Evidence Brief on Protective Immunity Post Infection with Omicron

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Données probantes sur l'immunité protectrice après une infection par Omicron

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Table of Contents

Introduction

What do we know about protective immunity post Omicron infection (against Omicron/other variants of concern?)

The SARS-CoV-2 variant of concern (VOC) Omicron (B.1.1.529) emerged in late 2021 and quickly displaced the Delta variant. Omicron has evolved into multiple sublineages such as BA.1, BA.2, BA.3, BA.4, and BA.5, each with additional mutations. Compared to previous variants, Omicron has a large number of mutations (>30 mutations in the spike (S) protein) - and thus, has been good at evading established immunity from prior infection or vaccination [1]. Omicron's ability to escape neutralizing antibodies that would stop the virus from entering and replicating in cells is due to the many mutations on the S-protein, particularly in key spots on the receptor binding domain (RBD) [1].

Although the literature on vaccine efficacy, role of waning immunity post vaccination, and/or previous infection with earlier variants is well established, little is known about immunity post Omicron infection. In this rapid review, real world data on reinfections post Omicron infection and post-Omicron immunogenicity studies (e.g., neutralizing/binding antibodies and memory immune markers such as T-cells and B-cells) are summarized across the different profiles of pre-Omicron immunity (vaccination and/or infection) studied. The different immune profiles as defined by the World Health Organization (WHO), include infection-induced immunity, vaccine-induced immunity and hybrid immunity. Hybrid immunity refers to immunity that comes from both vaccination with one or more doses of a COVID-19 vaccine and immunity via infection with SARS-CoV-2 before or after vaccination [2]. Reinfection is defined as a previous confirmed and resolved SARS-CoV-2 case that has a subsequent infection of SARS-CoV-2 and it is confirmed as two different infections by laboratory evidence [3]. The risk of reinfection and level of immune markers measured as neutralizing antibodies and cellular immunity activity against a pathogen can be indicative of protective immunity. However, it is important to note that markers of protective immunity do not necessarily or directly equate to protection. Instead, immune markers indicate that the immune system is primed to respond to a pathogen, which may result in prevention of infection or reduced morbidity.

Studies on animal models of immunity post Omicron were excluded. Studies published before July 26, 2022 were included.

Key points

Twenty-three studies were identified, including six observational studies on the risk of reinfection and 17 *in vitro* studies on the kinetics and durability of neutralizing antibodies and memory immune response markers (B-cell and T-cell) post infection with any of the

Omicron sublineages. For the neutralization studies, results were divided into two sections: an analysis of differences in the levels of immune response markers post Omicron by individual vaccination and/or prior infection status and a comparison of the differences in level of neutralization of the different Omicron sublineages and other VOCs post Omicron infection. Out of the six observational studies on the risk of reinfection, five were pre-print articles, not yet published in full and one was a Letter to the Editor (LTE). Of the 17 *in vitro* studies, six were pre-print articles and three were Letters to the Editor.

Overall, the studies indicate that the risk of reinfection is lower and correlates of immunity are higher (stronger response) for:

- People with 2 or more doses of COVID-19 vaccination. There may be an additional benefit to having had the third dose, but more studies are required.
- Protection against the Omicron variant that caused the first Omicron infection is the highest. Protection against other Omicron variants was lower, but still significantly higher than compared to people who did not have an Omicron infection when matched by immunity (vaccination and infection) prior to getting Omicron.
- Omicron infection boosted correlates of immunity (neutralizing antibodies and cellular immune response – T-cell/B-cell activity) against all previous variants for those that had prior immunity (vaccination and/or infection), whereas those with no immunity prior to Omicron infection had limited cross protection against other variants.

Risk of reinfection post Omicron infection (six studies):

- Short-term reinfections (20-60 days after initial Omicron infection) post Omicron infection can occur, however, the risk is low as infection with one Omicron strain offers significant protection against reinfection with the homologous strain (i.e., BA.1 to BA.1 reinfection, >95%) and a slightly less robust protection for a heterologous Omicron strain (i.e., BA.1 to BA.2 reinfection >85%), but still higher compared to people not infected with Omicron [4, 5, 6, 7, 8, 9].
- Protective immunity of a prior Omicron infection (BA.1 or BA.2) against BA.4/BA.5 reinfection is robust but slightly lower (76%) than for BA.1/BA.2 reinfections (>86%) for those with two doses [4, 8] and three doses (94% vs. 96%) [9].
- In three studies, prior immunity from vaccination or infection before the first Omicron infection offered higher protection against reinfections (e.g., 96% vs. 72% [7]) compared to those without prior immunity [5, 6, 7]. There were a disproportionate number of reinfections among individuals who were unvaccinated [6, 7] many of which were of a young age (<20 years old) [5].

- In a Canadian study, the risk of reinfection with Omicron BA.2 after a BA.1 infection was lowest and the same for those who had two or three COVID-19 mRNA vaccinations (Comirnaty and/or SpikeVax) [7].

Neutralizing antibody responses post Omicron infection (17 studies):

- Post infection with Omicron, levels of neutralizing antibodies were higher against the homologous strain (i.e., BA.1 to BA.1) compared to that against a heterologous strain of Omicron (i.e., BA.1 to BA.2) [1, 10, 11, 12, 13, 14, 15].
- Infection with Omicron BA.1 neutralizes BA.1 most efficiently followed by BA.2, BA.2 sublineages BA.2.13 and BA.2.12.1 and then BA.4/BA.5, which were most resistant to neutralization for both BA.1 and BA.2 convalescent sera (i.e., samples from people that have recovered from COVID-19) [1, 10, 11, 12, 13, 14, 15].
- Sera from vaccinated Omicron convalescents had higher and broader neutralizing antibody responses against Omicron sublineages and previous VOCs compared to unvaccinated Omicron convalescent sera [14, 15, 16, 17, 18].
- BA.1 or BA.2 convalescents with no prior immunity from vaccination and/or infection neutralized BA.4/BA.5 poorly [16, 18].

Memory B-cell and T-cell responses post Omicron infection (three studies):

- Post Omicron breakthrough (2 or 3 dose vaccinated) infection, the level of B-cell responses significantly increased and was broader compared to uninfected, 2 or 3 dose vaccinated individuals [10, 19].
- Omicron breakthrough infection does not elicit Omicron specific S-protein memory B-cell responses. Responses remain broad against conserved epitopes that are in common between the S-proteins of Omicron, the original variant and previous VOCs [10, 19].
- BA.1 breakthrough infection elicits B-cells that are most reactive against BA.1 RBD and are most cross-reactive against the RBD of Beta, followed by BA.2 and Delta [19].
- Infection with Omicron did not elicit significant changes in spike-specific T-cell responses in individuals regardless of prior immunity [20].

Overview of the evidence

This review contains evidence from six observational studies of reinfection and 17 *in vitro* neutralization/immunogenicity studies. The lab-based *in vitro* studies had to include samples from individuals post infection with Omicron. Sub-groups of results by prior immunity (infection and/or vaccine) were compared with samples from individuals who were not infected with Omicron. Neutralization was generally tested against a panel of live

or pseudo-viruses containing SARS-CoV-2 original variant and VOCs. Although several trends in immune response post Omicron infection were seen across the studies, detailed below, there was heterogeneity observed in the outcomes which can be due to differences in study participants, sample collection times post infection, clinical severity of infection, the study design and measurement methods. The results of *in vitro* studies provide limited indirect evidence about the potential risk of reinfection with Omicron or other variants and thus, we have low certainty in these results.

The reinfection studies included three case-control studies and three retrospective cohorts of cases infected with Omicron once or multiple times during the study. From these data, the risk of reinfection across groups with different prior immunity was examined. The retrospective cohort studies are of moderate to high risk of bias due to their retrospective designs. Confounding was not controlled for in these studies as they did not include multivariable analyses. Compared to prospective cohort studies, these studies have a greater potential for confounding and missing data as the results are limited to what has been collected in the past and the quality of these data. All three studies are large and the findings are directly answering the question about risk of reinfection, so our confidence in this outcome is low to moderate. The three test negative case-control studies assess the odds of a prior Omicron infection in cases with an Omicron BA.2 or BA.4/BA.5 reinfection and compared it to the odds in test negative controls. In this way, the findings directly answer the question about the effectiveness of a previous Omicron infection against reinfection with a different strain. These studies are at moderate to high risk of bias due to their retrospective designs, thus we have low confidence in these findings.

The following knowledge gaps exist in the current literature on immunity post Omicron infection:

- The correlation between markers of immune response post Omicron infection such as neutralizing antibodies and individual risk of reinfection or level of protection from different titers were not available.
- There is a lack of understanding on the correlation of memory immunity via B-cells and T-cells and the level of protection they offer against reinfection post infection with Omicron.

Data on the long-term immune response after an Omicron infection are still limited to short timeframes. Studies included in this review examined immune responses 0.5-3 months after an Omicron infection which corresponds to peak immune response. Data on long-term waning immunity (i.e., >3 months) post Omicron infection have not been published.

