4 boosting combinations (homologous BNT162b2, homologous mRNA-1273, 2-dose BNT162b2/mRNA-1273 booster, and 2-dose mRNA-1273/BNT162b2 booster). However, five months and more after boosting, estimated booster effectiveness against confirmed infection waned, ranging from –2.8% to 14.6%. Against severe COVID-19, estimated mRNA booster effectiveness was 87.4% 15 to 60 days after boosting and 87.2% 5 to 6 months after boosting, with no significant difference comparing vaccine combinations (145).

In terms of severe outcomes, Cerqueira-Silva et al. found that hybrid infection confers a more durable protection against deaths and hospitalization than infections throughout 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) (146). A similar pattern is valid for BNT162b2 and Ad26.COV2.S 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.COV2.S after 2–9-week, 97.5 vs 47.2) and higher for BNT162b2 than Ad26.COV2.S against infection (146). As per a study conducted by McMenamin et al., the booster of BNT162b2 provided substantial additional protection against severe COVID-19 (136).

Collie et al., in a study conducted in South Africa, found that the vaccine effectiveness was 56.3% during the BA.1–BA.2 wave and 47.4% during the BA.4–BA.5 wave (18). Although boosting with a third dose-maintained vaccine effectiveness against severe disease caused by all four sub lineages at 1 to 2 months, the vaccine effectiveness had decreased by 3 to 4 months to an effectiveness of 50.0% during the BA.1–BA.2 wave and 46.8% during the BA.4–BA.5 wave. This indicates that boosting maintains vaccine effectiveness against severe disease caused by the current omicron sub lineages. Nonetheless, the evidence of rapid waning of durability indicates the need for regular boosting as early as 4 months after the last dose and the need for vaccines to incorporate variants of concern to maintain protection.

Effectiveness of three doses of mRNA vaccines

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 (128). 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 Janssen/Ad26.COV2.S vaccine offered an effectiveness of 27.9% at 14 days to 1 month since the last dose, which stabilized to 29.2% in 2-4 months since the last dose. One dose of Janssen/Ad26.COV2.S 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.COV2.S (127).

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 (137).

Robilotti et al. in their study demonstrated improved vaccine-derived protection against COVID-19 infection in three dose versus two dose mRNA vaccinees during the Omicron surge (147). The advantage of three dose vaccination was maintained irrespective of prior COVID-19 infection status. The infection rate ratio for triple versus twice vaccinated HCWs was 0.667 for an estimated three dose vaccine effectiveness of 33.3% compared to two doses only during the Omicron dominant period. Sharma et al. conducted a wider cohort study (matched) with a total of 1 226 322 participants (mostly male, 97,5% - 98,4%) in US (148). They found that the third dose of mRNA-1273 provided additional protection over the primary series, 37.1% (95% CI, 32.2–41.7), 63.5% (95% CI, 53.7–71.6), and 75.0% (95% CI, 55.4–88.0) against infection, hospitalization, and death, respectively. The median time since completion of primary series before follow-up was around 268 days.

Effectiveness of vaccines on against the Omicron BA.1, BA.2, and other variants

Two studies compared the vaccine effectiveness against BA.1- BA.2 VOC, showing contrasting results. No difference in protection was found against both variants (149), while a drastic reduction of effectiveness was found after the transition to BA.2 (from 90% to 54%) with two doses (150). With three doses, the effectiveness remains stable at 80% (150). Chemaitelly et al., observed no significant differences in the effectiveness of mRNA vaccines (BNT162b2 and mRNA-1273) against symptomatic infections. Both vaccines provide comparable, moderate, and short-lived protection against symptomatic BA.1- and BA.2 Omicron infections (131).

