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INVITED REVIEW

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COVID-19 and plasma cells: Is there long-lived protection?*

Doan C. Nguyen[1] | Pedro A. Lamothe[1] | Matthew C. Woodruff[2,3,4] | Ankur S. Saini[2,3,4] | Caterina E. Faliti[2,4] | Ignacio Sanz[2,3,4] | Frances Eun-Hyung Lee[1,4]

[1]Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Emory University, Atlanta, Georgia, USA

[2]Division of Rheumatology, Department of Medicine, Emory University, Atlanta, Georgia, USA

[3]Emory Autoimmunity Center of Excellence, Emory University, Atlanta, Georgia, USA

[4]Lowance Center for Human Immunology, Emory University, Atlanta, Georgia, USA

Correspondence
Frances Eun-Hyung Lee, MD, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Emory University, Atlanta, GA, USA.
Email: f.e.lee@emory.edu

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Summary

Infection with SARS-CoV-2, the etiology of the ongoing COVID-19 pandemic, has resulted in over 450 million cases with more than 6 million deaths worldwide, causing global disruptions since early 2020. Memory B cells and durable antibody protection from long-lived plasma cells (LLPC) are the mainstay of most effective vaccines. However, ending the pandemic has been hampered by the lack of long-lived immunity after infection or vaccination. Although immunizations offer protection from severe disease and hospitalization, breakthrough infections still occur, most likely due to new mutant viruses and the overall decline of neutralizing antibodies after 6 months. Here, we review the current knowledge of B cells, from extrafollicular to memory populations, with a focus on distinct plasma cell subsets, such as early-minted blood antibody-secreting cells and the bone marrow LLPC, and how these humoral compartments contribute to protection after SARS-CoV-2 infection and immunization.

KEYWORDS
antibody secretion, antibody-secreting cell, COVID-19, long-lived plasma cell, SARS-CoV-2

1 | INTRODUCTION

The SARS-CoV-2 pandemic arose in China at the end of 2019 and has caused over 450 million infections and more than 6 million deaths worldwide. Initially, the virus caused a wide range of clinical manifestations from asymptomatic and mild to severe and critical, leading to death in ~1.5% of infected individuals. Elderly patients were initially at risk of severe disease together with those who had co-morbid conditions, such as diabetes and obesity. Pneumonia and respiratory failure often led to hospitalization; however, this infection caused gastrointestinal and endothelial injury leading to systemic illness affecting multiple organ systems that included the brain and many others.[1] With mild illness even after recovery, post-acute sequelae of SARS-CoV-2 infection (PASC) has also been reported without clear underlying pathophysiologic mechanisms.[2] At first, sequelae were thought to occur only after severe infection, but now PASC has been commonly reported after

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both mild and severe disease at frequencies as high as 10-30% making it even more puzzling. Therefore, understanding immune mediators of protection from infection and severe disease as well as the immune mechanisms of the sequelae are critical to overcoming this pandemic.

Viral neutralizing antibodies (nAbs) secreted by LLPC provide durable protection after infection. Prior to COVID-19, the best-known pandemic was the 1918 H1N1 influenza virus, which offered life-long serologic protection after primary infection.[3] However, reinfections could occur from new re-assorted influenza viral mutants and not necessarily from the previously circulating strains. But, in COVID-19, unlike influenza virus infections, antibody responses after SARS-CoV-2 infection whether it be mild or severe appear to persist for only 18-20 months.[4,5] Thus, antibody protection after SARS-CoV-2 infection may not necessarily be long lasting and a cause of breakthrough infections. Additionally, similar to influenza viruses, the evolution of new viral variants of SARS-CoV-2 for which there is little cross-protection may be another cause of repeat coronavirus infections with the recent Delta[6] and Omicron[7] mutants despite history of previous infection.[8–10]

In the United States and then globally, vaccines to SARS-CoV-2 were introduced within a year after the start of the pandemic which was an incredible scientific achievement. These vaccines provided robust protection especially with high titers of nAbs and afforded safeguards for severe disease. However, the primary vaccine series were effective only short-term and exhibited waning efficacy within months.[11–14] Thus, the CDC guidance now recommends a booster dose 6 months after the initial primary two-dose immunization. Despite shielding from hospitalizations, waning vaccine titers were not necessarily effective against new viral variants, causing many breakthrough infections (BTI) even though most were mild. In all, following emerging viral mutants, the understanding of the mechanisms of durable humoral protection from infection and vaccination is vital in the fight against this pandemic.

2 | B CELLS AND LONG-LIVED PLASMA CELLS IN VIRAL INFECTION

During a canonical respiratory viral immune response, naive B cells encounter viral antigens, become activated, and differentiate into antibody-secreting cells (ASC) from extrafollicular (EF) or germinal center (GC) B cells. Some naive B cells enter the GC to engage with the antigen and T follicular helper cells (Tfh) to undergo rounds of expansion, somatic hypermutation (SHM), and antigen-specific positive selection. Ultimately, successful GC-derived clones differentiate into high-affinity ASC and memory B cells (MBC) and are thought to become long-lived. The decision of GC B cells to remain in the GC, exit as MBC, or further differentiate into ASC have been studied in mouse models[15] but are not well described in human studies[16] (Figure 1).

At steady state, healthy humans have a low ASC frequency in the circulation (i.e., <1% of the total B cells)[17–19] but during acute viral infections, ASC rapidly burst into the bloodstream with a rise in protective pathogen-specific antibody levels.[18,20,21] Typical ASC

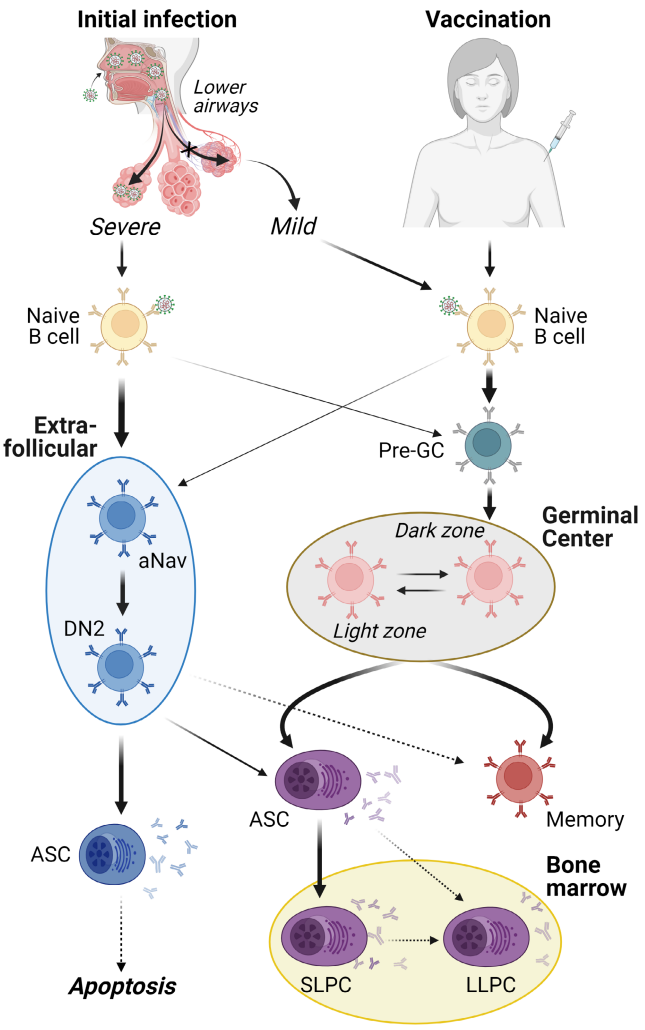

FIGURE 1 B cell response development in COVID-19. Primary infection with SARS-CoV-2 results in a spectrum of disease severity with differing impacts on humoral response development. (Right) Mild COVID-19 or vaccination results in a GC-focused response, allowing normal accumulation of somatic hypermutation, affinity maturation, memory formation, and plasma cell development. The extent of LLPC development in GC-focused COVID-19 responses remains a critical open question with important implications in response longevity. (Left) Severe/critical COVID-19 results in an extrafollicular (EF)-biased response with the rapid development of low-mutation effector B cells (DN2) and plasmablasts. While the neutralizing capability of these populations has been confirmed, the impact of EF-biased responses on memory formation, plasma cell development, and bone marrow engraftment is less clear. Heavy arrows—dominant pathway; Light arrows—secondary pathway; Dotted arrows—unconfirmed pathway. GC, germinal center; aNav, activated naive B cells; DN2, double negative (i.e., $IgD^{-}CD27^{-}$ B cells that also lack expression of CXCR5 and are involved in the EF response that is outside the GC but can still have T cell help); ASC, antibody-secreting cell; SLPC, short-lived plasma cell; LLPC, long-lived plasma cell

responses after acute infection range from 2 to 10% of total B cells; but in some specific infections such as with Hantavirus and Dengue viruses, ASC may account for up to 70-80% of all circulating B cells.[17,18,22–24] Whether the magnitude of the responses reflect

primary versus secondary exposures or result from the different types of viruses is not entirely clear.