Risk of reinfection post Omicron infection

Three large retrospective cohort studies and three test negative case-control studies report on risk of reinfection post infection with Omicron (Table 1). The three retrospective cohort studies are based on cohorts established from Qatar's national database [4], a Danish COVID-19 surveillance system [5], and an Austrian COVID-19 variant surveillance program [6]. All three studies used different definitions of reinfection: a documented infection >35 days after initial infection when Omicron was predominant (Qatar study) [4], an infection that occurred within 20-60 days following initial infection with Omicron (Danish study) [5] and a reinfection that occurred >30 and <60 days after a primary PCR-confirmed Omicron infection (Austrian study) [6]. Prior to Omicron, reinfection was defined as either laboratory evidence of two different infections or a documented infection >90 days after initial SARS-CoV-2 infection [3]. The three case-control studies analyzed the odds of a prior primary Omicron infection in cases with a BA.2 reinfection [7], a BA.4/BA.5 reinfection [8] or a BA.5 and BA.2 reinfection [9] compared to test negative controls. The studies identified cases and controls from the Quebec, Canada provincial laboratory database [7], from Qatar's national COVID-19 database [8] and from the Danish COVID-19 surveillance system [9]. All three studies used different definitions of a previous Omicron infection: a nucleic acid amplification testing (NAAT) positive test ≥30 days before a positive test during the study period (Canadian study) 7, a SARS-CoV-2-positive test ≥90 days before another positive test during the study period (Qatar study) [8], and a positive SARS-CoV-2 PCR test ≥60 days before a new infection during the study period (Danish study) [9].

Results from reinfection studies (n=6):

- Across all studies, findings showed that reinfections were occurring, but at a significantly lower rate than first Omicron infections.
    - The retrospective cohort from Qatar reported 0.9% (1062 cases) reinfections in February 2022, which equated to 95% protection post BA.1 and 86% post BA.2 [4].
    - Similarly in Quebec, prior Omicron BA.1 infection among those with 2 doses of COVID-19 vaccination had reduced the risk of any BA.2 reinfection by 96% and of a symptomatic BA.2 reinfection by 98% [7].
- Reinfection with a heterologous Omicron strain (i.e., BA.1 to BA.2 reinfection) was more common than reinfection with a homologous strain of Omicron (i.e., BA.1 to BA.1 reinfection) [5, 6].
- Previous infection with BA.1 or BA.2 provided significant protection against reinfection with BA.4 or BA.5 [8, 9]. Reinfections with BA.4/BA.5 were more likely than BA.1/BA.2 reinfections (2 doses 76% [8] vs. >86% [4], and less difference among

those with 3 doses 94% vs. 96% [9]) as BA.4/BA.5 showed greater capacity for immune evasion [8, 9].
    - A case control study from Qatar found that effectiveness of a previous Omicron infection (likely BA.1 or BA.2) against symptomatic BA.4/BA.5 reinfection was 76.1% and against any BA.4/BA.5 reinfection was 79.7% which was lower than the protection conferred against BA.1/BA.2 among those with 2 doses vaccination [8].
    - A case control study from Denmark found that among triple-vaccinated individuals, the estimated protection of a previous BA.1 or BA.2 infection against reinfection with BA.5 was 93.6%, which was slightly lower than the estimated protection against a BA.2 reinfection of 96.3% [9].
- Three studies [5, 6, 7] found that reinfections were more likely among unvaccinated individuals compared to those that received at least one dose of vaccination.
    - The Danish retrospective cohort of 263 individuals with two positive tests within the study period showed that there were some reinfections with BA.2 following a BA.1 infection. Most individuals that experienced reinfection were unvaccinated and of young age (<20 years old) [5].
    - Similarly, the Austrian cohort of 242 individuals with rapid reinfections of <60 days with different or the same Omicron strains had a disproportionate proportion (75%) of unvaccinated individuals and 24% were in vaccinated individuals [6].
    - The Canadian case-control study found that a prior Omicron BA.1 infection without vaccination reduced the risk of BA.2 reinfection by 72% while a prior Omicron BA.1 infection in those that had 2 doses of COVID-19 vaccination had a reduced risk of BA.2 reinfection by 96% [7]. However, there was no difference in risk of reinfection among those with 2 vs. 3 doses of COVID-19 vaccination [7].

Immune response markers post infection with Omicron

This section summarizes 17 studies that report on post Omicron immune responses measured ≥14 days post Omicron infection for individuals with prior vaccination and/or infection immunity and ≥30 days for individuals without prior immunity (Table 2). These sample collection thresholds were selected to isolate outcomes that correlate to maximal immune response post infection as samples collected during the acute infection phase can confound the results. The sample collection window post infection ranged from 14-74 days across studies for individuals with prior immunity with most studies sampling around ~14 days post infection. For individuals without prior immunity, the sample collection window post infection was around the ~30 days mark across all the studies. The included

studies were also limited to studies that reported >five participants to have an adequate sample size for the results to be relevant. Partial results were extracted from eight studies where some results did not meet the inclusion criteria/threshold for appropriate sample collection time post infection with Omicron [14, 15, 16, 17, 18, 20, 21, 22]. All 17 studies reported on circulating serum neutralizing antibody levels after infection, while four studies also reported on IgG and/or IgA antibody levels post Omicron infection [19, 20, 23, 24]. Three studies reported on memory immune markers such as B-cell and T-cell activity in addition to neutralizing antibodies in the same sample (Table 3) [10, 19, 20].

Neutralizing antibody responses post Omicron infection (n=17)

Seventeen studies analyzed serum from people post Omicron infection for neutralizing antibody (nAb) responses to Omicron sublineages BA.1, BA.2, BA.3 and BA.4/BA.5 as well as previous variants such as the original variant (Wuhan-1, D614G), Alpha, Beta, Gamma and Delta (Table 2). The nAb titers and comparisons of serum neutralization responses against a panel of pseudovirus and/or live viruses were examined using a variety of neutralization assays such as, pseudovirus neutralization assay, live virus neutralization assay, focus reduction neutralization test (FRNT), fluorescent focus-reduction neutralization test (FFRNT), S-Fuse neutralization assay and plaque reduction neutralization test. The variability in methods across studies limit the comparability of study results.

Differential neutralization of Omicron sublineages BA.1, BA.2, BA.4/BA.5 after BA.1 or BA.2 infection

- Seven studies found that neutralizing responses against the infecting Omicron strain (homologous) is higher than neutralizing responses against other Omicron sublineages (heterologous) regardless of prior immunity (vaccination and/or infection) [1, 10, 11, 12, 13, 14, 15].
    - The highest neutralization was seen with the homologous Omicron strain. For instance, convalescent BA.1 sera had the highest neutralization of BA.1 and reduced neutralization of all other sublineages [10, 11].
    - Although some Omicron sublineages had greatly reduced neutralization activity,(e.g., BA.4 /BA.5) there was still some neutralization of all sublineages following BA.1 and BA.2 infection [1, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 21, 24].
- Convalescent BA.1 serum (i.e., sera from people that recovered from BA.1 infection) neutralized BA.1 most efficiently followed by BA.2 and then BA.4/BA.5 [1, 10, 11, 12, 13, 14, 15].
    - BA.2 sublineages BA.2.13 and BA.2.12.1 showed lower neutralization than BA.2 in both BA.1 and BA.2 convalescent sera with BA.2.12.1 more resistant to neutralization than BA.2.13 [11, 13].

- Seven studies reported BA.4/BA.5 had the lowest neutralization titres of all the Omicron sublineages for both BA.1 or BA.2 convalescent sera [1, 10, 11, 13, 16, 18, 24].

Differences in neutralizing antibody responses post BA.1 or BA.2 infection by prior vaccination/infection status

- Double or triple vaccinated individuals who had an Omicron breakthrough infection elicited greater neutralizing antibody responses, as well as IgG and IgA antibody titers against Omicron sublineages and previous VOCs compared to vaccinated individuals who did not have an Omicron infection [10, 11, 19, 21, 22, 23, 24, 25] and unvaccinated individuals who had an Omicron infection [14, 15, 16, 17, 18].
    - Convalescent BA.1 sera had the highest neutralization of BA.1, followed by BA.2 and BA.4/BA.5 with 100-fold, 35-fold and 15-fold higher responses respectively, in those vaccinated (2 or 3 doses) who had BA.1 infection compared to those vaccinated and uninfected [10].
    - Among BA.1 convalescent sera with 2 doses of vaccine, neutralizing antibody titers were 2.2, 4.8, 9.6, 12.0, and 17.9-fold higher against BA.1, BA.2, Beta, Delta and the original variant, respectively, compared to unvaccinated BA.1 convalescent sera [17]. A similar pattern of higher neutralization was seen in another study of BA.1 convalescent sera with 2 or 3 doses of vaccine where titers were 38-fold, 31-fold, 33-fold, 25-fold higher against BA.2, BA.1, the original variant and Delta, respectively, compared to unvaccinated BA.1 convalescent sera [14].
    - BA.4/BA.5 were poorly neutralized by BA.1 or BA.2 convalescent sera from individuals with no prior immunity (vaccination or infection) [16, 18].
    - One experiment showed that neutralizing responses against the homologous Omicron strain compared to other Omicron sublineages differed depending on prior vaccination status [17]. Unvaccinated BA.1 convalescent sera had high neutralization of BA.1, but not other variants, whereas vaccinated BA.1 convalescent sera neutralized the original variant, Delta, Beta, and BA.2 more efficiently than BA.1 [17].
    - Another study reported BA.1 breakthrough cases with 2 or 3 doses of vaccine efficiently neutralized Delta, the original variant, BA.1 and BA.2 , whereas Delta was not neutralized well in unvaccinated BA.1 convalescent sera [15].
- There was no significant difference in neutralizing antibody titers after an Omicron infection among those with one, two or three doses of vaccine.
    - Only one study looked at neutralizing antibody responses in BA.1 convalescent sera by the number of vaccine doses (1, 2 or 3) received prior to infection and reported no difference in neutralization [25].