Yan et al. showed that the BNT162b2 vaccination was effective against COVID-19-related mortality and severe complications amidst the Omicron BA.2 pandemic, and risks decreased further with the third dose

(151). Vaccine effectiveness against COVID-19-related mortality after two doses of BNT162b2 and CoronaVac were 90.7% and 74.8% in those aged ≥65, 87.6% and 80.7% in those aged 50–64, 86.6% and 82.7% in those aged 18–50. Vaccine effectiveness against severe complications after two doses of BNT162b2 and CoronaVac were 82.1% and 58.9% in those aged ≥65, 83.0% and 67.1% in those aged 50–64, 78.3% and 77.8% in those aged 18–50. Further risk reduction with the third dose was observed especially in those aged ≥65 years, with vaccine effectiveness of 98.0% for BNT162b2 and 95.5% for CoronaVac against mortality, 90.8% and 88.0% against severe complications.

The effectiveness of pre-Omicron primary infection against pre-Omicron reinfection was 85.5% (95% CI: 84.8-86.2%). Effectiveness peaked at 90.5% (95% CI: 88.4-92.3%) in the 7th month after the primary infection but waned to ~70% by the 16th month. Effectiveness of pre-Omicron primary infection against Omicron reinfection was 38.1% (95% CI: 36.3-39.8%) and declined with time since primary infection. The effectiveness of primary infection against severe, critical, or fatal COVID-19 reinfection was 97.3% (95% CI: 94.9- 98.6%), irrespective of the variant of primary infection or reinfection, and with no evidence for waning (152).

Kislaya et al. showed that the SARS-CoV-2 Omicron BA.5 lineage is associated with higher odds of reinfection compared with Omicron BA.2, regardless of the vaccination status (153). Although less effective compared with BA.2, COVID-19 booster vaccination still offers substantial protection against severe outcomes following BA.5 infection. Malato et al. demonstrated that the previous SARS-CoV-2 infection had a protective effect against BA.5 infection and this protection was maximal for previous infection with BA.1 or BA.2 (154). These data should be considered in the context of breakthrough infections in a highly vaccinated population, given that in Portugal more than 98% of the study population completed the primary vaccination series before 2022 (154). Breakthrough infections with the BA.5 subvariant were less likely among persons with a previous SARS-CoV-2 infection history in a highly vaccinated population, especially for previous BA.1 or BA.2 infection, than among uninfected persons (154). Infection with BA.1/BA.2 of a population mostly vaccinated provided significant protection against BA.5 reinfection (154).

In another study conducted by Link-Gelles et al., VE against COVID-19–associated hospitalization 7–119 days and ≥120 days after receipt of dose 3 was 92% and 85%, respectively, during the BA.1 period, compared with 69% and 52%, respectively, during the BA.2/BA.2.12.1 period (155). Patterns were similar for ED/UC encounters. Among adults aged ≥50 years, VE against COVID-19–associated hospitalization ≥120 days after receipt of dose 3 was 55% and ≥7 days (median = 27 days) after a fourth dose was 80% during BA.2/BA.2.12.1 predominance (155).

3.3.1.2 Hybrid immunity

Hybrid immunity (infection plus one or two boosters) showed highest protection against Omicron infections and severe outcomes

Hybrid immunity, conferred with two or booster doses plus infection, provides significant protection (146, 149, 154, 156-161) than vaccination alone against Omicron infection and severe outcomes (149, 159, 162, 163), with some exceptions Carazo et al (164).

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% (149). 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 (149). 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 (162). An extensive test-negative control study found protection increases with hybrid immunity (two doses plus BA.1 infection), but a third dose does not confer improvement to that hybrid protection on 258 007 HCWs in Canada (164). Carazo et al and Ntiziora et al. found that the protection conferred by full or booster vaccination is 5-fold lower than that one conferred by hybrid immunities among 1,305 vaccinated HCWs (160, 164). Furthermore, Ferrara et al. determined an incidence rate of 2.5 cases per 1000 person-days (95% confidence interval [CI] 2.0–3.0) in vaccinated subjects with previous infection, versus 0.8 per 1000 person-days (95% CI 0.3–2.0) for vaccinated population (165). All the studies argue that hybrid immunity confers higher protection than vaccination.

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 (146, 162, 166).

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 (146, 149, 162, 166). Severe outcomes were defined by Cerquere-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) (146), 73% (as a maximum of 6 months after vaccination) (156), and 81% against hospitalization (162). In terms of severe outcomes, hospitalization rate was lower in vaccinated subjects with previous infection than patients with vaccination only.