Typical serum titer responses reveal an early GC-independent phase with the appearance of low-affinity primarily IgM,[21,25] followed by high-affinity, class-switched, pathogen-specific durable IgG and IgA. After the initial robust rise in Ab titers, the decay kinetics of the antigen-specific levels are twofold as shown in non-human primate models. The first is a rapid fall-off due to apoptosis of short-lived ASC and then a slower decline or "memory" Ab after months likely from LLPC generation and maintenance.[26] The main source of serum "memory" Abs arises from circulating GC-derived MBC which differentiate into ASC to mature into tissue-resident LLPC, both of which are extremely rare and produce highly diverse and affinity-matured Abs.[27–30] In mice, LLPC have been identified in the spleen, the gut, and the bone marrow (BM), and are found weeks following the initial induction.[31]

The mechanisms of how human LLPC are generated and maintained are not entirely clear. However, it is known to include GC and MBC responses and the migration of ASC to long-lived tissue sites such as the BM niches. In humans, LLPC were found in the BM $CD19^{-}CD38^{hi}CD138^{+}$ compartment from natural viral infections that occurred over 40 years ago. However, exposures to repeat viral infections and vaccination were localized in other BM compartments such as $CD19^{+}CD38^{hi}CD138^{+}$ subsets and the LLPC subsets.[32] After the initial burst into the blood, most early-minted ASC or plasmablasts undergo apoptosis triggering the rapid primary decline of Ab titers. Only some ASC eventually enter long-lived tissue sites such as the BM to submit to further development and maturation through factors provided by the specialized microniche.[33] These cells are likely responsible for the second slower Ab decay. Histology shows that LLPC have unique morphology from nascent ASC such as increased cytoplasm/nucleus ratio and higher number of mitochondria. Although LLPC are derived from early-minted ASC, they are transcriptionally and epigenetically different illustrating ongoing maturation in the BM sites.[34] These special molecular and epigenetic pathways enhance longevity, minimize energetic needs, and upregulate programs to acquire resistance to apoptosis in order to maintain antibody secretion for a lifetime.[34] In this review, we will investigate whether ASC after SARS-CoV-2 infection and new COVID-19 mRNA vaccines follow the canonical B cell and LLPC maturation programs or if these humoral responses are fundamentally altered.

3 | ASC RESPONSE IN SARS-COV-2 INFECTION

3.1 | Primary infection: virus-specific antibodies are highly diverse, peak early, and decline

The majority of primary SARS-CoV-2 infections elicits a robust systemic viral-specific Ab response initially within 1-2 months,[35–37] although the Ab magnitude among infected individuals is heterogenous with peak levels varying over 200-fold.[37,38] By and large, Ab levels were reduced by 5-fold to 10-fold compared to the peak at 5 months[35–37,39] with some studies showing that they remain detectable for 5-12 months,[37,39–45] 13-14 months,[46,47] and some suggesting 18-20 months,[4,5] in the absence of vaccination and reinfection. However, the pandemic started only 2 years ago, and so longer durability data are just not available.

After an early peak within 2-5 weeks, Abs decline in a fashion that varied by isotype, viral antigen-specificity, and age.[37,48,49] While IgM and IgA often wane rapidly and become undetectable after 2-3 months,[50,51] IgG decays at a slower rate. Additionally, different viral antigens such as nucleocapsid (N), receptor-binding domain (RBD), and spike (S) also give rise to variable kinetics. For example, the serum N-Ab decay more rapidly compared to RBD- or S-Ab. The estimated average half-life in most infections of S-specific IgG, IgM, or IgA1 is 14-33, 8, or 6 weeks, respectively.[37,52] On average, the fastest waning Abs were N-specific IgG with two-third the levels at 4-9 months and undetectable levels in 33% of the patients. By 1 year, almost all patients had no measurable N-specific IgG.[53–57] S-specific IgG decays slowest, waning to less than one-third of the peak levels at 8-10 months. However, nearly all patients (90-97%) have detectable S-IgG titers at 12-13 months.[53–55] Finally, not all SARS-CoV-2-infected patients developed demonstrable serum Abs, with some studies reporting 5% to 33% of PCR-positive patients particularly in young adults who did not seroconvert.[58–60]

Antibodies that functionally neutralize correlate with total virus-specific Abs and RBD-specific Abs.[61] Both total virus-specific and nAbs usually peaked between 3 and 5 weeks after infection, but also rapidly decayed with an average half-life of 8-13 weeks.[37,41,50,52,62–65] However, it appears that in mild to moderate infections, nAbs could last for at least 5-7 months.[14,39,66–70] Both total viral-specific Abs and nAbs rapidly wane initially, but then declined at a much slower rate to remain relatively stable with time.[37,39,51,71–73] In all, infection-induced serum S- and RBD-specific IgG were positively correlated with nAbs, and these antibodies peaked within a few months and initially wane rapidly and then with a slower decay over the first year.[37,52,53,56,74–76] Whether this slower decay will ultimately plateau as seen in other infections to provide LLPC and life-long protection remains at large.

Increased Ab responses were associated with older age, male sex, and hospitalization.[38] However, disease severity seemed to have the greatest effect on the magnitude of infection-induced Abs.[38,73,77,78] In general, severe infections were associated with both a more rapidly rise and a higher peak in both binding and neutralizing Abs.[40,51,79,80] These Abs rocketed rapidly within days of symptom onset[40,81] especially in hospitalized or critically ill patients compared to mild (outpatients or asymptomatic) subjects.[40,50,51,54,56,73,79] Moreover, unlike conventional responses, the majority of these responses did not generate an early IgM response followed by the conventional class-switched IgG and IgA.[50,77] Instead, a class-switched IgG with neutralization was detected early in these critically ill patients. Later monoclonal antibody studies showed low or germline mutation frequencies found in severe infections, implicating unique nonconventional B cell origins.[81–83]

3.2 | Germinal centers are disrupted in severe COVID-19 infection

Unlike typical viral infections, early studies showed that in severe SARS-CoV-2 infections, the GC are impaired[84,85] and are associated with large plasmablast expansions and enhanced Ab levels compared to mild disease[37,40,77,86] (Figure 1). The decreased numbers of Tfh in the draining lymph nodes (LN) and spleen provided evidence that functional GC fail to form during critical illness.[84,85] Furthermore, in these severely ill patients, a robust EF B cell response dominates with higher ASC expansion and correlated with nAb levels.[81,86] Corroborating this model, multiple potent nAbs were isolated from severe patients exhibiting only few mutations suggesting that EF responses can give rise to effective nAbs.[83,87] Interestingly enough, both mild and severe COVID-19 infections showed evidence of class-switched MBC with higher mutation frequencies[41,78,88,89] and strong Tfh cell responses.[90–92] Thus, a strong EF response may not always occur at the exclusion of GC B cell responses. However, the collapsed GC in the critically ill patients give rise to a massive early EF ASC response, causing the rapid rise in Ab titers.

3.3 | SARS-CoV-2-specific ASC responses

The rapid and transient expansion in the circulation of ASC is generally a hallmark of early B cell responses during acute viral infections.[21] Initial infections with SARS-CoV-2 give rise to an early Ab peak within the 2nd week post-induction that wanes substantially and rapidly over time (declining by 5-fold to 10-fold within 3-4 months or to <7% of the peak at 5-6 months) (Figure 2).[19,35–37,51,71–73,77,93–95] This fast decay most probably reflects apoptosis of many circulating short-lived IgG and IgA ASC, known to appear within a few days after initial antigen exposure.[20,22–24,32,96,97] In severe infections, circulating ASC defined as $CD19^{+}CD27^{hi}CD38^{hi,}$ which included $CD138^{+}$ subsets were expanded although their frequency was not associated with virus-specific IgM.[81,86] A similar pattern was seen in Dengue infections, where higher ASC expansions were associated with more severe illness.[86,98,99] Hence, the rapid antibody decay is a manifestation of apoptosis of the nascent blood ASC.

Early ASC may serve as a biomarker of disease severity,[40,81] which at the same time, raises concerns about a potential pathogenic role of ASC.[86,98,99] One study showed that the expansion of ASC in the circulation in hospitalized patients with COVID-19 infection decreased 28-day mortality although the differences were small, suggesting ASC might actually also serve as a marker of disease resolution.[100] Whether ASC expansions are pathogenic or bystander effects from certain proinflammatory cytokines supporting ASC survival, such as IL-6 and TNF-α, which are coincidently elevated in severe COVID-19,[81,86,101–103] is not entirely clear.

A meaningful ASC response depends not only on quantity but also on quality, such as nAb and different isotypes. Different isotypes IgM, IgA, and IgG were notable in the serum and/or mucosal sites 1-2 weeks post-symptom onset.[40,77,104] In COVID-19, although IgA is normally responsive at mucosal sites, virus-specific IgA ASC were also expanded in the circulation.[95,105] Additionally, SARS-CoV-2 neutralization was correlated more closely with IgA than IgM or IgG in the first weeks after symptom onset.[95] Despite this result, the IgA responses were not associated with disease severity and serum IgA concentrations decreased by 1 month. However, mucosal neutralizing IgA remained detectable in the saliva for more than 3 months, suggesting locally differentiated IgA ASC may have a longer half-life than systemic IgA ASC and confer protection from reinfection.[95] In all, IgA ASC can be found in the blood and mucosal sites during an acute infection. However, it is not clear if mucosal IgA ASC differentiate locally or systemically and then migrate to the mucosal sites in acute illness.