    - One study found that there was no significant difference in neutralizing antibody activity against BA.1, BA.2, BA.2.12.1, BA.4/BA.5 between sera from those with 3 dose vaccination and those with 2 dose vaccination plus Omicron BA.1 or BA.2 infection [13].
- One study reported higher IgG titers in Omicron BA.1 or BA.2 breakthrough infections (3 dose vaccination) with no history of SARS-CoV-2 infection compared to Omicron breakthrough cases with a history of prior infection by the original variant [20].

Memory B-cell and T-cell responses post Omicron infection (n=3)

Memory B-cells and T-cells are important immune correlates of protection against reinfection in the long-term as these markers persist despite a decline in circulating antibodies. There are two studies [10, 19] which analyzed memory B-cell responses and one study [20] that examined T-cell activity 2-7 weeks post Omicron infection (Table 3). Various flow cytometry-based phenotyping assays were used to measure memory B-cell and T-cell levels, viral antigen targets and activity. The types of memory B-cells and T-cells analyzed included Omicron BA.1 spike-protein specific B-cells, RBD specific B-cells, RBD-reactive IgG+ B-cells, RBD-reactive IgA+ B-cells, spike-specific T-cell, nucleocapsid- and membrane-specific T-cells. Since there is variability across the studies in terms of viral antigen targets and the types of molecular biology techniques used to measure responses, comparability of results across studies are limited.

- B-cell responses found significantly increased levels of B-cells post Omicron infection [10, 19].
    - In convalescent BA.1 individuals who had 2 or 3 doses of vaccination, the frequency of BA.1 S-protein specific memory B-cells was significantly higher compared to those with 3 doses of vaccination and no history of infection [10].
    - A similar trend was observed in another study which reported that BA.1 breakthrough (2 or 3 doses vaccination) infection elicited higher IgA+ B-cell responses to the RBD of the original variant and BA.1 compared to those with 2 or 3 doses of vaccination and no history of infection [19]. However, this was not true for the original variant- and BA.1-RBD-reactive IgG+ B-cells, as the frequency of IgG+ B-cells were similar for both the BA.1 breakthrough and fully vaccinated with not history of infection cohorts [19].
- The ratio of B-cells post Omicron breakthrough (2 or 3 doses vaccination) infection that were targeting the RBD of BA.1 versus the S-protein showed Omicron breakthrough infection elicited a higher ratio of RBD-specific memory B-cells over S-protein specific B-cells [10].

- Both studies [10, 19] found that the memory B-cell responses from BA.1 breakthrough (2 or 3 doses) infection do not seem to be Omicron specific, rather are broadly against conserved epitopes that are in common between the S-proteins of Omicron, the original variant and previous VOCs.
- Cross-reactivity of the B-cells elicited by BA.1 breakthrough infection was highest for BA.1 RBD, followed by Beta, BA.2 and Delta [19].
- T-cell responses post Omicron infection found that T-cell responses did not differ by Omicron BA.1 versus BA.2 infection [20]. Moreover, spike-specific T-cell responses were similar for individuals with and without Omicron infection, regardless of the type of prior immunity (e.g., 3 doses vaccination vs. 2 doses vaccination and prior infection) [20].
    - Omicron breakthrough infection contributed to nucleocapsid- and membrane-specific T-cell priming as these specific T-cell responses were significantly higher for Omicron breakthrough cases than among vaccinated individuals with no history of Omicron infection.

Methods

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a refworks database and an excel list that can be searched. Targeted keyword searching was conducted within these databases to identify all relevant citations on post Omicron immunity. The database was filtered for “Omicron” articles and then the following immune search terms were used to isolate potentially relevant articles on post Omicron immunity: reinfect*, re-infect*, recurrent, re-positive, longitudinal, immun*, neutraliz* and neutralis*. The search netted 1721 citations up to July 26, 2022, which were screened based on title and abstract for relevance to the review. Each potentially relevant reference was examined to confirm it had relevant data and relevant data was extracted into the review. This review contains research published up to July 26, 2022.

Inclusion criteria: studies had to assess immune response and/or risk of reinfection post infection with Omicron in at least a subset of the results, otherwise they were excluded. Exclusion criteria: case reports, case series and studies with a small sample size (n<5) were excluded from this review. Animal models of post Omicron immunity were excluded. In order to assess immune response elicited by Omicron infection, studies with sample collection time <14 days post infection for individuals with prior immunity via vaccination

and/or infection with an earlier variant and <30 days for individuals without prior immunity were excluded. Four studies did not report on sample collection times post infection and were also excluded.

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Evidence tables

Table 1: Observational studies on the risk of reinfection post infection with Omicron (n=6)

Study	Method	Key outcomes
Chemaitelly (2022) [4] *Preprint* Retro-spective cohort Qatar Dec 2021-Feb 2022	This study aimed to assess effectiveness of BA.1 infection against reinfection with BA.2 and effectiveness of BA.2 infection against reinfection with BA.1. In Qatar Delta variant was not detected after Jan 8, 2022. To distinguish between BA.1 and BA.2, s-gene target failure (BA.1) on RT-PCR was used as a proxy. Two retrospective matched cohorts were constructed from the national database of data Jan – Feb 21, 2022. Control cohorts were comprised of matched test-negative control (Nov – Dec 2021). Reinfection was defined as a documented infection >35 days after initial infection. Thus, the start of follow-up was 35 days post testing positive (or negative). Median follow-up was 12-14 days in both cohorts. The BA.1-against-BA.2 study (n=20k) followed a cohort of BA.1 infections and compared incidence of BA.2 with the control cohort. The BA.2-against-BA.1 study (n=101k) followed a cohort of BA.2 infections and compared incidence of BA.1 with the control cohort. Regression analysis adjusted for vaccination status (unvaccinated 1, 2, 3 doses), age, sex, nationality.	BA.1-against-BA.2 study • Cumulative incidence of infection was 0.03% (95%CI 0.01-0.07%) for the BA.1-infected cohort and 0.62% (95%CI 0.51-0.75%) for the control cohort, 15 days after the start of follow-up. • The hazard ratio for infection was 0.05 (95%CI 0.02-0.12). The effectiveness of BA.1 infection against reinfection with BA.2 was 94.9% (95%CI 88.4-97.8%) after 15 days of follow-up. BA.2-against-BA.1 study • Cumulative incidence of infection was 0.03% (95%CI 0.02-0.04%) for the BA.2-infected cohort and 0.17% (95%CI 0.15-0.21%) for the control cohort, 15 days after the start of follow-up. • The adjusted hazard ratio for infection was 0.14 (95%CI 0.09-0.23). The effectiveness of BA.2 infection against reinfection with BA.1 was 85.6% (95%CI 77.4-90.9%) for a 15 day follow-up. Conclusions: 0.9% (1062 cases) had reinfections after an Omicron infection with a different Omicron sublineage. However, there was a large difference between cases and controls, indicating that short-term reinfection (1-2 months post infection) is unlikely.
Stegger (2022) [5] *Preprint*	This study aimed to investigate whether Omicron BA.2 reinfections occurred within 20-60 days following initial infections with BA.1 in the time period when these two variants emerged and became dominant.	• In the randomly selected group of 263 paired samples that were analyzed, the following reinfections were identified: BA.1 -> BA.1 = 17