Protection against severe outcomes increases with hybrid immunity (natural immunity and boosters). The effectiveness of BNT162b2 and Ad26.COV2.S booster dose (within 2-9 weeks) was 95.7% and 97.5%, respectively (146). 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 (156). 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) (162). Nadig et al. found that hospitalization rate is lower in vaccinated subjects with previous infection than patients with vaccination only (159).

Finally, 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 deaths and 1.7% of hospitalization cases respectively (146, 166).

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 first booster dose (mRNA 41.2% vs BNT162b2 44.7% after 1 month) (149), while natural infection effectiveness ranged from 65% to 75% at 4-6 months and 32% to 53% at 10-12 months (149, 156, 162, 166). 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. (162).

Hybrid immunities against severe outcomes is durable 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) (146). This was confirmed by studies on elderly, as reported in the following chapter (167-169). A similar pattern is valid for BNT162b2 and Ad26.COV2.S 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.COV2.S after 2-9 week, 97.5 vs 47.2) and higher for BNT162b2 than Ad26.COV2.S against infection (146).

3.4. Risk groups (elderly & immunocompromised)

3.4.1 Humoral

3.4.1.1 Immunocompromised groups

Twenty-six 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 (37, 85, 170-192).

Immunocompromised groups generate a weak binding and neutralizing antibody response to the Omicron variant after mRNA vaccination or infection.

Generally, studies demonstrated that the humoral response of immunocompromised groups to the Omicron variant, was much weaker compared to earlier SARS Cov 2 variants post mRNA vaccination or infection (175, 177, 188, 189, 192). Overall studies found that immunocompromised groups did not generate a robust neutralizing antibody response to the Omicron variant after 2 doses of mRNA vaccination especially compared to healthy vaccinees (Pfizer/ Moderna) (170, 172, 176, 188, 189). Khan et al. and Geisen et al. further demonstrated that vaccinated HIV positive individuals experienced a significant drop in neutralization against the BA.4 and BA.5 Omicron sub-variants (37, 181). Humoral immune response escape by the BA.4 and BA.5 subvariants was even greater in unvaccinated HIV positive individuals (37).

Three or 4 doses of mRNA vaccines elicit stronger and longer lasting antibody response

Alternatively, there is evidence suggesting that a third or fourth dose of mRNA vaccination enhances and sustains antibody response against the Omicron variant in a higher proportion of immunocompromised groups (170, 172, 174, 178-180, 182-184, 186, 187, 190-192). 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 (170, 172). Similarly, Tillmann et al. and Thakkar et al. demonstrated that additional booster mRNA doses of 3 to ≥4 times elicited a stronger antibody response in previous non or low responding hemodialysis and cancer patients respectively (190, 191). Additionally, Tillmann et al. and Kontopoulou et al. found that breakthrough infections in immunocompromised group post 3 or 4 doses of mRNA vaccination, were clinically mild (184, 191). Interestingly, Di Giacomo et al. found that although immunocompromised groups generated a weaker response to the Omicron variant, post 3 doses of mRNA vaccination or infection, they were still able to mount antibody responses comparable to healthy groups (180). Furthermore, Vergori et al. showed that neutralizing activity against the BA.1 subvariant grew more robust after a third dose of mRNA vaccination in HIV positive individuals, although response remained weaker compared to earlier variants (192).

Nonetheless, Di Giacomo et al. observed lower levels of neutralizing antibodies against Omicron post 3 doses of mRNA vaccination and subsequent breakthrough infections in both immunocompromised and healthy groups alike (180). Additionally, 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 (174). Additionally, Kennedy et al. found that immunosuppressive treatments such as infliximab in inflammatory bowel disease patients were associated with attenuated and waning antibody response (183). It is also important to note that despite increased humoral response against Omicron with increasing booster doses, a common theme in the assessed studies was that neutralization of Omicron was still substantially weaker compared to earlier variants.