Another study showed that RBD-specific ASC are released into the blood transiently during acute COVID-19 with high IgM and low IgG ASC frequencies.[106] However, these results may have been skewed with antigen-labeled flow cytometry which only select for ASC that retain surface BCR expression. From B cell to ASC differentiation, surface Ig receptors are often downregulated.[32,97] Interestingly, only IgM ASC preferentially express surface BCR compared to IgG ASC.[82] Hence, antigen-specific surface flow cytometry of ASC may neglect the majority of blood ASC in this infection.

3.4 | Memory B cell evolution and cross-variant reactive antibodies in COVID-19 infection

Understanding MBC specificity and kinetics is key to predicting durability of protection from reinfection. After infection, it is well-established that a strong MBC response is elicited. While most Ab response metrics decrease within 4-6 months, the frequency of circulating MBC remain relatively stable for 6-9 months after infection (including mild and asymptomatic),[36,42,52,107–109] and may even increase before plateauing during convalescence.[37,41,52,78]

It appears that even after viral clearance, the MBC response continues to mature. Perhaps more importantly, infection-induced MBC continue to accumulate somatic mutations over 12 months comparable to those acquired in other acute viral infections.[85,110] This maturation results in the emergence of unique clones and the production of memory Abs with increased affinity.[36,107,111] Although class-switched MBC evolved in both mild and severe COVID-19,[41,78,88] such affinity maturation might not be the same. For example, B cell repertoires in severe patients are enriched for clonally expanded and unmutated ASC and MBC clones, consistent with EF-dominant responses,[81] whereas in mild illness, they are characterized by clonally diverse and mutated MBC.[112] Evolution of MBC after infection was observed over 12 months together with persistence of GC after infection intimated antigen persistence.[36,42,113] Interestingly enough, some asymptomatic individuals 4 months after the onset of COVID-19 infection showed persistence of SARS-CoV-2 nucleic acids in the intestinal biopsies, demonstrating antigenic persistence.[36] With each new emerging mutant, whether MBC in the LN continue to rapidly evolve to generate higher affinity clones that

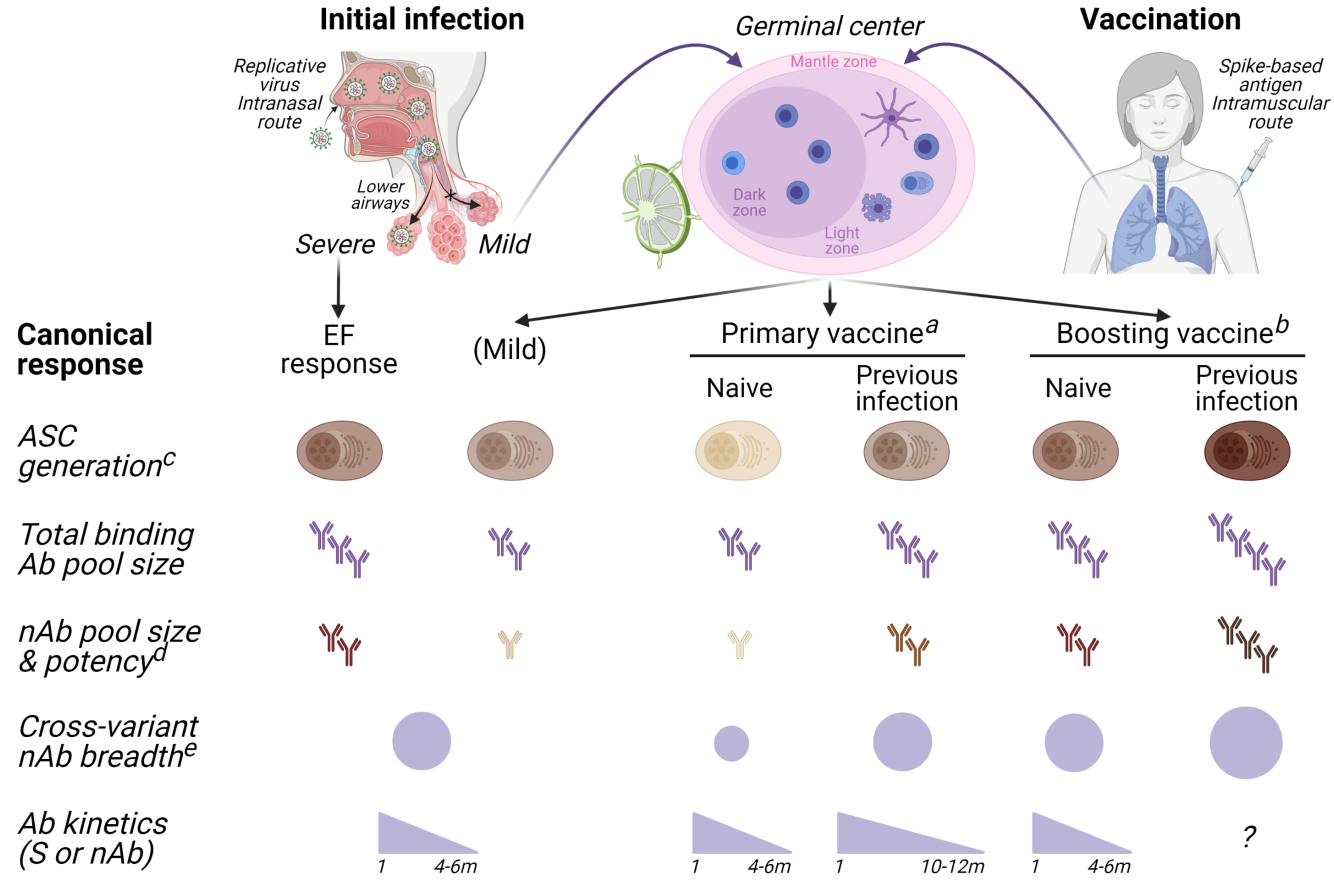

FIGURE 2 ASC kinetics and Ab effector functions during responses to infection with and vaccination against SARS-CoV-2. Initial infection induces ASC that produce virus-specific, low-affinity serum Abs. In general, mild infection, priming vaccination, or tertiary vaccination generates a GC response, by which the derived MBC undergo continued clonal evolution over 6-12 mo, leading to the production of more potent and broader nAbs. The frequency of ASC generally correlates with the magnitude of the serum Ab levels (total binding Ab pool size). Dose 1 vaccine induces a robust GC response resulting in the generation of virus-specific ASC (and MBC) including in infection-naive subjects and which is substantially enhanced either by Dose 2 (in infection-naive subjects) or in previously infected (recovered) subjects—and further enhanced by boosters (in infection-naive subjects). The highest total binding Ab production is observed in recovered, tertiary vaccinees. Dose 1 ignites potent nAbs (in about half the subjects) that are enhanced by Dose 2 and further enhanced by booters—against the wildtype but less potent against variants (decreasing cross-variant nAb potency). S-specific and nAbs wane over 4-6 mo following infection, although total binding Abs could be detected 18-20 mo post-infection. The nAb waning period of time in COVID-19-naive vaccinees also are usually 4-6 mo; it may last longer in previously infected subjects (i.e., 10-12 mo). Ab, antibody; nAb, neutralizing antibody; ASC, antibody-secreting cell; EF, extrafollicular; S, spike

could provide a stronger and more cross-reactive protection will require further study.

3.5 | Lack of bona fide LLPC in response to COVID-19 infection

High-affinity "memory" nAbs in the serum are the effector molecules of long-term protection. While ASC provide robust Ab response during the acute infection, tissue-resident LLPC in the BM are the cellular origins of such persistent "memory" Abs. LLPC secrete Ab continuously in the absence of antigen.[114] After mild SARS-CoV-2 infections, plasma cells specific for SARS-CoV-2 have been identified in the BM 7-11 months after infection.[45] However, BM niche is known to contain both LLPC and other shorter-lived subsets[32] (Table 1), and this study[45] did not demonstrate whether these viral-specific ASC were residents of the BM LLPC subset[32] (i.e., PopD; Table 1). Furthermore, the serologic data after acute infection[37,39,51,71–73,77] may not be consistent with the presence of LLPC, and thus, whether this infection generates bone fide LLPC still remains unknown (Figure 1).