Retrospective cohort Denmark Nov 2021–Feb 2022	Using data from the Danish COVID-19 surveillance system, a subset of samples of individuals with 2 positive samples more than 20 and less than 60 days apart were selected for analysis (n=263). Omicron lineage was confirmed by whole genome sequencing (WGS) and compared to randomly sampled Danish BA.1 and BA.2 genomes.	BA.1 -> BA.2 = 47 BA.2 -> BA.2 = 3 Delta -> BA.1 = 26 Delta -> BA.2 = 140 Delta -> Delta = 30 • Of the 47 BA.1/BA.2 reinfection cases, 42 (89%) were unvaccinated and the majority were under the age of 20 (70%). None were hospitalized or died during the follow-up period. • Most individuals (29/33; 89%) reported symptoms during the BA.2 reinfection though mainly mild and comparable to their initial BA.1 infection. • The CT values for Omicron BA.2 reinfections were higher, indicating a lower viral concentration compared to the initial BA.1 infections (p=0.006). • There was no sign of clustering among BA.2 or BA.1 variants involved in reinfection compared with the randomly selected BA.1 and BA.2 sequences.
Carazo (2022) [7] *Preprint* Case-control Canada Mar-Jun 2022	This study aimed to estimate protection against Omicron BA.2 reinfection conferred by a pre-Omicron or Omicron BA.1 primary infection, with and without a history of vaccination with Comirnaty Pfizer BNT162b2 or SpikeVax Moderna mRNA-1273, using a test-negative case control design. The study population included all HCWs paid by the Quebec publicly-funded healthcare system and/or registered as members of a health college. Cases with a nucleic acid amplification testing (NAAT) positive result for SARS-CoV-2 and controls were identified using the provincial laboratory database. 37,732 presumptive Omicron BA.2 cases were compared to 73,507 randomly-selected test-negative controls.	Immunity from a prior pre-Omicron infection • Among the 2,521 (6.7%) cases reinfected with BA.2 after a prior pre-Omicron infection, 4.3% were unvaccinated and 32.3% and 40.8% had been vaccinated with two and three doses, respectively. • A prior pre-Omicron infection (without vaccination) reduced the risk of any BA.2 reinfection by 38% (95%CI 19-53) and of symptomatic reinfection by 51% (95%CI 22-69). • A prior pre-Omicron infection with 2-doses of vaccination, reduced the risk of any BA.2 reinfection by 69% (95%CI 64-73) and of symptomatic reinfection by 81% (95%C: 76-85). Similarly, a prior pre-Omicron infection with 3-doses of vaccination, reduced the risk of any BA.2 reinfection by

	The odds of a pre-Omicron or Omicron BA.1 prior primary infection (PI) with/without vaccination or of vaccination alone without a prior primary infection were compared among cases and controls. Prior primary infection was defined as a NAAT positive specimen collected at least 30 days before a specimen collected during the study period. The 30-day interval was chosen to capture all potential BA.2 reinfections following prior BA.1 primary infection.	70% (95%CI 66-74) and of symptomatic reinfection by 83% (95%CI 78-86). Immunity from a prior Omicron BA.1 infection • Among the 659 (1.7%) cases reinfected with BA.2 after a prior Omicron BA.1 infection, 19% were unvaccinated, and 39.8% and 36.9% had been vaccinated with two and three doses, respectively. • A prior Omicron BA.1 infection (without vaccination) reduced the risk of any BA.2 reinfection by 72% (95%CI 65-78) and of symptomatic reinfection by 86% (95%CI 79-91). This protection was similar to that provided by a prior pre-Omicron infection plus two or three vaccine doses and higher than that provided by 3 dose vaccination alone without a prior infection. • A prior Omicron BA.1 infection in those that were double vaccinated, reduced the risk of any BA.2 reinfection by 96% (95%CI 95-96) and of symptomatic reinfection by 98% (95%CI 97-98). Results were similar for 3 doses + BA.1 infection. • Over five months following Omicron BA.1 primary infection, a non-significant decline in protection against BA.2 reinfection was observed among unvaccinated individuals (from 82% at 30-59 days to 70% at 90-160 days). But, protection remained between 96% and 97% for the 30-159 days of follow-up among those vaccinated with two or three doses.
Altarawneh (2022) [8] *Preprint* Case–control	This study aimed to estimate the effectiveness of previous infection in preventing reinfection with BA.4/BA.5 using a test negative case control design. The study population included the resident population of Qatar. Data was collected from the national,	Immunity from a prior pre-Omicron infection • Effectiveness of a previous pre-Omicron infection against symptomatic BA.4/BA.5 reinfection was 15.1% (95%CI -47.1-50.9%), and against any BA.4/BA.5 reinfection irrespective of symptoms was 28.3%

Qatar May-July 2022	federated databases for COVID-19. Cases (SARS-CoV-2-positive tests) and controls (SARS-CoV-2-negative tests) were exact-matched in a one-to-five ratio by sex, 10-year age group, nationality, comorbid condition count, calendar week of testing, method of testing (PCR or RA), and reason for testing. 6500 cases with a BA.4/BA.5 infection were matched to 27 051 controls and 1232 cases with a symptomatic BA.4/BA.5 infection were matched to 4545 controls for the analysis. Previous infection was defined as a SARS-CoV-2-positive test ≥90 days before this study's SARS-CoV-2 test. Previous infections were classified as pre-Omicron versus Omicron based on whether they occurred before or after the Omicron wave that started in Qatar on December 19, 2021.	(95%CI 11.4-41.9%) of the immunity from a prior Omicron infection. • Effectiveness of a previous Omicron infection against symptomatic BA.4/BA.5 reinfection was 76.1% (95%CI 54.9-87.3%), and against any BA.4/BA.5 reinfection was 79.7% (95%CI 74.3-83.9%).
Vera-Lise (2022) [6] *LTE* Retrospective cohort Austria Jan-May 2022	This study aimed to investigate whether rapid Omicron reinfections occurred within 30-60 days following initial infections with a different or same Omicron sublineages. Using data from the Austrian Covid-19 variant surveillance program, a sample of cases with a second diagnosis date more than 30 and less than 60 days apart after a primary PCR-confirmed Omicron infection were analyzed. Mutation analyses were only performed for the first positive SARS-CoV-2 test result.	• Overall, there were 242 cases of rapid reinfection of <60 days with different or same Omicron sublineages. BA.1 -> BA.1 = 60 BA.1 -> BA.2 = 138 BA.1 -> BA2+ORF3a:H78Y = 27 BA.2 -> BA.2 = 14 BA.2 -> BA2+ORF3a:H78Y = 1 BA.2 -> BA.1 = 2 • Out of the 242 cases, 76% were in unvaccinated individuals and 24% were in vaccinated individuals. Among the vaccinated individuals, 24% received at least one dose, 79% received a second dose and 16% a third dose. • In the 242 reinfection cases patients were more likely to report symptomatic infection in the second infection compared to the first Omicron infection and low CT values (CT 24.38 ± 4.64). Among the symptomatic cases of the first

		infection, the proportion of unvaccinated persons was 4.9 times more than the proportion of those who were vaccinated at least once. With reinfection, the proportion of unvaccinated persons was 3.4 times more than the proportion of those who were vaccinated at least once.
Hansen (2022) [9] *Preprint* Case-control Denmark Apr-Jun 2022	This study aimed to estimate, (1) the protection of a previous infection conveyed against a new infection with BA.5 among triple vaccinated individuals, (2) the vaccine effectiveness against infection with BA.5 relative to BA.2, and (3) the severity of infection with BA.5 relative to BA.2. Protection of a previous infection against BA.5 was analyzed using a test-negative case-control study design. Cases with a positive test for BA.5 infection identified through whole genome sequencing (WGS), were selected from the Danish COVID-19 surveillance system and compared to controls with a negative PCR test for SARS-CoV-2 during the outcome period. All cases and controls were triple-vaccinated with either the Comirnaty Pfizer BNT162b2 or SpikeVax Moderna mRNA-1273 vaccines. The proportion among BA.5 cases and test-negative controls that had been exposed to a previous Omicron BA.1 or BA.2 infection were compared. Previous exposure was defined as a positive SARS-CoV-2 PCR test at least 60 days before a new infection during the study period. Additionally, for comparison, all analyses were repeated with cases being those who tested positive during the outcome period with BA.2 rather than BA.5.	• Of the 4,809 triple-vaccinated cases who tested positive for BA.5 during the study period, only 98 (2%) had a previous BA.1 or BA.2 infection. By contrast, among the 164,369 triple-vaccinated, test-negative controls, 29,832 (18.1%) had a previous BA.1 or BA.2 infection. • The estimated protection was 93.6% (95%CI 92.1 to 94.8%) suggesting that a previous BA.1/BA.2 infection is highly protective against reinfection with BA.5. • A previous Omicron infection was even more highly protective against reinfection with BA.2 than for BA.5, with an estimated protection against BA.2 of 96.3% (95%CI 95.8 to 96.7%). Note: vaccine effectiveness data and analyses of severity across Omicron sublineages were not extracted.