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, Sanders et al., Lasagna et al., and Becker et al. (178, 185, 188, 193) In a study by Kumar et al., 18.3% of organ transplant recipients had detectable levels of neutralizing antibodies against Omicron 1 month after their third dose of mRNA vaccine (193). However, this decreased to 15.7% of the participants 3 months post the third dose (193). Similarly, Sanders et al. and Lasagna et al. demonstrated that antibody response waned significantly 6 months post 2 or 3 doses of mRNA vaccination in kidney transplant recipients and cancer patients respectively (185, 188). In these studies, neutralization against the Omicron variant was significantly attenuated or completely missing 6 months after vaccination (185, 188).

Hybrid immunity generates a stronger humoral response in immunocompromised groups

Based on the studies examined there is growing evidence that infection combined with vaccination generates a more robust and longer lasting humoral response in immunocompromised groups (179, 180,

183). Kennedy et al. found that anti-SAR-CoV-2 antibody concentrations were higher and sustained longer in immunosuppressed participants who were previously infected with COVID-19 (183). Similarly, Cheng et al. found that hemodialysis patients with a history of COVID-19 infection had a significantly higher neutralizing capacity against the Omicron variant post 4 doses of mRNA vaccination (183). In addition, previous infection with BA.4 or BA.5 was able to trigger strong cross reactive neutralizing antibodies in HIV positive individuals in previously vaccinated and unvaccinated groups alike (85).

3.4.1.2 Elderly groups

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

This review includes 9 studies examining the humoral response of elderly groups (>55 years) to the Omicron variant, post vaccination or infection (30, 33, 34, 80, 194-198).

Mwimanzi et al. and Renia et al. found that following 2 doses of mRNA vaccine elderly adults mounted a weaker humoral response (197, 198). While Mwimanzi et al. found that older age was associated with a less durable antibody response, Reina et al. found no link between age and humoral response durability (197, 198). In fact, Renia et al. saw that elder groups took longer to develop vaccine acquired immunity, and a more sustained response was developed 6 months post vaccination. In addition, Mwimanzi et al., Renia et al., Belik et al., and Furukawa et al. demonstrated that humoral response to the Omicron variant was significantly stronger after a third dose of mRNA vaccination (30, 33, 197, 198). While Belik et al. found a weaker immune response in the older age groups (55-65 years), when compared to younger adults, even after the third dose, Furukawa et al. and Mwimanzi et al. saw that titres of neutralizing antibodies against Omicron post a third dose of mRNA vaccination were increased similarly in all age groups (30, 33, 197, 198). Notably, despite increased antibody response post a third dose, neutralization of the Omicron variant remained weak (33, 197).

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 (196). Mwimanzi et al. also found a greater decline in Omicron neutralization amongst elderly groups 6 months post a third dose of mRNA vaccination (197). 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 (195). Additionally, vaccination with a single dose of mRNA vaccine enhanced antibody response in previously infected individuals more significantly than naïve individuals receiving 2 doses (195). 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 (194). 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 (194). Opposing the aforementioned results, Gilboa et al. observed that in participants aged 65 years or older, IgG and neutralizing antibodies declined more rapidly in infected individuals (34).

3.4.2 Cellular

3.4.2.1 Immunocompromised groups

Twelve studies were included in this report that examined cellular response in immunocompromised groups (103, 105, 108, 178, 185, 188, 189, 199-203).

Cellular response is weaker in immunocompromised groups

Storti et al. reported that spike-specific IL-2-producing CD4+ T cells and cytotoxic spike-specific IFN-γ and TNF-α-producing CD8+ T were lower in multiple myeloma patients compared to healthy participants (189). Similar waning of T cells was observed by Davidov et al. in liver transplant patients 19 weeks post a third dose of mRNA vaccine (199).

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

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 original SARS-CoV-2 vaccine strain (105). 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 (108). Peled et al. and Lasagna et al. demonstrated similar results in heart transplant and solid tumor patients respectively, where durable T cell response was maintained 6 months post a third dose of Pfizer vaccination (185, 201). Additionally, T cell response was 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 (108). Similarly, Lin et al. demonstrated that primary antibody deficiency patients were still able to mount a durable CD4+ T cell response, specific to SARS-CoV-2, that was similar to healthy groups post mRNA vaccination (200).