3.6 | Transcriptional profiles of ASC in COVID-19 infection

ASC single cell profiling from COVID-19-infected patients is often sorted from total peripheral blood mononuclear cell (PBMC) samples.[115,116] Despite acute and recovered time points and known

TABLE 1 Phenotype of blood and bone marrow ASC subsets

Blood ASC subsets	Pop2	Pop3	Pop5
CD19	+	+	–
CD138	–	+	+
CD38	++	++	++
Bone marrow ASC subsets	**PopA (SLPC[a])**	**PopB (Intermediate)**	**PopD (LLPC[b])**
CD19	+	+	–
CD138	–	+	+
CD38	++	++	+

[a]Short-lived plasma cell.
[b]Long-lived plasma cell.

expansions, these cells are relatively rare in the blood. Therefore, single-cell studies using PBMC can at best enumerate the ASC, B cell, and other lymphocytes but have major limitations in understanding the transcriptional profiles of ASC due to the small number of ASC recovered from PBMC isolations. Using PBMCs, one study explored the transcriptional profile of ASC from COVID-19 during acute infection from those who shed virus <7 days versus <14 days and healthy adults. COVID-19 had higher percentage of ASC with significantly reduced naive BC frequencies as compared to healthy controls. As expected, they could only see higher level of B cell activation-related genes and ASC differentiation were upregulated in the COVID-19 patients.[115] Another PBMC study showed that ASC from a severe cohort had interferon responsive genes such as *FOS*, *IFI6*, and *MX1*,[117] suggesting the potential of EF B cell origins found in autoimmunity and recently described severe COVID-19.[81,118] However, the ASC numbers analyzed were small. Qi et al.[119] re-analyzed data from three published PBMC single-cell datasets from mild and severe COVID-19 and showed that metabolic genes regulating oxidative phosphorylation were expressed at highest level in ASC of severe COVID-19. Although interesting, the progressive upregulation this pathway had been previously appreciated in B cell to ASC differentiation.[120,121]

The novel single-cell technologies have proven to be extremely powerful in deeply characterizing the transcriptional profiles and the VDJ sequences of plasma cells. However, the rare frequencies of ASC despite their large expansions together with the propensity for apoptosis are the major technical limitations of further enriching this population for single-cell studies. Hence, using total PBMC isolations to study ASC on a single-cell level has many limitations. To properly analyze the heterogeneity of ASC subsets and their possible role in severe and mild COVID-19 infection, strategies for better enrichment will be needed to provide insights into the ASC metabolic, homing, survival, and maturation pathways to become a LLPC.

3.7 | Neutralizing versus non-neutralizing antibodies in COVID-19 infection

Neutralization is thought to be the main mechanism of immune protection to most infections, including SARS-CoV-2. This mechanism is achieved by blocking the engagement of the SARS-CoV-2 S protein to its cognate receptor ACE2. As expected, many nAbs target the RBD.[122,123] During severe COVID-19 illness, patients have higher levels of Abs and exhibit an oligoclonal ASC expansion.[86] Although higher nAb titers are seen in severe disease,[124,125] the potency of neutralization is actually associated with survival and favorable clinical outcomes.[126,127] Amanat et al.[128] showed that mRNA vaccines can elicit more potent antiviral polyclonal responses than those seen with infection, but vaccines can actually induce a majority of non-nAbs. While the benefits of nAb are known, the exact role played by non-nAbs is still under intense investigation.

Before vaccines were available, passive transfer with convalescent plasma was approved for clinical use. Concerns about potential risk of antibody-dependent enhancement (ADE) of infection in SARS-CoV-2 with non-nAbs were raised.[77,129–134] These concerns were based on evidence of that virus-specific Abs can promote cellular infection through Fc receptors. This phenomenon has been seen with several other endemic coronaviruses (eCoV),[135] including feline infectious peritonitis virus,[136] SARS-CoV-1,[137–142] and MERS.[143] Additionally, in SARS-CoV-1, Fc-mediated Ab function can skew macrophage activation to a more inflammatory state in the lung leading to tissue injury.[144] Furthermore, Abs against SARS-CoV-2 could facilitate viral entry into myeloid cells through Fc receptors in vitro.[145,146] Although studies have shown viral genetic and protein content inside macrophages,[147–150] there is still debate whether this cell type is permissive to productive SARS-CoV-2 viral replication.[151] To our knowledge, there is no evidence of clinically significant ADE with SARS-CoV-2 infection or vaccination.

In vivo animal models of SARS-CoV-2 infection have revealed that Fc-mediated Ab function improves disease outcomes and reduces viral replication. Consistent results have been seen in mice,[145,152–155] hamsters,[154] and macaques.[145,156,157] In humans, Fc patterns differentially correlate with disease outcomes. Patients with clinically more severe COVID-19 disease exhibited a more proinflammatory pattern of Ig Fc glycosylation than those with mild disease.[158,159] On the contrary, Fc-mediated antiviral functions of non-nAbs have also been observed in vitro, including antibody-dependent complement deposition (ADCD),[156] antibody-dependent cellular phagocytosis (ADCP),[152,156] and antibody-dependent cellular

cytotoxicity (ADCC).[160,161] ADCP was associated with lower inflammation and clinically milder COVID-19 than ADCD.[162] Interestingly, adults after mRNA vaccination have a distinct pattern not seen with infection.[159,163] This finding demonstrates how different immunity to vaccination and infection can be. In another study, Zohar et al.[164] showed that in severe SARS-CoV-2 infection, Fcγ receptor binding and Fc effector activity were compromised and associated with COVID-19 non-survivors.

Another potential protective mechanism of non-nAb is through the soluble Fcγ-binding protein (Fcγbp) located on mucosal surfaces. Fcγbp is a large molecular weight mucin-like secretory Fc receptor protein secreted by human goblet cells in the large and small intestine. Virus-Ab complexes can engage the soluble Fcγbp attached to mucin and facilitate viral clearance.[165] Fcγbp may be one potentially protective non-nAb functions in COVID-19, and there are likely other innate-like functions of non-nAb. In sum, although non-neutralizing, these Abs can cause pro- or anti-inflammatory based on different Fc functionalities.

4 | ASC RESPONSES TO SARS-COV-2 VACCINATION

4.1 | Primary vaccine series: nAbs are robust and predictive of vaccine efficacy (VE) but wane

The currently available COVID-19 vaccines use SARS-CoV-2S antigen and are developed from two distinct platforms: mRNA-based and adenovirus-based vector vaccines.[166] These vaccines exhibit high initial efficacy at preventing infections (91-95%) as well as hospitalization and severe disease (97%).[11,167-175] In addition to individual protection provided to vaccine recipients, massive vaccination could reduce community transmission,[176] although the absence of residual mucosal IgA with systematic vaccines may have hindered this potential benefit[177,178] (Figure 3).

Similar to SARS-CoV-2 infection, mRNA vaccination induces early and robust production of S-specific IgM, IgA, and IgG in the circulation[179-183] (Figures 2 and 3). The GC disruptions present in severe COVID-19 patients[81,84] are not observed after mRNA vaccination and active SARS-CoV-2-specific GC responses can detected for several months.[183] However, with vaccination, the expansion of ASC is often less robust compared to acute infections (i.e., average of 2-6% and mostly <20% of the total circulating B cells).[18,22-24] In contrast with infection that exposes the infected patient to epitopes across the entire viral proteome, vaccines only include S epitopes.[166] Therefore, as expected and unlike infection, vaccination incites a largely homogeneous S-specific response among vaccinees.[184-186]

After receiving the first dose of mRNA vaccine, about only half of the recipients produce nAbs, which, to most of the vaccinees, increase after the second dose.[187-189] In comparison with the two-dose mRNA vaccination strategy, the single-dose adenovirus vaccine used in the United States elicits lower S-specific Abs.[175,190,191] However, it sufficiently primes the immune system and provokes a durable humoral and cellular immunity lasting up to 8 months.[192] As with infection, serum binding S-specific IgG elicited by vaccination (both mRNA-based and adenovirus-vectored) positively corelate with nAbs[40,74-76,193-195] and are associated with VE.[74,193-196] Thus,

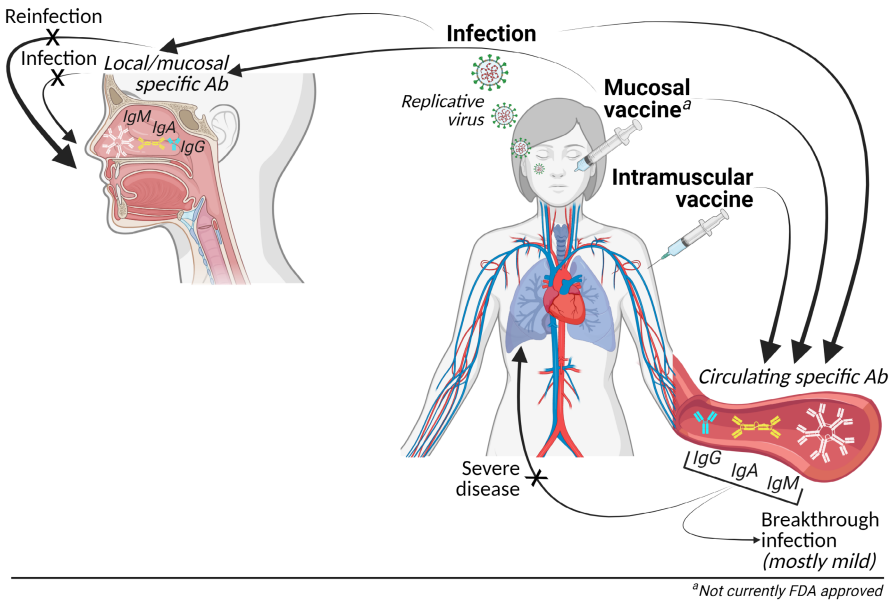

FIGURE 3 Mucosal and systemic antiviral responses after SARS-CoV-2 infection and vaccination. Mucosal exposure to viral antigen (by natural infection or by intranasal immunization) leads to in situ as well as systemic activation of virus-specific adaptive immune cells. With intramuscular immunization, mucosal exposure to antigen is not present, therefore, only generating systemic but not mucosal immune responses. With mucosal antigen exposure, there is generation of tissue-resident memory lymphocytes and ASC that locally prevent infection upon subsequent virus exposures. Without mucosal responses but in the presence of systemic antiviral responses, there is protection against severe disease but less so against the early infection at the mucosal entry site. Ab, antibody; BTI, breakthrough infection

like infection, nAbs have been identified as a surrogate marker/predictor of VE.