Table 2: *In vitro* studies on the level of neutralizing antibodies post infection with Omicron (n=17)

Study	Method	Key outcomes
Studies with sample collection ≥14 d for people with prior immunity and ≥30 days for people without prior immunity (n=13)		
Quandt (2022) [10] *In vitro* study Germany Nov 2021-Jan 2022	This study aimed to characterize the effect of Omicron breakthrough infection on the magnitude and breadth of serum neutralizing activity and memory B-cells on individuals that were double- or triple-vaccinated with Comirnaty Pfizer BNT162b2. Plasma samples were collected from four groups: Omicron-naïve individuals double- (VAX2) (n=23, collection 22 or 162 days) or triple vaccinated (VAX3) (n=24, collection 28 or 84 days) and individuals double (VAX2+O)- (n=8) or triple-vaccinated (VAX3+O) (n=11) that subsequently had a breakthrough infection with Omicron BA.1 (sample collection 44-46 days). Serum neutralizing capacity was assessed using a pseudovirus for SARS-CoV-2 original variant (Wuhan), Alpha, Beta, Delta, Omicron BA.1, BA.2, BA.4/BA.5. Live virus neutralization test were conducted with the original variant (Wuhan), Beta, Delta and Omicron BA.1. **Note B-cell data in Table 3.**	Post vaccination immunity • VAX2 neutralization of Omicron BA.1, BA.2 and BA.4/BA.5 was virtually undetectable. Beta and Delta neutralization was reduced. • VAX3 higher neutralization of Alpha, Beta and Delta. BA.1 and BA.2 were lower and BA.4/BA.5 was 5-fold lower than the original variant, but detectable. Breakthrough infection immunity • Omicron breakthrough infections in vaccinated individuals mediated broad neutralizing activity and was strikingly better than those infection naïve with two doses. • VAX2+O and VAX3+O both had responses that were 100-fold (BA.1), 35-fold (BA.2) and 15-fold (BA.4/BA.5) higher than VAX2 or VAX 3. And broadly neutralized previous variants. Neutralization of BA.4/BA.5 was closer to neutralization of SARS-CoV-1. • VAX2+O and VAX3+O neutralized SARS-CoV-1 pseudovirus more effectively than vaccinated Omicron-naïve individuals.
Kaku (2022) [19] *In vitro* study US	This study investigated serum antibody and peripheral B-cell responses in mRNA-vaccinated individuals who had recently experienced BA.1 breakthrough infections. Serum and peripheral blood mononuclear cell (PBMC)	Breakthrough infection immunity Serum IgG and IgA • BA.1 breakthrough cases had similar IgG binding titers to the S-protein and RBD of BA.1 and the original variant, while uninfected vaccinated individuals had 2- to 4-fold and 4- to 9-fold reduced IgG titers to BA.1 S and

Dec 2021-Jan 2022	samples were collected from individuals who experienced Omicron BA.1 breakthrough infections (n=4 with 2 doses and n=3 with 3 doses of vaccination, samples collected 14-27 days following PCR-confirmed infection). Samples were compared to uninfected vaccinated individuals with 2 doses after one month (n=12) and 6 months (n=11) and 3 doses after one month (n=11). Vaccines were either Comirnaty Pfizer BNT162b2 or SpikeVax Moderna mRNA-1273. Serum IgG and IgA responses to the original variant Wuhan-1 and Omicron BA.1 S-proteins and RBD subunits were analyzed following breakthrough infection. Serum neutralizing activity against the original variant D614G, Omicron BA.1, Delta, Beta and SARS-CoV-1 was analyzed using a murine leukemia virus (MLV)-based pseudovirus assay. **Note B-cell data in Table 3.**	BA.1 RBD, respectively, relative to the original variant. • Post BA.1, individuals had higher IgA binding titers to BA.1 RBDs relative to uninfected vaccinated individuals. NAbs • Uninfected vaccinated individuals had 3.5- to 11-fold and 7- to 22-fold lower nAb titers against Beta and BA.1, respectively, relative to the original variant (D614G), while post BA.1 individuals showed similar nAb titers against the original variant (D614G) and all VOCs tested. • BA.1 breakthrough cases and uninfected vaccinated individuals had similar low nAb titers against SARS-CoV-1.
Zheng (2022) [25] *LTE* *In vitro* study China Jan-Feb 2022	This study aimed to determine the neutralizing response against the original variant, Beta, and Omicron BA.1 in sera from those infected with Omicron BA.1 who were either vaccinated (2 doses) or unvaccinated compared to 3 dose vaccinated with no history of infection. The study sample included 430 patients infected with Omicron BA.1, 341 of whom had received 1 (n=6), 2 (n=178), or 3 (n=157) doses of inactivated vaccines (BBIBP-CorV Sinopharm, CoronaVac Sinopharm, and other), 49 who received 1 (n=15) or 2 (n=34) doses of adenovirus-vectored vaccines (Ad5-nCoV), 2	Post Omicron immunity • In the Omicron BA.1 infected unvaccinated patients, NT50 against the original variant was higher than that against BA.1. Breakthrough infection immunity • The number of vaccine doses received before BA.1 breakthrough infection did not significantly affect the NT50 after infection. • Among BA.1 infected patients who had received 3 doses of inactivated vaccines, the overall plasma neutralizing titer of moderate patients was higher than that of mild patients. • Those who had received the inactivated vaccine had a similar level

	who received 3 doses of recombinant protein subunit vaccine (ZF2001), and 38 patients who were unvaccinated. Plasma samples were collected from 135 Omicron convalescent patients 1 month after hospital discharge (60 mild cases and 75 moderate cases). Furthermore, plasma from Omicron convalescent patients who had received 3 doses (n=42) were compared with uninfected individuals who also received 3 doses (n=114). SARS-CoV-2 virus neutralization assays (CPE) were used to determine the nAb titers against the original variant, Beta, and Omicron BA.1. Results expressed as NT50.	of neutralizing antibody titers. Slightly higher NT50 against the original variant, Beta, and Omicron BA.1 was observed in those who had received the adenovirus-vectored vaccine. • The NT50 of Omicron convalescent patients who had received 3 doses, was 2.2, 4.5, and 8.7 times that of the healthy vaccinated individuals when neutralizing the original variant, Beta, and Omicron BA.1, respectively.
Tuekprakhon (2022) [1] *In vitro* study UK Est Jun 2022	This study aims to report on the antigenic characterization of BA.4/BA.5 compared to the other Omicron sublineages. Serum samples were collected from individuals who received a third dose of the Vaxzevria Astrazeneca ChAdOx1-S (n=41) or Comirnaty Pfizer BNT162b2 (n=19) vaccines ~28 days (range 25-56) post third dose and from 26 individuals infected with Omicron BA.1 (at least 10 days post PCR). Among the BA.1 infected, 21 were had 2 doses, 3 received 3 doses and 2 received 1 dose. Early samples (n=12) were taken 17 days from symptom onset and later samples (n=14) were taken 28 days following symptom onset. Performed pseudotyped lentivirus neutralization assays on pseudotyped lentiviruses expressing the S gene from the Omicron sublineages BA.1, BA.1.1, BA.2, BA.3 and BA.4/BA.5	Post vaccination immunity • In individuals boosted with Vaxzevria Astrazeneca ChAdOx1-S, nAb titres for BA.4/BA.5 were reduced 2.1-fold compared to BA.1 ($p<0.0001$) and 1.8-fold compared to BA.2 ($p<0.0001$). • In individuals boosted with Comirnaty Pfizer BNT162b2, nAb titers for BA.4/BA.5 were reduced 3.1-fold ($p<0.0001$) and 3.1- fold ($p<0.0001$) compared to BA.1 and BA.2, respectively. Breakthrough immunity • In BA.1 breakthrough infections, nAb titres against BA.4/BA.5 were significantly less than BA.1 and BA.2 at the early time point; BA.4/BA.5 titres were reduced 1.9-fold ($p=0.0005$) and 1.5-fold ($p=0.0015$) compared to BA.1 and BA.2 respectively. • At the later point, BA.4/BA.5 titres were reduced 3.4-fold ($p=0.0001$) and 2-fold ($p=0.0017$) compared to BA.1 and BA.2, respectively.

	together with the original variant (WA-1) used as control.	
Cao (2022) [11] *In vitro* study China Est Jun 2022	This study aimed to investigate the neutralization evasion ability of Omicron sublineages BA.1, BA.1.1, BA.2, BA.3, BA.2.12.1, BA.2.13 and BA.4/BA.5 against the plasma obtained from 3-dose vaccinated individuals, BA.1 convalescents with previous vaccination, and those vaccinated with a history of prior infection with SARS-CoV-2 (pre-Omicron). Samples were collected from 40 individuals who received 3 doses of CoronaVac Sinopharm, 39 individuals who received 2 doses of CoronaVac Sinopharm and 1 booster dose of ZF2001, 54 BA.1 convalescents who had received 3 doses of CoronaVac Sinopharm, and 30 SARS-CoV-2 convalescents who received 3 doses (2 doses of CoronaVac Sinopharm and 1 dose of ZF2001). Samples were collected 4 weeks after the booster shot or 4 weeks after infection. Pseudovirus neutralization assays were performed against the original variant D614G, Omicron BA.1, BA.1.1, BA.2, BA.3, BA.2.12.1, BA.2.13 and BA.4/BA.5.	Post vaccination immunity • In individuals that received CoronaVac Sinopharm or ZF2001 booster, BA.1, BA.1.1 and BA.2 showed no significant difference in plasma neutralization resistance. Breakthrough immunity • BA.1 convalescents who had received 3 doses had significantly higher neutralization against the original variant D614G and BA.1 compared to the 3-dose vaccinees without BA.1 infection. • BA.2 sublineages BA.2.13 and BA.2.12.1 showed increased immune evasion capability than BA.2, with BA.2.12.1 stronger than BA.2.13, and BA.4/BA.5 conferring even stronger antibody escape in BA.1 convalescents who had received 3 doses. • The NT50 of BA.1 convalescents against BA.2.13, BA.2.12.1 and BA.4/BA.5, compared to that against BA.1, was reduced by 2.0, 3.7 and 8.0- fold, respectively. Post vaccination and prior infection • In vaccinated SARS-CoV-2 convalescents, BA.2 sublineages and BA.3/BA.4/BA.5 caused a striking neutralization loss.
Yu (2022) [12] *LTE* *In vitro* study US	This study aimed to evaluate neutralizing antibody responses against the original variant (WA1/2020) and Omicron BA.1 and BA.2 in individuals who did not have previous SARS-CoV-2 infection and were vaccinated and boosted with Comirnaty Pfizer BNT162b2 (n=24) compared to individuals with a history of SARS-CoV-2 infection with no vaccine (n=1), two doses of the	Post Omicron immunity • In Omicron BA.1 infection cases (7/8 vaccinated) the median neutralizing antibody titers were 4046, 3249, and 2448 for the original variant, BA.1, and BA.2, respectively. The median neutralizing antibody titer for BA.1 was 1.3 times the median neutralizing antibody titer for BA.2. Post vaccination immunity