Moreover, studies conducted by Lasagna et al., Mandelon et al., Sannier et al., and Becker et al. found that cellular immunity increased upon receipt of a third and fourth dose of an mRNA vaccine (103, 105, 178, 202). 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 (103). Madelon 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 (105). However, Thümmler et al.

found that even after a third mRNA vaccination, SARS-CoV-2-specific IFN-γ responses were much lower in kidney transplant recipients (203). Yet still, SARS-CoV-2-specific IL-2 responses remained similar to that of healthy participants (203).

T cell response wanes with time from vaccination

Sanders et al. observed that T cell responses deteriorated significantly in immunocompromised groups 6 months post mRNA vaccination. Of note, SARS-CoV-2 T cells had become undetectable in a significant proportion of dialysis patients and the majority of kidney transplant recipients 6 months post vaccination, (188).

3.4.2.2 Elderly groups

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 (194). 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 (194). Conversely, Renia et al. (198) found that while baseline CD4 Th1 was substantially lower in the elderly group pre-vaccination, Th1 response was similar to younger groups post vaccination. Additionally, this study found that older adults produced more IFN-γ than younger groups post vaccination (198).

3.4.3 Vaccine Effectiveness

3.4.3.1 Immunocompromised groups

The absence of studies on the risk group population of immunocompromised individuals have been highlighted as a gap in the literature in the mid-term report (June 2022). From this new updated research, the team identified three main studies on the following population groups. Adams et al. found that two doses of vaccination elicited protection from hospitalization in immunocompromised groups with a vaccine effectiveness of 60% against hospitalization (204). Furthermore, Kawano et al. investigated incidence and severity of COVID-19 in systemic autoimmune rheumatic disease patients from the first wave through the initial Omicron wave (205). The results showed a reduction in the risk of hospitalization of 71% in the initial Omicron wave compared to the beginning of the outbreak (205). Despite a reduction in severe outcomes, the absolute number of cases in the initial Omicron phase was similar to those observed previously, suggesting a substantial impact on patients with SARDs and the healthcare systems caring for them. This trend analysis was conducted on a sample where more than half of the participants are pre-vaccinated/ unvaccinated (64.7%), 3.5% partially vaccinated, 15.7% two-dose mRNA or one-dose J&J and 16.1% additional doses. Montez-Rath demonstrated that the risk for infection in dialysis patients does not vary along with the number of doses (one or two) (186). As mentioned in the previous section, the risk for

infection was higher among patients with circulating RBD IgG <23 than RBD IgG ≥23, showing that antibody level can address the need and timing for additional vaccine doses.

3.4.3.2 Elderly groups

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

Eleven studies included in this report assessed vaccine effectiveness against Omicron in elderly groups (129, 134, 167-169, 206-210). Overall, the studies found that vaccines provided significant protection against severe COVID-19 illness and hospitalization in elderly groups. Baum et al. found that the effectiveness of the second dose of the Pfizer vaccine against hospitalization was 91% and rose to 95% after the administration of the third dose (206). Furthermore, Grewal at el. found that each dose of an mRNA vaccine increased vaccine effectiveness with maximum effectiveness observed in the fourth dose recipients (167). 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 (129).

The fourth dose enhances protection against severe outcomes, but not against infection

The findings showed that a fourth dose enhanced protection from asymptomatic and symptomatic infections as well as severe clinical outcomes (129, 134, 167-169, 206-210). Brosh-Nissimov et al. in the multicenter cohort study of 1049 patients in Israel, found that a recent fourth dose among older hospitalized patients was associated with significant protection against mechanical ventilation or death (OR, 0.51; 95% CI, .3–.87) compared with 3 doses (210). The fourth dose group showed better outcomes than unvaccinated patients (34% vs 51%) that were younger and mostly not immunocompromised. Muhsen et al. confirmed the high protection of the fourth BNT162b2 dose against hospitalization and deaths, but found a moderate protection against infection (169).