Consistent with epidemiological data of VE, S-specific binding and neutralizing Abs induced by vaccination exhibit a time-dependent reduction.[12,13,74,174,197,198] Moreover, most ASC undergo apoptosis rapidly after their peaks in peripheral blood (i.e., 5-7 days post-induction), resulting in a sharp fall of total Abs.[20,23,24,32,114] Ab waning often occurs within 4-6 months, yet it starts to become evident at 3-10 weeks after the second dose.[199] Ab decrease is more profound in immunosuppressed patients[13,200] and exhibits a more intense decline in the older individuals.[13,179,201–203] Nevertheless, Abs (including nAbs) may still be detected 6-8 months post-vaccine.[192,204]

4.2 | Breakthrough infections with waning Abs and emerging immune-escape variants

Vaccine breakthrough infection (BTI) refers to individuals who get infected 2 weeks or more after the initial vaccination series. Despite the initial high VE against infection, BTI cases of COVID-19 have become increasingly common—first by the Beta variant,[205,206] then quickly followed by the Delta variant,[13,174,197,207–215] which emerged in the late spring–summer of 2021,[6,8,216,217] and currently with the dominating Omicron variant.[7]

While there is a significant reduction in VE (54-85%) with most variants, numerous observational studies suggest that VE remains substantial (90-100%) against hospitalization and severe infections.[8,12,206,218–221] Despite high viral loads and persistent viral RNA shedding, BTI are mostly mild or asymptomatic[209,222] and are associated with substantially lower risk of developing long COVID symptoms than infections in unvaccinated individuals.[223] The facts that most BTI are associated with lower disease severity[8,209,222,224] suggest that nAbs elicited by wildtype antigens remain protective against severe infection to SARS-CoV-2 variants. Nonetheless, such protection of severe disease in BTI may be attributed to vaccine-induced S-specific T cell responses, as variants can evade Abs but not the T cell immunity.[225–230] Of note, in addition to nAb evasion and waning immunity, the lack of protective mucosal IgA mucosal in the setting of mRNA-based (i.e., intramuscular) vaccination[177,178] might also be a contributing factor in BTI (Figure 2).

The antigenic variants that emerge and become the predominant strain are mostly those that escape pre-existing immunity. Compared with the wildtype, the Alpha, Beta, Gamma, and Delta variants exhibit a several-fold drop in vaccination-induced nAbs[231–233] (Table 2) that further decreases over time.[53] Moreover, VE against variants is predicted to lose more than half of its power at 12 months,[231] which may explain the BTI and reinfection with variants are increasingly occurring.[70,206,234,235]

All this was further complicated by the emergence of Omicron in the fall of 2021. Once identified, this highly transmissible Omicron variant spread rapidly worldwide and by mid-winter it accounted for nearly 100% of new US infections.[7] Compared to the ancestral strain, Omicron has 56-60 mutations throughout its genome (Table 2). Of these mutations, 31-37 are in S with 15-16 of those in RBD.[236,237] While RBD accounts for only 15% of S, it is the target of over 90% serum nAbs.[123] Importantly, 8-10 of the 15-16 RBD mutations are present in receptor-binding motif (RBM), which directly interacts with ACE2 receptor (and most monoclonal nAbs).[236,237] For comparison, Delta and Gamma have 10-12 and 12-13S mutations—with 1-3 and 3 localized in RBD, respectively.[237] Consequently, Omicron-specific nAbs are low or undetectable in individuals that had previously had infection to other strains or have been vaccinated with wildtype S. This makes Omicron very effective at evading immune responses and VE drops to 57% with this variant.[210,238–240] Omicron also escapes 85% of existing monoclonal nAbs.[241] Vaccination, with or without a booster, provides better protection against Delta than Omicron,[238,240] but BTI with Delta are associated with higher disease severity than with Omicron.[221]

4.3 | Booster vaccines increase nAbs and reduce infection with nAb-escaping variants

The rapid waning of VE (and correlatively, nAbs) and the everchanging SARS-CoV-2 have made necessary the implementation of an additional vaccine dose. This is usually a third dose called a booster for mRNA-based vaccinations (or a second dose after the one-dose adenovirus vector vaccine regimens). This approach of a COVID-19 booster vaccination (administered 5-9 months after the two-dose regimens) has shown to reduce the infection risk, severe illness, and deaths,[238,240,242] including older individuals[243–245] and immunosuppressed patients.[246] It also more rapidly decreases the viral RNA loads in patients with BTI and temporarily restores the declining immunity previously evoked by two-dose vaccination.[210,211] Regardless of the type of initial and vaccine technologies used, boosters substantially raise the levels of binding Abs (by 5-fold to 55-fold) and of cross-variant nAbs (by 4-fold to 73-fold) against multiple strains, including Beta, Gamma, Delta, and Omicron.[231,238,247–250] Importantly, the highest nAb production against Omicron is observed in BTI with Delta (i.e., infection on two-dose vaccination) or two-dose vaccinated convalescent individuals,[251–253] emphasizing the superior neutralization potency of hybrid immunity against immune-evading variants. Boosters can also potentially decrease the BTI infectiousness risk (i.e., disease transmission by variants).[210,239] Even though boosters contain wildtype S, they can restore waning immunity and expand its breadth, possibly prolonging protection against reinfection with either the ancestral strain or variants.

4.4 | Memory B cell responses in COVID-19 vaccination

Like infection, primary vaccination against SARS-CoV-2 also provokes a strong MBC recall response and with booster vaccines eliciting expansion of MBC that rapidly enhance production of cross-variant nAbs.[183,247] Similarly, the frequency of circulating MBC

TABLE 2 Protection induced by homologous vaccine boosting or wildtype virus infection against evolving SARS-CoV-2 virus

Variant of concern	Wildtype	Alpha	Beta	Gamma	Delta	Omicron
Sequence mutation[a]						
Genome	–	25-26	22-23	25-26	24-36	56-60
S	–	10-11	10-11	12-13	10-12	31-37
RBD	–	1-2	3-4	3	1-3	15-16
RBM	–	1-2	2	2	1-3	8-10
nAb potency[b]	+++++	++++	++	+++	+++	+
Vaccine- or infection-induced protection[b]	+++++	++++	++	+++	+++	+

Note: Natural infection with wildtype SARS-CoV-2 virus or receipt of a homologous vaccine booster after completion of the two-dose wildtype S-based vaccine series induces nAb potency (and hence, protection) of the highest level against the wildtype virus, which decreases gradually against variants of concern. In general, the most or the least reduced protection is observed in the variant bearing the most numerous or the least numerous numbers of mutations, respectively, in RBD/RBM sequence (i.e., most epitopic changes or more conserved epitopes, respectively). It is the generated MBC that increase in the number and continue to clonally evolve for at least 6-12 mo after (mild) infection or upon boosting that give rise to Abs with higher potency and broader breadth in neutralizing activities against the evolving virus. See texts for detail. Sequence mutation is retrieved from https://covdb.stanford.edu/page/mutation-viewer/.

Abbreviations: nAb, neutralizing antibody; RBD, receptor-binding domain; RBM, receptor-binding motif; S, spike.

[a]Varies by sublineages.

[b]By homologous boosting (3rd dose) or wildtype virus infection; the more (+), the stronger.

remains relatively stable for 6-9 months post-vaccine.[181] In contrast to infection where class-switched MBC continuously evolve over time,[36,42,113] the evolution of vaccine-generated primary MBC is either little or no change in the blood or secondary lymphoid organs weeks after the second dose.[111,113,254]

4.5 | Lack of bona fide LLPC in response to COVID-19 vaccination

To be long-term effective, a vaccine must generate LLPC, which deliver durable recall protection through constitutively secreting circulating "memory" Abs as a rapid primary response. In reality, not all vaccines generate and maintain LLPC. For example, while tetanus, smallpox, or MMR vaccines offer long-lasting protection (i.e., long-lived vaccines: LLV), pneumococcal 23-valent (PSV23), hepatitis B, or influenza vaccine confers short-lived efficacy (i.e., short-lived vaccines; SLV).[27,255–258] Although the mechanisms for LLV and the generation and maintenance of LLPC remain poorly understood,[34,114] infections with a whole, replicative virus often induce long-lasting response even though viral Ag component-based vaccines usually lead to short-lived immunity.[114]

Concerns have been raised that COVID-19 vaccines more likely belong to the SLV group.[259–261] The acquired humoral immunity rapidly waning within 4-6 months after completing two-dose and post-boosters (i.e., VE decreases to 66% and 78% within 4 months[262]) (Figure 2) is inconsistent with LLPC being generated and maintained. Indeed, mRNA vaccination, instead of consistently provoking a primary LLPC response, may just trigger a secondary recall.[113,260,263] The nature of such recall response might be that of immunity conferred by pre-existing cross-reactive MBC and cross-reactive memory T cells,[263] which were previously elicited from prior vaccination[113] or previous eCoV infection), which may be mostly non-neutralizing and non-protective against the newest virus.