Est Mar 2022	vaccine (n=2), and three doses (n=5). SARS-CoV-2 infection was diagnosed during a time when the Omicron BA.1 was responsible for > than 99% of new infections. Samples were taken at a median of 14 days post-infection. Neutralizing antibody responses were analyzed using pseudovirus antibody assays.	• After two doses of the vaccine, the median neutralizing antibody titers against the original variant, BA.1, and BA.2 were 658, 29, and 24, respectively. This declined to 129 for the original variant and to less than 20 for both BA.1 and BA.2 six months post-vaccine. Two weeks after the third dose, the mean neutralizing antibody titers increased against the original variant, BA.1, and BA.2 increased to 6539, 1066, and 776, respectively.
Shete (2022) [23] *Preprint* *In vitro* study India Mar 2020–Oct 2021	Investigated six individuals with Omicron BA.1 (n=1) or BA.2 (n=5) infections that had a history of SARS-CoV-2 infection (March 2020 to October 2021, B.1 variant) and 2 doses of Covishield Astrazeneca ChAdOx1-S vaccination. With samples available at different immune states. Naso/oropharyngeal swab and blood specimens were collected at four different time points in the pandemic: • primary SARS-CoV-2 infection, • 2 months after vaccine dose 2, • pre-reinfection (7 months after dose 2) • reinfection (10 months after dose 2). IgG immune response was determined using SARS-CoV-2 S1-RBD specific IgG ELISA. NAb titers of sera against Delta, Omicron and B.1 variant were measured using a plaque reduction neutralization test.	Post Omicron immunity • NAb titers demonstrated a significant boost in immune response post reinfection compared to pre-reinfection sera. A ~1000-fold rise was observed in nAb titers in reinfection sera against Omicron compared to smaller increases for B.1 (8.2 fold) and Delta (39.2 fold) compared to neutralization post the first infection. Post vaccination immunity • Sera collected 2 months post second dose vaccination demonstrated a rise in the neutralizing antibody titers against B.1 (6.8-fold), Delta (24.5-fold), and Omicron (114.8-fold), compared to post the primary infection. • The pre-reinfection sera collected 7 months after the second vaccination demonstrated reductions in IgG antibodies titer, waning immunity, (2.8-fold) and in the NAb titers against B.1 (3.3-fold), Delta (5.9-fold), and Omicron (17.3-fold), compared to two months post second dose.
Hachmann (2022) [13]	Evaluated neutralizing antibody titers against the original variant	Post Omicron immunity

In vitro study US Est Jun 20221	(WA1/2020) isolate along with BA.1, BA.2, BA.2.12.1, and BA.4 or BA.5 in participants who had been vaccinated and boosted with Comirnaty Pfizer BNT162b2 who had never had a COVID infection (n=27) and in participants who had been infected with Omicron BA.1 or BA.2 a median of 29 days earlier (range, 2 to 113). For those infected with Omicron, samples were collected 14-74 days, median 29 days post positive PCR. Neutralizing antibody titers were measured using a pseudovirus neutralizing antibody assay.	• Cases infected with BA.1 or BA.2 had lower median neutralizing titers against BA.2.12.1 and BA.4/BA.5 by a factor of 1.5 and 2.9, respectively compared to BA.1 neutralization. • Post Omicron BA.1 or BA.2 infection neutralization of the original variant was highest and the median neutralizing titer was lower by 6.4-fold against BA.1, 5.8 -fold against BA.2, 9.6-fold against BA.2.12.1, and 18.7-fold against BA.4/BA.5. Post vaccination immunity • Neutralizing antibody titers against Omicron sublineages 6 months post 2 doses of vaccine were much lower than that against the original variant (20 vs. 124). • After the booster, titers increased substantially. Compared to original variant, the neutralizing titer was lower by a factor of 6.4 against BA.1, 7.0 against BA.2, 14.1 against BA.2.12.1, and 21.0 against BA.4/BA.5. • When compared to median titers against BA.1, the titers against BA.2.12.1 and BA.4/BA.5 were lower by a factor of 2.2 and 3.3, respectively. Conclusion: neutralizing activity against BA.1, BA.2, BA.2.12.1, BA.4/BA.5 Omicron variants is similar for boosted and vaccinated + Omicron infected participants. Those who were not infected by Omicron or boosted showed little neutralizing activity against any Omicron sublineage.
Planas (2022)[24] *Preprint* *In vitro* study France	This study aimed to assess the durability and magnitude of neutralizing antibody responses against different Omicron variants, up to 16 months after Comirnaty Pfizer BNT162b2 vaccination and also, in vaccine recipients who experienced BA.1 or BA.2 breakthrough infections.	Post vaccination immunity • After the second dose, neutralization against Omicron BA.1, BA.2 and BA.5 was barely detected whereas D614G and to a lesser extent Delta were neutralized. • After the booster dose, BA.1 and BA.2 showed significantly lower neutralization, compared to the

Dec 2021–Feb 2022	Sera was collected from 27 fully vaccinated healthcare workers (HCW) some of whom were triple-vaccinated (n=22, samples collected 132 days post third dose) and experienced an Omicron BA.1 or BA.2 breakthrough infection (n=11, samples collected median 80 days post infection). Nasal swabs were collected at 1 month post-third dose for n=25 participants or 1-3 months after BA.1 or BA.2 breakthrough infection (n=7 participants sampled 1-3 times, representing a total of 15 samples). S-Fuse neutralization assay was used to measure serum nAb titers against the original variant D614G, Delta and Omicron BA.1, BA.2 and BA.5.	original variant and Delta, with BA.5 neutralization barely detectable. Breakthrough infection immunity • Breakthrough BA.1 or BA.2 infections post third dose caused a consistent increase of anti-S IgGs and nAbs against the different variants. Overall, nAb and IgG levels increased by 2.9-fold post breakthrough infection. Cross-neutralization against Delta, BA.1 and BA.2 variants significantly increased. The nab titer was lower against BA.5. • For nasal swab samples, breakthrough BA.1 or BA.2 infection triggered a 2.2- and 12- fold increase in IgGs and IgAs, respectively. Triple vaccinated, uninfected individuals did not show neutralizing activity against Delta or Omicron variants whereas, nasal swabs collected after BA.1 or BA.2 infection presented detectable neutralization against all variants. This neutralizing activity was higher against D614G, BA.1 and BA.2 than against Delta and BA.5.
Seaman (2022)[14] *Preprint* *In vitro* study US Est Mar 2022	Plasma samples from 50 individuals with symptomatic SARS-CoV-2 infection (19 Delta and 31 Omicron BA.1) were collected to assess viral genotype, viral load, and host antibody response at the time of breakthrough infection and after recovery. Among BA.1 infected individuals, 7 were unvaccinated, 14 were fully vaccinated (2 dose) and 10 were boosted (3 dose). Fully vaccinated individuals received either two doses of SpikeVax Moderna mRNA-1273 or Comirnaty Pfizer BNT162b2 or a single dose of Ad26.CoV.2S Johnson & Johnson. Boosted individuals received three doses of either SpikeVax Moderna	Post Omicron immunity • Neutralizing antibody responses against Omicron BA.1 pseudovirus increased significantly ($p < 0.0001$) post BA.1 infection between acute infection and convalescence. • Substantial increases in cross-neutralization was observed against Delta pseudovirus after BA.1 infection ($p < 0.001$). • In BA.1-infected individuals at convalescence, BA.2 pseudovirus was the most resistant to neutralization with a 1.8-fold reduction in BA.2 titers compared to BA.1. • For both Delta and Omicron infections, compared to boosted or vaccinated patients, unvaccinated patients had 38-fold lower neutralization titers against BA.2 and