The vaccine effectiveness of fourth doses against Omicron infection ranged from 25.8% to 49% while VE against severe deaths varied from 72% to 89.6% in elderly.

In a sample of 43 775 subjects, of whom 24 088 (55.0%) and 19 687 (45.0%) received the fourth and third dose (4 months earlier), respectively, the vaccine protection was 34% against infection, 64% to 67% against hospitalizations for mild-to-moderate and severe illness, and 72% against deaths (169). Similarly, McConeghy et al. found a vaccine effectiveness of 25.8% against SARS-CoV-2 infection, 73.9% against severe COVID-19 outcomes, and 89.6% against COVID-19–associated deaths alone (168). Grewal at al. corroborated these findings as their test-negative case-control study conducted in Canada with a total sample size of 61344 subjects, reported the following results: the VE of a fourth dose was 49% (95% CI 43% to 54%) against infection, 69% (61% to 76%) against symptomatic infection, and 86% (81% to 90%) against severe outcomes (167). Therefore, the vaccine effectiveness against severe outcomes is enhanced with the fourth dose. Beznik et al. emphasized the importance of the type of vaccine and recent covid infection (209). Infection risk decreased 47% with three vaccine doses of mRNA-1273 compared to BNT162b2 [0.53 (0.31-0.90)], 81% with any fourth mRNA vaccine dose [0.19 (0.12-0.30)], and 48% with infection in the 3 months prior to beginning of the Omicron wave [0.52, (0.27-0.99)] (209).

Vaccine effectiveness wanes over time in elderly groups.

However, studies demonstrated that vaccine effectiveness waned over time (129). 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 (129, 134). Baum et al. found that 91–180 days post second dose vaccination, vaccine effectiveness against hospitalization had decreased from 91% to 76% (206). Similar results were observed by Gazit et al., after a fourth dose of mRNA vaccination (207). Relative effectiveness of the fourth dose of Pfizer waned significantly by the 10th week, 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 (207). This is consistent with what was also found by Bar-On, 2022, et al. (129).

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 (208). 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 (208). 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 September 30th, 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 (B.1.1.529) and its subvariants (BA.2, BA.3, BA.4/BA.5) was observed in all types of conferred immunities (natural, vaccine-acquired, and hybrid immunity). Recently, one of the highest immune response evasions was observed to Omicron BA.5, where neutralization was the least susceptible (15, 37) and vaccines effectiveness was the weakest (18, 153) to Omicron BA.4, and BA.5 subvariants. 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 elicit a diverse memory B cell repertoire against Omicron. While 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 Omicron variant breakthrough infections (110, 111, 211).

Elucidating a correlate of protection for SARS-CoV-2 is crucial to understand the extent and duration of protection of the diverse adaptive immunities against infection for individuals and populations of interest. Although establishing a specific threshold can become quite tricky as various endpoints (e.g. symptomatic infection or severe disease), populations (e.g. immunocompromised and elderly), and emerging variants of concern can lead to variation in correlates of protection, a few studies have drawn direct associations between certain biomarker levels and protection against SARS-CoV-2 (34, 36, 46, 47). Based on the found literature, the most easily measurable biomarker was humoral where binding and neutralizing antibody levels demonstrated to have significant correlation with protection against infection. Overall, higher levels of binding and neutralizing IgG or IgA antibodies resulted in higher levels of protection, where antibody levels correlated well with neutralization titer against multiple SARS-CoV-2 variants and overall infection protection. Various studies validate these results, where higher antibody levels decrease the risk of infection while not completely eliminating it (19, 212, 213). With the continuous emergence of variants of concern and breakthrough infections still occurring in individuals with significant levels of antibodies, more work is urgently needed in this area.