In a single study, mRNA vaccines are reported to induce persistent GC reactions that last for months,[183] where blood circulating ASC peak around 3-4 weeks and decline until becoming virtually absent at 7 weeks. The presence of genuine LLPC is again not entirely evident.[16,32,103] Surprisingly, S-specific GC B cells and ASC residing in LN are detected for up to 6 months post-vaccination.[254] At this time point, when Ag-specific MBC are formed and display levels of mutation similar to the GC-derived clones, highly mutated S-specific ASC are present in the BM.[254] If persistent GC reactions and possibly reactivation of pre-formed MBC are ongoing for up to 6 months (which is a very long time for typical GC activities),[254] they would keep seeding the BM with newly generated ASC. Hence, it is crucial to consider not only the presence of those newly generated ASC but also the actual timing of their arrival in the BM. Additionally, identification of ASC within the BM compartment does not necessarily mean they are LLPC due to the heterogeneity of the plasma cells in this site.[32] Consequently, new ASC arrivals in the BM may not have sufficient time to mature. Thus, BM samples collected within months post-infection or post-vaccination may or may not become LLPC. Currently, there are no sequential studies to assess the actual timing of newly generated ASC and their arrival in the BM. Moreover, there are no immune correlates of durability which can only be conclusively determined by a tincture of time. Thus, like natural infection, definitive evidence of bona fide LLPC[16,32,103] in response to vaccination against SARS-CoV-2 is currently lacking. This potential absence of vaccine-induced LLPC might indeed be one of the reasons for reinfections and BTI within months.[68]

4.6 | Transcriptional profiles of ASC after vaccination

The exact mechanism of the efficiency of mRNA-based vaccines against SARS-CoV-2 remains largely unclear. Recent studies have tried to resolve this query by characterizing the transcriptional profile of ASC post-vaccination. Studies have shown that the first dose generated polyclonal non-neutralizing IgA-dominant ASC response with some S2-specific plasmablasts with low SHM, whereas the second dose provided neutralizing B cell responses to S1 with RBD.[264,265] A mass cytometry-based study identified expansion of metabolically active, class-switched plasmablasts expressing CD71, CD98, and cytochrome C between day 0 and 28 post-vaccine.[266] Similarly, Amanat et al.[128] reported that some of the isolated S2-specific mAbs had cross-reactivity toward human coronaviruses, suggestive of recall responses which were initially induced by seasonal beta-coronavirus exposure. To support this model, some of the cross-reactive mAbs showed extensive SHM. Ultimately, NTD and RBD antibodies co-dominated the response induced by SARS-CoV-2 mRNA vaccination, indicating alternative targets for vaccine.[128]

Although abovementioned studies have provided the initial characterization of ASC response after vaccination, they are mostly qualitative using PBMC,[267,268] thus resulting in the same limitations as previously described in single-cell analysis of ASC after infection. Furthermore, these studies are devoid of transcriptional comparisons of ASC between SARS-CoV-2-infected and vaccinated individuals but enumerate ASC subsets within total PBMC populations. For example, the CITE-seq-based study showed an enrichment of plasmablasts in COVID-19-infected patients but not after vaccination.[268] This may have resulted apoptosis of ASC using frozen PBMC. From the limited number of plasmablasts, these studies showed that COVID-19 patients were enriched in oxidative phosphorylation, type I and type II IFN responses, fatty acid metabolism, and mTORC1 signaling genes as compared to healthy donors. Additionally, plasmablasts of mRNA vaccinated and healthy donors were transcriptionally overall similar except for TNF-NFkB pathway activation. A similar observation was made where volunteers were vaccinated with inactive COVID-19 vaccine.[267] Although interesting, limited numbers of ASC analyzed would require further validation with enriched ASC populations.

5 | HYBRID IMMUNITY IN SARS-COV-2 INFECTION AND VACCINATION

5.1 | Local vs systemic protection: Abs at the viral entry site

While infection incites a specific mucosal response dominated by potent neutralizing IgA early on at the site of viral entry,[95] intramuscular vaccines only lead to the production of circulating but not residual mucosal IgA[177,178] (Figure 3). However, intramuscular vaccines can induce virus-specific IgG in the upper respiratory mucosal sites.[269] With intranasal (adenovirus-vectored) vaccines, both circulating and mucosal IgA are accelerated to protect against infection and transmission in animals,[270] similar to mucosal immunity after infection. Altogether, as protection is not a single outcome with conclusive correlates, it would be important to understand the durability of both mucosal and systemic humoral responses.

5.2 | Protection conferred by vaccination versus infection: equivalent, superior, or inferior?

To control reinfection at both population and individual levels, it is essential to understand whether protection elicited by vaccination might be more durable than by infection.[271] Initially, high levels of protection (>90-95%) against reinfection were observed equally after vaccination[11,167–174] and infection,[69,235] in part due to similar early decay rate of nAbs after infection and vaccination (approximately 60 days).[74,179] Also, similar protective Ab response was also observed between individuals after two vaccine doses and those who had a previous COVID-19 infection after only one vaccine dose.[272] Thus, protection elicited by vaccination and infection originally appeared to be relatively equivalent.

While infections with the 1918 influenza pandemic virus elicited life-long protection,[3] after influenza vaccines, humoral immunity rapidly declines within 6 months.[273] For COVID-19, protective immunity conferred by vaccines was most sufficient within 2 months, although it may last 4-6 months.[11,167–174] Immunity after infection appeared to last 4-9 months.[36,69,186,235] However, observational studies suggest prior infections, especially those caused by Delta, drove greater protection against reinfection and severe disease than did full vaccination at 3-8 months.[14,70,274,275] The reinfection risk among the survivors from initial infection drops remarkably by 80-95% over 6-9 months and even at 12 months.[54,67,69,235,276–280] Even if patients were reinfected, they had lower incidence of severe disease. Thus, protection elicited by infection may be superior.

On the contrary, other studies suggest vaccines may provide better protection. For example, cross-neutralization occurred sporadically in the sera among previously infected patients but if previously infected individuals are vaccinated, nearly all developed cross-neutralizing titers against multiple variants.[281] Immunization of non-infected patients also elicited cross-neutralization but at lower rates. Yet, another study showed that there was higher fold reduction of neutralization titers to new spike variants in patients with history of COVID-19 infection vs vaccine recipients.[282] Additionally, and in favor of vaccination, an epidemiologic study of COVID-19-hospitalized infections showed 5.5 times higher rates among previously infected patients compared to fully vaccinated adults within 90-179 days after infection or vaccination.[283] Prior to the circulation of Delta, COVID-19 infections were higher among persons who survived previous infection, suggesting that vaccination appeared superior; however, when Delta became the predominant circulating strain, case rates were higher among persons who were vaccinated compared to those who survived previous infection, demonstrating

immunity from infection was indeed superior.[221] Whether this is true also for Omicron will require further study.

The differences between infection versus vaccine-induced protective durability may be influenced by several immunological factors. The different aspects may drive MBC evolution and selection to distinctive Abs. For example, infection-induced MBC appears to undergo greater affinity maturation than those induced by vaccination, possibly generating more robust and durable immunity.[36,42,107,111,113] Antigen persistence in infection is weeks while for mRNA vaccines, it is days.[36] The route of Ag delivery probably plays a role with mucosal routes in infection and intramuscular with the current mRNA vaccines. Infections with its sundry of proteins in the intact virus compared to the adynamic pre-fusion S in the vaccines likely also manifests different immune responses.[284] In sum, while infection-induced immunity may be generally superior to vaccine-elicited one,[114] virtues of immunity provided by vaccination in addition to protection from infection can be appreciated.

5.3 | Hybrid immunity confers better protection than vaccine or infection alone

Hybrid immunity, which is induced by prior infection in combination with vaccination, may drive stronger and longer-lasting protection against reinfection and severe disease compared to either immunity from infection or vaccination alone during 3-8 months from induction. During the Delta-virus surge in the summer 2021, previously infected persons who received the vaccine were protected against reinfection and severe disease better than adults who received just two doses of the vaccine.[14,70,274,275,285,286] Although all immunity wanes, vaccination after infection induced a rapid nAb titer which had higher cross-variant neutralizing activity compared to healthy adults after just two vaccine doses[42,107,187–189,197,272,281,287–290] (Figure 2). Also, BTI significantly enhanced Ab responses to elevate IgA production (possibly owning to the intranasal route of Ag exposure) and broaden cross-nAb potency against variants.[291] Importantly, hybrid immunity appears the most protective against Omicron, which is the most mutated and most immune evasive variant to date.[5,251–253,292,293] Overall, hybrid immunity appears to offer an immune response that is more robust, more durable, and with the best cross-variant neutralization than immunity from vaccine or infection alone.