	mRNA-1273 or Comirnaty Pfizer BNT162b2. Samples were collected at the time of acute infection, median four days (2-10) and again at convalescence, median 17 days (14 – 24) after the onset of symptoms or positive PCR. Neutralizing antibody responses against, Omicron BA.1, BA.2, Delta and D614G original variant pseudoviruses were analyzed using pseudovirus neutralizations assays.	31-fold lower against BA.1, 33-fold lower against the original variant and 25-fold lower against Delta. • Significantly higher neutralization titers against BA.1 and BA.2 were observed in convalescent serum from BA.1-infected participants compared to Delta-infected participants. Post BA.1 nAbs have greater breadth than post Delta nAbs. • Based on a component analysis of sources of variability in results, 67% of the variability is explained by vaccination status and a modest 19% was explained by infecting variant.
Nutalai (2022) [21] *In vitro* study UK Est Jun 2022	This study aimed to assess differential sensitivity to neutralization of the Omicron sublineages BA.1, BA.1.1, and BA.2 using sera collected from individuals who were vaccinated with 3 doses and those who were infected with BA.1. Sera was collected from individuals 28 days following 3rd doses of Vaxzevria Astrazeneca ChAdOx1-S (n=41) or Comirnaty Pfizer BNT162b2 (n=20) vaccines and from cases infected with BA.1. Early samples (n=12) were taken ≤14 days from symptom onset (median 13 days); later samples (n=16) were taken ≥21 days following symptom onset (median 38 days). All BA.1 infected cases had received at least 2 doses (4 Vaxzevria Astrazeneca ChAdOx1-S, 16 Comirnaty Pfizer BNT162b2, and 1 Ad26.CoV.2S Johnson & Johnson) and 3 of the late convalescent cases received a 3rd dose of vaccine following Omicron infection. Live virus neutralization assays were performed on the original variant (Victoria), Alpha, Beta,	Post vaccination immunity • There was a major reduction in neutralization titre for all Omicron viruses for both vaccines. • For individuals that received 2 or 3doses, BA.1.1 and BA.2 showed small but significant reductions in titers relative to BA.1. Breakthrough infection immunity • At early sampling, all BA.1 infected cases had high titers to the original variant Victoria with FRNT50 close to 1/3,000. Cases also showed broad neutralization of tested VOCs with FRNT50 > 1/1,000 for all viruses except Omicron. • At the later time point, BA.1 infected cases had increased nAb titers against all variants including BA.1 (3.1-fold; P=0.0097).d

	Gamma, Delta and Omicron BA.1, BA.1.1, and BA.2. Results reported as FRNT50.	
Karaba (2022) [22] *LTE* *In vitro* study US Est Jun 2022	In this study, surrogate neutralization against BA.1, BA.2, and BA.3 Omicron sublineages, and the vaccine strain were evaluated in sera from individuals who were boosted (N=36) or had a breakthrough infection during the BA.1 surge after boosting (N=18). Samples were taken 1-3 weeks and 1-3 months post-boost from boosted uninfected participants, and 1-3 weeks and 4-7 weeks post-infection from individuals with a breakthrough infection.	Breakthrough infection immunity • Across all four variants tested, the median surrogate neutralization was highest in the 4–7 weeks post-breakthrough infection group followed by the uninfected group at 1–3 weeks post-boost. • In the boosted uninfected group, surrogate neutralization decreased between 1–3 weeks and 1–3 months but increased in the breakthrough group between 1–3 weeks and 4–7 weeks. • In the boosted uninfected group, the median neutralization was less than 20% for all variants at 4-7 weeks whereas in the breakthrough group the median neutralization was more than 20% against all three sublineages (BA.1, BA.2, and BA.3) at 4–7 weeks.
Blom (2022) [20] *In vitro* study Sweden Jan–Feb 2022	This study analyzed serological and T-cell responses following Omicron BA.1 or BA.2 infection in 56 triple-vaccinated health-care workers with and without prior infection with the original variant. A surrogate virus neutralization test (sVNT) was used to assess neutralization of SARS-CoV-2 variants (original variant, Delta, BA.1 and BA.2). Blood samples for immune response were collected 1 week, 2 weeks, 3 weeks, 5 weeks, and 7 weeks after the first positive qPCR sample. Live micro neutralization assay based on cytopathic effects (CPE) was performed for the original variant and the Omicron BA.1 variant.	Breakthrough infection immunity Spike IgG • Anti-spike IgG titers against the original variant, Delta, BA.1, and BA.2 increased by 2-fold 2-5 weeks post Omicron BA.1 or BA.2 breakthrough infection. • Serological responses were significantly higher in Omicron BA.1 or BA.2 breakthrough cases with no history of SARS-CoV-2 infection (n=40) than in Omicron BA.1 or BA.2 breakthrough cases with history of prior infection caused by the original variant (n=16). • Serological response correlated with cycle threshold (CT value). NAbs • sVNT titers against the original variant, Delta, BA.1, and BA.2 increased by 2-fold 2-5 weeks post

	Note T-cell data in Table 3.	Omicron BA.1 or BA.2 breakthrough infection.
Studies where one of the following two criteria are met: sample collected ≥14 d for people with prior immunity and ≥30 days for people without prior immunity (n= 4)		
Khan (2022) [17] *In vitro* study South Africa Nov 2021-Jan 2022	This study evaluated nAb titers against the original variant (D614G), Delta, Beta, Omicron BA.1 and BA.2 in individuals with Omicron BA.1 infection (fully vaccinated or unvaccinated) and in individuals with Delta infection. Plasma samples were collected from individuals with Omicron BA.1 infection (n=39, samples collected initially 3–9 days after symptom onset, median 6 days and again at 19–27 days post-symptom onset, median 23 days) and from those with Delta infection (n=14). Among BA.1 infected individuals, 15 were fully vaccinated (2 doses of Comirnaty Pfizer BNT162b2 or Ad26.CoV.2S Johnson & Johnson) and 24 were unvaccinated. Neutralizing responses against the original variant (D614G), Delta, Beta, Omicron BA.1 and BA.2 were analyzed using a live virus neutralization assay. Results reported as FRNT50.	Post Omicron immunity • BA.2 neutralization was moderately and not significantly lower relative to BA.1 neutralization in both vaccinated and unvaccinated BA.1 infected individuals. • In vaccinated BA.1 cases, neutralization of the original variant and VOCs was higher relative to BA.1. In unvaccinated BA.1 cases, neutralization of the original variant and VOCs was lower relative to BA.1. • Compared to unvaccinated BA.1 infected participants, vaccinated BA.1 infected individuals had 2.2, 4.8, 9.6, 12.0, and 17.9-fold higher neutralization of BA.1, BA.2, Beta, Delta and the original variant, respectively.
Khan (2022) [18] *Preprint* *In vitro* study South Africa Nov-Dec 2021	In this study live Omicron BA.4 and BA.5 viruses were tested against neutralizing immunity elicited to Omicron BA.1 infection in participants who were Omicron BA.1 infected but unvaccinated (n=24) and participants vaccinated with Comirnaty Pfizer BNT162b2 or Ad26.CoV.2S Johnson & Johnson with breakthrough Omicron BA.1 infection (n=15). Samples were collected from BA.1 infected unvaccinated individuals	Post Omicron immunity • Vaccinated BA.1 infected participants had 3.2-fold lower neutralization for BA.4 and 2.6-fold lower for BA.5, while unvaccinated BA.1 infected individuals had 7.6-fold lower neutralization of BA.4 and 7.5-fold lower for BA.5. • Absolute BA.4 and BA.5 neutralization levels were 5-fold higher in the vaccinated BA.1 infected group compared to the unvaccinated BA.1 infected group.

	20-28 days post-symptoms, median 23 days and vaccinated participants 18-27 days post-symptoms, median 23 days. Neutralizing responses against Omicron BA.4 and BA.5 were analyzed using a live virus neutralization assay. Results reported as FRNT50.	
Stiasny (2022)[15] *Preprint* *In vitro* study Austria Est Apr 2022	This study aimed to analyze the neutralizing capacity of serum samples obtained from individuals with the original variant, Omicron BA.1 and BA.2 infections, individuals with a Omicron breakthrough infection, and those who had received three doses of a vaccine with and without prior infection. Serum samples were collected from 6 groups: those vaccinated with 3 doses without a prior infection (n=30, samples collected 3 weeks and 3 months post third dose) and with a prior infection with the original variant (n=9, samples collected 3-4 weeks post third dose), those with a primary infection with the original variant (n=22, samples collected 3 weeks and 6 months post infection), those with a primary BA.1 infection (n=18, samples collected 3-4 weeks post infection), those with a primary BA.2 infection (n=7, samples collected 3-4 weeks post infection) and those with a Omicron breakthrough (2 or 3 doses vaccination) infection (n=11, samples collected 3-4 weeks post infection). A live virus neutralization assay of samples was performed against the original variant D614G, Delta, Omicron BA.1 and BA.2.	Post vaccination immunity • Individuals vaccinated with 3 doses efficiently cross-neutralized Omicron variants, although titers were significantly lower than for the original variant. Individuals vaccinated with 3 doses with a prior infection with the original variant also cross-neutralized Omicron variants. Median titers declined substantially between 3-4 week and 3 months for all variants. Prior infection immunity • Primary infections with the original variant, Omicron BA.1, and Omicron BA.2 neutralized the homologous strain more efficiently than the heterologous strains. Median titers declined slightly between 3-4 week and 3 months for Omicron BA.1 and BA.2 and substantially for the original variant and Delta. • Primary infection with the original variant neutralized Omicron poorly. Post Omicron immunity • Primary BA.1 infection showed some cross-neutralization against the original variant, Delta, and BA.2 but to a lesser extent than BA.1. • Primary BA.2 infection did not cross-neutralize any other virus strain tested. Breakthrough immunity • Omicron breakthrough infection neutralized the BA.1 and BA.2 as