Our review suggests 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 (214). The same was observed in irritable bowel syndrome patients treated with infliximab, who were unable to mount a robust humoral response (178). Various studies found that elderly groups generated a weaker immune response post vaccination compared to younger groups (25 192, 193). Frasca et al. described defects in B cells as a result of ageing, which have led to reduced antibody response to influenzas vaccinations in elderly groups (215). These observed defects could be the reason behind lower antibody responses in elderly groups to COVID-19 vaccines (215). However studies assessing vaccine effectiveness have demonstrated that mRNA vaccines have still provided elderly groups with protection from severe COVID-19 illness and hospitalization (167, 206-208). Ultimately, our findings suggest that despite a weaker humoral response, elderly groups can mount sufficient levels of an immune response post mRNA vaccination in order to have protection from severe COVID-19 infection. Additionally, humoral response and protection was enhanced with additional doses of the mRNA vaccine (25, 28, 162, 192, 193).

With the increasing vulnerability and susceptibility of individuals to get infected with the predominant subvariant BA.4 and BA.5 and with the ongoing and possible emergence of more virulent and infectious variants such as BQ.1.1, a second booster dose has been greatly looked forward and encouraged in vulnerable populations and even younger and healthier ones. According to the found literature, a fourth dose boosted the humoral response in its recipients, especially in vulnerable populations. In low-baseline

responders and individuals who failed to develop detectable neutralizing antibodies prior to the second booster, including elderly and immunocompromised patients, a fourth dose of the mRNA COVID-19 vaccine demonstrated an ability to mount an adequate immune response (36, 190, 191). Nonetheless, in young and healthy individuals, a fourth dose demonstrated to elicit a smaller increase in humoral response against Omicron and its subvariants, especially against the currently predominant subvariants BA.4/BA.5. These results indicate that the first generation COVID-19 vaccines might have reached their limit of protective outcomes in these populations. In fact, the highest humoral response increase against the newly emerged subvariants was found in individuals that experienced BA.1 breakthrough infections (71, 97). Similar results were also obtained in immunocompromised groups where infection with BA.4/BA.5 generated much stronger cross-reactive neutralization compared to infection with the BA.1 subvariant, in immunocompromised groups (85). Overall, these results highlight the advantages of the exposure to the current and newly emerging subvariants and suggest that bivalent Omicron BA.1 or even BA.5 vaccines could lead to higher Omicron BA.1, and BA.4 and BA.5 neutralization than with the previous original strain vaccines. Indeed, preliminary results from phase 2-3 clinical trials on Moderna's and Pfizer and BioNTech bivalent BA.1 booster dose have elicited neutralizing antibody responses against omicron that were superior to those with first-generation vaccines, without evident safety concerns (216-218). Based on the promising results of a BA.1 bivalent vaccines, the EMA and FDA have even approved the administration of a BA.4/BA.5 bivalent COVID-19 vaccines as a booster (219, 220). This approval took place before results on the BA.5 bivalent vaccine were shared publicly – a decision they made prior to human results due to the similar composition of the successful Comirnaty Omicron/Omicron BA.1 vaccine, quality, and manufacturing process confirmed to meet EU standards for quality (219). In fact, to stay up to date with vaccines and therefore protected against current threats, the Center for Disease Control and Prevention from the United States (CDC), continues to provide updated information on COVID-19 vaccination (221). Currently, the CDC recommends everyone to stay up to date with COVID-19 vaccines by recommending the administration of an updated (bivalent) booster dose in all age groups as soon as 2 months after the second primary series or latest booster. This recommendation varies if individuals have recently been infected with COVID-19, where a booster dose is recommended up to 3 months after infection (221).

On 24 October, the first human results on the bivalent booster vaccine against BA.5 became available to the public (222). This initial data found that 3-5 weeks post booster shot, individuals who received a fourth vaccine dose with bivalent BA.4/BA.5 had similar neutralizing antibody titers as those receiving a fourth monovalent mRNA vaccine against all SARS-CoV-2 variants, including BA.4/BA.5 (222). In addition, geometric mean titers (ID50) against SARS-CoV-2 variants were lowest for boosted sera and highest for BA.4/BA.5 breakthrough sera (222). The study argues that these initial results might be indicative of immunological imprinting – a phenomenon reported in influenza vaccination in some SARS-CoV-2 antibodies (223-225). Overall, further research in next-generation vaccines should be prioritize to provide broader protection against the predominant subvariants and any future emerging variants such as BQ.1, BQ.1.1, BJ.1, XBB.