6 | THE ASC RESPONSE IN COVID-19: PREDICTING LONG-TERM ANTIBODIES

6.1 | Protection is not a single outcome but correlated with nAbs that wane

The long-term control of the COVID-19 pandemic depends on understanding durability of protection, which is based on memory induced by infection and/or vaccination. Protection against symptomatic reinfection and severe illness is normally assessed epidemiologically since a single immune outcome is not available. Immune protection is likely attributed by multiple aspects of memory responses involving dynamic interplays of viral replication and pathogenesis with key humoral and cellular components that include Abs, B cells, and T cells (and secreted products).[195,225,229,294,295] The current lack of standardized or consensus quantitative Ab (particularly nAb) assays across studies further complicates this assessment.[296]

Although Ab responsiveness represents only a partial picture of the overall immune responses, the magnitude of serum nAbs in most viral infections and vaccination is highly predictive of protection against reinfection.[74,126,297] Immunologically, this effect is based on nAb functions which are to block the entry of virus into its target cells through binding viral surface Ag epitopes. Indeed, the success of vaccines to date has relied on nAbs. For SARS-CoV-2, passive transfer of monoclonal nAbs, which mostly recognize viral RBD,[298–300] offers protection against infection and severe disease in outpatients[301] and macaques.[229] nAbs can contribute to over 68% vaccination-induced protection.[195] Moreover, in severe disease, fatal outcomes are associated with the delayed nAb kinetics.[302] Overall, nAbs are positively correlated with protection against symptomatic (not asymptomatic) reinfection and severe disease.[126] Thus, while MBC have recently been proposed to serve as an indicator of protection beyond declining nAbs, nAbs may be a surrogate measure of protection in COVID-19.[303,304]

6.2 | Predicting long-term Abs against SARS-CoV-2: lessons from endemic coronaviruses

The maintenance of long-term protection in COVID-19 can only be conclusively defined with the passage of time. However, as SARS-CoV-2 and other coronaviruses, including SARS-CoV-1, MERS-CoV, and eCoV, are related phylogenetically and antigenically, the natural history and immune durability of coronaviruses may provide insights to predict potential outcome for SARS-CoV-2. eCoV circulate worldwide and elicit SARS-CoV-1-specific MBC (and memory T cells) in many adults.[263,305–308] Durability of the response to eCoV varies significantly and is also strain-dependent.[309] Most infections with eCoV, such as OC43, NL63, 229E, or HKU1, as well as SARS-CoV-1 and MERS-CoV, led to Ab responses that last for only several months,[310,311] although some wane within 12-18 months.[306–308] Thus, they were thought to be short-lived. However, one report showed they persist for up to 3 years while another suggested longer durability but they were just modeling studies.[68,312,313] SARS-CoV-1 nAbs appear 5-10 days post-symptom onset[314] but may wane even more rapidly than total Ag-specific Abs, raising questions whether there is humoral durability after infection with any coronavirus.[312] During initial SARS-CoV-1 outbreaks, nAbs were detected for 16-24 months.[306–308,312,315] Using linear mixed models, Ab levels associated with protection against reinfection last 1.5-2 years.[74,316] In sum, it is not clear that after infection life-long protection is maintained with coronaviruses.

6.3 | Original antigenic sin and how pre-existing immunity affects SARS-CoV-2 antibodies

After 2 years into the pandemic and the widespread administration of vaccines, the immune landscape of COVID-19 is ever changing with a variety of MBC responses among individuals with vaccine-induced, infection-induced, or hybrid immunity. Questions arise whether MBC are always helpful or can be potentially harmful to new emerging variants. Original antigenic sin (OAS) refers to an immunological phenomenon when the recall immunity generated by a previous strain dominates over the primary response to the new virus, resulting in potentiating disease severity.[317] Dominance of pre-existing Abs that cross-react but do not likely neutralize the novel virus actually interferes with effective responses to the new infection. The best example of OAS is perhaps the 1918 influenza pandemic, which explains the increased morbidity of young adults. Recent studies suggest that these deaths may have resulted from past MBC responses, causing a rapid EF ASC response to the old but similar virus and delayed new naive B cell responses to the new viral subtype to mediate effective viral clearance. OAS is also known by various terms, such as immunological imprinting, Ag imprinting, Ag seniority, negative interference,[318] and recently, back-boosting.[319] For SARS-CoV-2, it is not clear if OAS will be problematic as new emerging variants arise; thus, close attention will be required.

eCoV, such as 229E, NL63, OC42, and HKU1, are among the most common causes of respiratory infections worldwide.[263,305–308] The pre-existing eCoV-specific MBC may be cross-activated upon SARS-CoV-2 exposure, which might influence the subsequent response to SARS-CoV-2 infection[263]—and probably vaccination.[113] While antigenic imprinting appear to be common and associated with disease severity in COVID-19, their overall protective impact has to date been largely neutral. In general, no protective correlation is observed,[320–325] which is likely due to the inability of the raising eCoV-specific Abs to normally neutralize the new virus.[35,323] However, cross-reactivity induced by recent eCOV infection could be relevant clinically as it can lessen disease manifestations[322,323] or facilitate faster recovery in COVID-19.[326] Notably, children develop robust and stable cross-reactive Abs beyond 12 months, which may be linked to their often milder or asymptomatic COVID-19.[327] Of note, recent in vitro studies using human FcγR-expressing cells suggest that these cross-reactive Abs may be worse than non-protective since they can induce ADE of infection with SARS-CoV-2 virus in these cells.[325,328] Whether this in vitro phenomenon is relevant to patient disease is not known. In sum, infection with SARS-CoV-2 enhances pre-existing, eCoV-specific Abs that are cross-reactive but mostly non-neutralizing against the new virus, unveiling in COVID-19 an OAS response that is often poorly protective and potentially harmful. In all, the current serum assays to study OAS are severely limited since serum cannot distinguish newly generated Abs arising from newly minted ASC from Abs secreted by previously established plasma cells in BM and spleen.

7 | AUTOREACTIVE FEATURES OF ASC AFTER SARS-COV-2 INFECTION

7.1 | Extrafollicular B cells in COVID-19 infection

An increasingly important component in the investigation of primary humoral immunity has revolved around the identification of non-canonical B cell activation pathways that initiate outside of traditional GC structures[329] (Figure 1). First described in mouse modeling of infectious disease,[330] the EF response pathway was initially described as an expedited pathway to the generation of short-lived ASC responsible for the earliest waves of Ag-directed Ab production. However, over the past decade, this model has developed nuance, with evidence that EF pathway effectors can undergo SHM and contribute in a limited manner through both the generation of EF-derived memory and LLPC generation.[331] These findings implicate the need to view the EF pathway as a potential integral component in all phases of immunity, not just in acute response. As such, understanding of primary B cell and ASC development requires careful evaluation of both GC- and EF-derived pathway activation.

While the balance of these pathways has been relatively limited in primary viral infection prior to the COVID-19 pandemic, extensive work in autoimmune disorders such as systemic lupus erythematosus (SLE) has revealed that disease severity in these patients is directly correlated with the extent of EF response bias. These responses are easily recognizable through the emergence of two t-bet-driven effector B cells—CD11c+IgD+CD27-activated naive (aN) cells and $CD11c^{+}IgD^{-}CD27^{-}$ double negative 2 (DN2) cells.[118] Both EF populations can be identified as expanded circulating components in patients with active/flaring autoimmune disease and have been directly linked by repertoire analysis to the expanded ASC populations that are widely identified in SLE as pathologic components of disease.[332] Importantly, ASC resulting from EF-dominated B cell responses in those disease systems have undergone low levels of SHM, low levels of negative selection, and have been directly linked to the emergence of self-reactivity within the humoral compartment.[332] Though both pathways can contribute to the formation of long-term memory and persisting humoral immunity, their relative dominance in an ongoing immune response has important implications.

While extensive mouse studies had established EF response activation as an important component in both primary infections and autoimmune models, its relevance to human infectious response had remained less clear due to the difficulty in establishing primacy in severe primary infection. Studying naive-derived responses to previously circulating seasonal viral infections in humans were often challenging to interpret due to unknown infection history and background memory B cells. However, the emergence of SARS-CoV-2 provided a unique opportunity to study a single primary "natural" viral infection in the global human population. Early in the pandemic, a lack of effective immunomodulatory therapies allowed scientists to observe the 'natural' response courses in infected individuals, studies which would not be possible today. Employing emerging

technologies including high-dimensional flow cytometry,[333] single-cell RNA sequencing,[334] VDJ repertoire analysis,[110] and advanced serological screening methods,[40] several groups, including our own, took advantage of these unique circumstance to characterize the natural development of B cell responses across a spectrum of primary viral disease severity.