		efficiently as the original variant and Delta.
Willett (2022) [16] *Preprint* *In vitro* study UK Est May 2022	An in-depth characterization of the antigenicity of the BA.4/BA.5 Spike protein was done by comparing sera (human and hamster) collected post-vaccination post-BA.1 or BA.2 infection, or post breakthrough infection of the vaccinated with the Omicron variant. In those who were vaccinated with BA.1 breakthrough infection, 5/6 had 3 vaccine doses and samples were collected 18-27 days post-positive test. In those who were vaccinated with BA.2 breakthrough infection, 5/6 had 3 vaccine doses and samples were collected 9-25 days post-positive test. Vaccinated individuals received either three doses of Comirnaty Pfizer BNT162b2 or two doses of Vaxzevria Astrazeneca ChAdOx1-S + 1 dose of Comirnaty Pfizer BNT162b2. Neutralizing antibody responses were analyzed using pseudovirus antibody assays.	• In the absence of vaccination or prior infection with BA.1 or BA.2 results in an antibody response that neutralizes BA.4/BA.5 poorly. • Using sera from unvaccinated individuals with only a single known exposure to BA.1, we found a 23-fold drop in relative neutralizing titres against BA.4/BA.5, and a 7.6-fold reduction against BA.2. Post Omicron immunity • A single human BA.2 convalescent sera showed a drop in cross-neutralization of BA.4 and BA.5 similar to that seen in a hamster model. Vaccinated and prior infection immunity • Breakthrough infection with Omicron in those who were vaccinated led to a broad neutralizing response against the new variants. • 3.3-fold reductions in neutralization were observed between BA.4/BA.5 and BA.1 for BA.1 breakthrough infection or 5.5-fold between BA.4/BA.5 and BA.2 for BA.2 breakthrough sera. Where the lineage was unspecified, there were comparable drops in titre against all Omicron lineages (between 2.3-3.5-fold).

Abbreviations: ELISA, enzyme-linked immunosorbent assay; Est, estimate; FFRNT, fluorescent focus-reduction neutralization test; FFRNT50, 50% fluorescent focus-reduction neutralization titers; FRNT, focus reduction neutralization test; FRNT50, focus reduction neutralization test titer (the inverse of the plasma dilution) required for 50% neutralization; HCW, healthcare worker; LTE, letter to the editor; NAbs, neutralizing antibodies; NT50, neutralization titers 50 or titers that neutralized 50% of virus activity; RBD, receptor binding domain; UK, United Kingdom; US, United States

Table 3: *In vitro* studies on B-cell and T-cell outcomes post infection with Omicron (n=3)

Study	Method	Key outcomes
Quandt (2022) [10] *In vitro* study Germany Nov 2021-Jan 2022	This study aimed to characterize the effect of Omicron breakthrough infection on the magnitude and breadth of serum neutralizing activity and memory B-cells on individuals that were double- or triple-vaccinated with Comirnaty Pfizer BNT162b2. Plasma samples were collected from four groups: Omicron-naïve individuals double- (VAX2) (n=23, collection 22 or 162 days) or triple vaccinated (VAX3) (n=24, collection 28 or 84 days) and individuals double (VAX2+O) (n=8) or triple-vaccinated (VAX3+O) (n=11) that subsequently had a breakthrough infection with Omicron BA.1 (sample collection 44-46 days). SARS-CoV-2 spike-specific B_{MEM} cells were assessed via a flow cytometry-based B-cell phenotyping assay using bulk peripheral blood mononuclear cells (PBMC). The assays identified B_{MEM} cells recognizing the S-protein or RBD of the original variant Wuhan, Alpha, Delta and Omicron BA.1. **Note nAb outcomes in Table 2.**	Post vaccination immunity • The frequency of S-protein specific B_{MEM} cells in VAX2 quadrupled at 5 months versus 3 weeks after 2nd dose. RBD specific B_{MEM} cells tripled across all VOCs reaching quantities similar to in VAX3. Breakthrough memory immunity • VAX2+O and VAX3+O had strongly increased frequency of S-protein specific B_{MEM} cells, higher than those of VAX3. • In all four groups, B_{MEM} cells against BA.1 S-protein were detectable at frequencies comparable to those against the original variant and other tested VOCs. However, the frequency of B_{MEM} cells against BA.1 RBD was slightly lower compared to the other VOCs. • Omicron breakthrough infection had a higher RBD/S protein-specific B_{MEM} cell ratio. • Omicron breakthrough infection in vaccinated individuals primarily enhances B_{MEM} cells response against conserved epitopes shared broadly between S-proteins of Wuhan and other VOCs rather than inducing large numbers of Omicron-specific B_{MEM} cells. • VAX2+O individuals appear to have a higher frequency of B_{MEM} cells and higher nAb titers against previous VOCs as compared to triple-vaccinated individuals.
Kaku (2022) [19] *In vitro* study	This study investigated serum antibody and peripheral B-cell responses in a group of mRNA-vaccinated individuals who had	Breakthrough memory immunity • Both the post BA.1 and uninfected vaccinated groups showed similar frequencies of the original variant- and BA.1-RBD-reactive IgG+ B-cells.

US Dec 2021-Jan 2022	recently experienced BA.1 breakthrough infections. Serum and PBMC samples were collected from individuals who experienced Omicron BA.1 breakthrough infections (n=7, samples collected 14-27 days following PCR-confirmed infection), some of whom were boosted (3 doses) (n=3). Samples were compared to a separate group of uninfected fully vaccinated (2 doses) or boosted individuals (3 doses). **Note nAb outcomes in Table 2.**	• BA.1 breakthrough infection (after both 2 and 3 doses) induces higher magnitude IgA+ B-cell responses to the original variant and BA.1 RBD compared to uninfected vaccinated individuals. • The proportion of B-cells that displayed the original variant/BA.1 RBD cross-reactivity out of the total RBD-directed B-cells was 48% at one month after two doses, 57% at 6-months, 70% following a booster dose and 83% following BA.1 breakthrough infection. • BA.1 breakthrough infection re-activates pre-existing vaccine-induced memory B-cells (MBC). • Compared to vaccine-induced anti-RBD antibodies, a lower proportion (>5%) of antibodies derived from BA.1 breakthrough showed loss of binding to Beta relative to the original variant. • The majority of B-cells activated by BA.1 breakthrough infection target conserved epitopes. • BA.1 RBD-reactive antibodies showed >90% neutralizing activity against the original variant D614G and BA.1, respectively. Cross-reactivity was also seen with Delta (79%), Beta (90%), and BA.2 (86%) RBDs with affinities within 10-fold of BA.1.
Blom (2022) [20] *In vitro* study Sweden Jan–Feb 2022	This study analyzed serological and T-cell responses following Omicron BA.1 or BA.2 infection in 56 triple-vaccinated health-care workers with and without prior infection with the original variant. PBMCs were isolated from whole blood to analyze T-cells. T-cell responses were analyzed in samples collected 7 (median 6.7, IQR 6-7.4) weeks post Omicron breakthrough infection, and in samples collected from participants who	Post Omicron memory immunity • There was no difference in spike-specific T-cell responses between participants with and without Omicron BA.1 or BA.2 infection, regardless of previous SARS-CoV-2 infection status. • Nucleocapsid- and membrane-specific T-cell responses were significantly higher for Omicron BA.1 or BA.2 cases without prior infection than cases without Omicron infection. • There was a similar T-cell response observed in BA.1-infected compared with BA.2-infected individuals.

	remained SARS-CoV-2 negative throughout the screening period (n=69). **Note nAb outcomes in Table 2.**	

Abbreviations: ELISpot, enzyme-linked immune absorbent spot; IGRA, Interferon-Gamma Release Assays; PBMC, peripheral blood mononuclear cell; RBD, receptor binding domain

Appendix

Table A1: Vaccine Brand and Generic names

Brand Name	Generic Name	Manufacturer
Vaxzevria	ChAdOx1-S (AZD1222)	AstraZeneca/ Covishield
Comirnaty	BNT162b2	Pfizer-BioNTech
	Ad26.COV2.S	Janssen (Johnson & Johnson)
SpikeVax	mRNA-1273	Moderna
Nuvaxovid	COVID-19 Vaccine (recombinant, adjuvanted)	Novavax Inc.
	CoronaVac	Sinopharm
	BBIBP-CorV	Sinopharm
Covaxin	BBV152	Bharat Biotech
Sputnik V	Gam-COVID-Vac	Russian vaccine- produced by 14 companies via partnership (Aug-21)

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