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, first, and second booster vaccination, especially against the Omicron variant (B.1.1.529) and its subvariants. A list of all the included studies discussing duration of protection can be found in Supplementary Material 2 (Data Protection Sheet). In a systematic review and meta-regression study on the duration of effectiveness of vaccination against COVID-19 caused by the Omicron variant, similar results were emphasized (226). Overall, 6 months after, the primary vaccine series led to little protection against symptomatic infections and to a more rapid decrease in vaccine effectiveness during the Omicron period (47.6% decrease [95% CI, 36.6-60.2]) than the pre-Omicron period (24.9% decrease [95% CI, 13.4-41.6]), where decreases in VE for severe diseases remained relatively the same (226). As for a first booster vaccination, the waning of protection against Omicron were generally higher than after the primary vaccine series for all outcomes where the mean decrease in vaccine effectiveness against symptomatic disease from one to four months was 24.3% (95% CI, 19.9-29.1), and 28.5% (95 CI, 18.3-40.5) projected out to 6 months (226). Regarding second booster doses (fourth dose), the durability of protection against Omicron infections remains relatively uncertain although a study analyzing the protection of a fourth dose over time demonstrated that for confirmed infections, a fourth dose appeared to provide only short-term protection and a modest absolute benefit (129).

When estimating the half-lives and decay rates of humoral responses, neutralizing antibodies were found to wane at higher levels than binding antibodies in vaccinated individuals (46), while in convalescent ones, total neutralizing antibodies demonstrated longer duration (26). A direct correlation between the humoral and cellular immunity and its longevity have also been found – a crucial measurement in maintaining long-term protective immunity. In the study of Wang et al., high levels of virus-specific CD4+ T cells at baseline were shown to correlate with long-term neutralizing levels indicating the possible role CD4+ T cells have in regulating the long-term humoral immunity in patients with previous COVID-19 (26). Additional differences in the duration and waning of humoral immunity were also noted between the different types of antibodies. For instance, the decay of IgG binding antibodies to variants, at 30 days after third or fourth vaccination, was more pronounced than the decay of the IgA response, hinting to the possible long-term advantages of IgA antibodies (36). These results can provide supporting evidence that next-generation vaccines targeting the mucosal immunity driven by IgA antibodies could provide a possible solution to the continuous waning of immunity against the newly emerged variants. As a matter of fact, the highest humoral and even cellular immunity was observed in hybrid immunity where infections triggered a strong IgA response and detectable Omicron-neutralizing activity (81). While the current COVID-19 vaccines currently continue to demonstrate a durable protection against severe outcomes and hospitalizations, their performance at reducing mild illnesses or transmission leave for much to be desired, especially against Omicron variants. By the possible use of nasal vaccines, the thin mucous membrane that line the nose, mouth, and lungs could, in theory, prevent even mild cases of illness and block transmission to other people – something the first-generation COVID-19 vaccines have been unable to achieve – while triggering a strong and durable IgA response. As of October 2022, two nasal COVID-19 vaccines, approved in India and China have been approved for use as a booster dose (227, 228). Although more evidence on the effectiveness and duration of protection of

such vaccines is scarce, data from phase II trial of CanoSino's inhaled vaccines found that the vaccine raised blood-serum antibody levels significantly more than a intramuscular booster dose (228).

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. This is particularly apparent concerning high risk groups where this report was only able to identify two relevant studies assessing cellular immunity in older populations. The results from this report do not apply to other important populations such as underage individuals (infants, children, and adolescents) and pregnant women, since those populations were excluded from our search strategy due to the already overwhelming literature regarding the general population and risk groups. Subsequently, due to our inclusion and exclusion criteria, studies on new and second-generation vaccines and other vaccine-platforms not approved in Switzerland were not included in the report. In addition to the identified gaps in literature, our report did not assess the risk of bias or quality of the studies included. Although we tried to be as exhaustive as possible, the current report gives a narrative summary of the current data in the literature that were limited by our eligibility criteria and that any specific research questions may require further analyses of data.

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