7.2 | Autoreactive features of COVID-19-induced ASC

Despite early speculation that disease severity might correlate with a failure of B cell development and antibody production, these concerns proved unfounded with early reporting of nAb titers across a spectrum of disease severity in the acute and recovery phase of COVID-19.[335] These serologically based studies were rapidly bolstered by cellular analyses identifying ASC expansion as a critical feature of patients with severe disease.[333] Importantly, dimensionality reduction and clustering analysis contained within that work revealed some indications of EF response intermediates in patients with highly expanded ASC, although a lack of markers dedicated to B cell classification made positive identification difficult. This robust ASC expansion was reminiscent of previous work in dengue where severe viral infection resulted in rapid ASC responses,[18] suggesting that the observed responses to COVID-19 may not be entirely unique. To further probe these responses, our group made use of directed B cell panels tuned to the identification of EF activation pathways to investigate emerging B cell responses across highly characterized patient groups with both mild/moderate and severe/critical COVID-19. Surprisingly, the responses identified were highly similar to activation profiles seen in patients with chronic autoimmune disorders[81], whereas mild/moderate patients displayed relatively modest activation of the EF pathway, expanding transitional B cell populations and unswitched memory compartments. Analysis of severe disease revealed significant increases in aN, DN2, and ASC compartments, similar to the B cell compositions identified in SLE patients with high-activity.[81]

In addition, serum collected from these patients revealed an important hallmark of reduced peripheral tolerance with increased circulation of antibodies derived from B cells expressing IGHV4-34 as a component of the BCR. This is significant because in germline configuration, these antibodies contain an inherent capacity for self-targeting.[336] In healthy individuals, while IGHV4-34^{+} clones can be readily identified in the naive B cell compartment, they are either negatively selected due to self-reactivity, or "redeemed" through SHM that eliminates the self-reactive potential of these clones.[337] Loss of this peripheral tolerance enforcement had been previously identified in flaring SLE and linked directly to the emergence of new autoreactivity.[332] This finding combined with extraordinarily low SHM frequencies identified by our group and others[110] within the ASC compartment were strongly suggestive that the course of severe infection may reflect some of the biology previously characterized in the context of autoimmune disease. This possibility of emerging autoreactivity was supported by several early reports of self-targeted antibodies against phospholipids,[338] nuclear antigens, and immune components such as type 1 interferons.[339]

However, despite the indications that some ASC targeting may be self-directed, patients displaying strong activation of the EF pathway nonetheless displayed higher levels of nAbs at early time points during acute infection whereas mild/moderate disease had more memory-oriented B cell composition.[81] Indeed, direct testing of individual ASC clonotypes emerging from this low-selection environment displays high specificity to the virus with more than 65% confirmed as SARS-CoV-2 specific.[82] However, despite this specificity, these cells are also prone to self-reactivity with clonotypes capable of binding nuclear antigens, naive B cells, and even glomerular basement membrane, a target often associated with pathology of the kidney and lung. Interestingly, these features appeared independently controlled. Individual clonotypes could display viral binding alone, self-reactivity alone, or even both.[82] Thus, these findings are consistent with a general reduction in negative selection thresholds and suggest that documented emergence of autoreactivity in these patients is more likely a function of altered tolerance than the result of molecular mimicry or non-specific clonal activation.

In patients with mild illness, a lack of these low-mutation ASC clonotypes together with lower levels of identified autoreactivity suggests that these features of ASC selection are highly responsive to the local developmental microenvironment. In this model, the EF response pathway could be envisioned as an emergency response mechanism. Under highly inflammatory conditions (reflecting severe viral illness), the slow process of GC-based B cell selection would be suppressed or even suspended[84] in favor of EF activation for the purpose of rapid antibody production and infection control. Previous work in mice suggests that even in these EF responses positive selection is likely to guide clonotype inclusion, thereby ensuring that the overall ASC mobilization will be generally viral specific. However, autoreactive clonotypes that have escaped central tolerance would also have the opportunity to respond under these circumstances, ultimately resulting in a mix of self-reactive and viral-reactive ASC pools. These mixed antibody responses, while actively and effectively participating in viral clearance, may also contribute to the overall inflammatory environment through innate activation and self-targeting to create a feed-forward loop of EF response bias (Figure 4). Ultimately, this bias may result in mounting tissue damage. Perhaps more interesting is how engagement of multiple antigens due to poor negative selection might combine to drive low-affinity clones toward response inclusion, although extensive molecular and cellular study would be required to confirm this phenomenon.

7.3 | Post-acute sequelae of SARS-CoV-2 infection (PASC) and the role of auto-Ab responses

Long COVID-19 syndrome (LCS), COVID-19 long hauler, post-acute COVID-19, long-haul COVID-19, or chronic COVID-19 is all terms referring to post-acute sequelae of SARS-CoV-2 infection (PASC). The

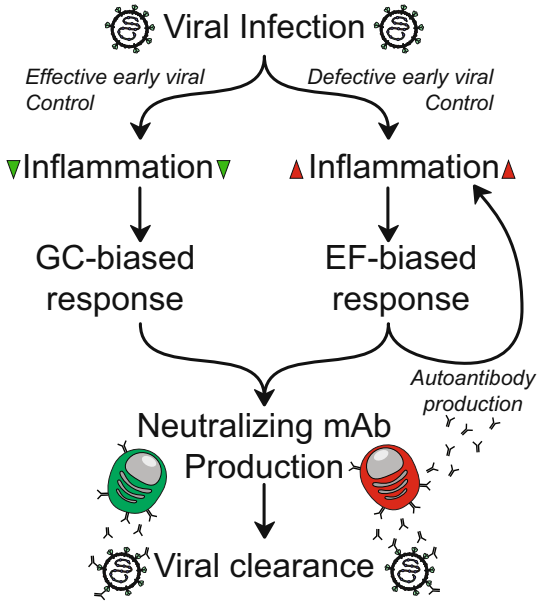

FIGURE 4 Model of autoantibody feedback. B cell activation pathway bias in COVID-19 is dictated by early viral control. (Right) High-inflammation microenvironments due to poor viral control drive EF-biased responses that, while rapidly generating neutralizing Abs, can result in autoantibody production through relaxed tolerance enforcement. These autoantibodies may contribute to inflammation and tissue damage, potentially reenforcing EF-biased response

incidence and prevalence of PASC are difficult to determine given that these non-specific symptoms overlap with other clinical conditions.[8,340,341] However, PASC is becoming one of the most important healthcare problems of our time.[341] Since SARS-CoV-2 infection can elicit auto-Ab responses, especially in those critically ill,[82] whether the autoimmune responses during the acute phase of infection persist to contribute to the pathogenic mechanisms in PASC is not known.

Targets of these auto-Abs have been documented to include self-Ag seen commonly in autoimmune conditions[342–345] and some have with molecular homology with SARS-CoV-2.[346] Some identified targets included phospholipids,[347–349] cytokines,[343,345] and type 1 interferons.[343,344,350] The disruption of these targeted self-molecules could potentially explain procoagulant states, immune dysregulation, and the weakened antiviral responses, respectively, conditions commonly observed in COVID-19.[351] Some researchers[352] have even hypothesized that anti-idiotype auto-Abs against SARS-CoV-2-specific Abs could structurally resemble the SARS-CoV-2 S epitopes with the potential to cause cellular dysfunction by engaging its cognate receptor ACE2. Notably, anti-ACE2 auto-Abs have been reported in COVID-19.[346] These proposed anti-idiotype Abs would also be able to induce ADCC if the appropriate Fc functionality is present. It is still unknown whether the generation of auto-Abs during acute infection correlates with PASC, but evidence is starting to emerge that patients with PASC harbor auto-Abs for longer than the acute infection process,[342,344,347] and overall immune perturbations last longer than the acute period.[353] Interestingly, SARS-CoV-2 mRNA vaccination does not appear to trigger auto-Ab responses.[354]

Forecasting who will eventually develop PASC could be helpful in anticipating complications and possibly directing treatment. Prediction models of self-reported symptoms and immune parameters have been suggested.[355] One showed particular IgM and IgG3 subclass signatures[356] and another one utilized a complex multi-omics analysis to show that during acute illness, auto-Abs and Th1-like responses, along with type 2 diabetes, SARS-CoV-2 viremia, and Epstein–Barr virus viremia may anticipate PASC.[344] Interestingly, the study also showed a signature of atypical memory B cells which were likely the previously described T-bet driven DN2 in SLE and severe COVID-19.[81,118] Ultimately, a better understanding the longevity of autoreactive ASC after EF-biased responses after acute COVID-19 infection may provide insight into one immune mechanism of PASC.

8 | CONCLUSIONS

After 2 years into the COVID-19 pandemic, we are still witnessing an ongoing "arms race" between an everchanging SARS-CoV-2 virus and an evolving immunity induced by infection or vaccination. Much progress has been made in understanding the cellular origins of such responses yet many questions remain unanswered about the durability of long-term protection. A better understanding of the balance between the EF and GC responses and the phenotype of ASC for the generation and maintenance of LLPC after infection and vaccination are still needed. The role of antigenic imprinting with each new emerging mutant will also be essential to develop a nimble vaccine strategy together with viral surveillance. Scientifically, the pandemic has proven itself to be an unprecedented opportunity to understand the immune response to primary viral infections. With the deep immunological insights of B cell and plasma cells, we will be prepared for the next one which is not a matter of if but when.

AUTHOR CONTRIBUTIONS

DCN, PAL, MCW, ASS, KEF, IS, and FEL wrote the manuscript.

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CONFLICT OF INTEREST

Competing interests: FEL is the founder of Micro-Bplex, Inc. FEL serves on the scientific advisory board of Be Biopharma, is a recipient of grants from the BMGF and Genentech, Inc. FEL has also served as a consultant for Astra Zeneca. IS has consulted for GSK,

Pfizer, Kayverna, Johnson & Johnson, Celgene, Bristol Myer Squibb, and Visterra. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Doan C. Nguyen https://orcid.org/0000-0002-5389-6731
Pedro A. Lamothe https://orcid.org/0000-0001-9262-2920
Matthew C. Woodruff https://orcid.org/0000-0002-5252-7539
Ankur S. Saini https://orcid.org/0000-0003-3963-6586
Caterina E. Faliti https://orcid.org/0000-0003-0487-1914
Ignacio Sanz https://orcid.org/0000-0003-4182-587X
Frances Eun-Hyung Lee https://orcid.org/0000-0002-6133-5942

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