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REVIEW ARTICLE

New insights into human immune memory from SARS-CoV-2 infection and vaccination

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Abstract

Since early 2020, the world has been embroiled in an ongoing viral pandemic with SARS-CoV-2 and emerging variants resulting in mass morbidity and an estimated 6 million deaths globally. The scientific community pivoted rapidly, providing unique and innovative means to identify infected individuals, technologies to evaluate immune responses to infection and vaccination, and new therapeutic strategies to treat infected individuals. Never before has immunology been so critically at the forefront of combatting a global pandemic. It has now become evident that not just antibody responses, but formation and durability of immune memory cells following vaccination are associated with protection against severe disease from SARS-CoV-2 infection. Furthermore, the emergence of variants of concern (VoC) highlight the need for immunological markers to quantify the protective capacity of Wuhan-based vaccines. Thus, harnessing and modulating the immune response is key to successful vaccination and treatment of disease. We here review the latest knowledge about immune memory generation and durability following natural infection and vaccination, and provide insights into the attributes of immune memory that may protect from emerging variants.

KEYWORDS
antibodies, COVID-19, immune memory, memory B cells, memory T cells, SARS-CoV-2

1 | INTRODUCTION—THE CHALLENGE OF THE NOVEL CORONAVIRUS PANDEMIC

The current coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which still poses a significant global health emergency. First identified in Wuhan, China, in late 2019,[1] SARS-CoV-2 has caused ~600 million infections and over 6 million deaths.[2] SARS-CoV-2 belongs to the *Coronaviridae* family, a group of enveloped viruses with a linear RNA genome (Figure 1A).[3] SARS-CoV-2 is closely related to SARS-CoV, which caused an outbreak in 2002-2003, and to a lesser extent to Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2013-2014.[4–7] Both these viruses caused significant morbidity, but unlike SARS-CoV-2, they were less infectious and did not spread globally. In addition to these epidemic outbreaks, there are four endemic coronaviruses that infect humans (NL63, 229E, HKU1, and OC43) causing seasonal common colds.[8–11]

The SARS-CoV-2 virus enters host cells through engagement of its spike receptor binding domain (RBD) to angiotensin-converting enzyme 2 (ACE2) expressed on the surface of host cells, particularly

in the respiratory tract, heart, kidney, and gastrointestinal tract.[12–15] In most individuals, SARS-CoV-2 infection causes a mild respiratory disease with symptoms such as fever, fatigue, and a cough.[16–18] However, a subset of patients with high viral loads mount a strong inflammatory response that can require hospitalization and respiratory support.[15,19–26] Individuals with comorbidities, such as asthma,[27–29] COPD and obesity,[18,30] and those who are immunocompromised[30,31] are at increased risk of severe disease. These conditions can result in an impaired immune function or increased expression of ACE2 leading to poor control of the virus and increased infectivity and viral load.[22,26,30]

While extremely tragic, the COVID-19 pandemic has provided the scientific community with the unique opportunity to study the immune response to a completely new pathogen in a formerly naive human population. Previously, detailed antibody and cellular response kinetics to viral infections were mostly derived from animal models.[32] Studies of human responses to infection are traditionally focused on the generation of antibodies and, only in recent years, technologies have been developed to detect, quantify, and phenotype immune memory cells.[33–35] Furthermore, the unprecedented speed in development of vaccines with new technologies already has enabled detailed evaluation of immunization responses in naive and previously infected individuals. The innate immune response is critical for the induction of an effective immune response against SARS-CoV-2,[36,37] and there is some evidence of "trained immunity."

In this review, we will focus on antigen-specific adaptive immune memory: antibodies, memory B cells (Bmem), and memory T cells (Tmem). While antibody, Bmem, and Tmem responses are induced, there is a need to understand the immunological basis of protection against severe disease, hospitalization and death, and to identify which immune component(s) confer this protection.

We here review current knowledge about the characteristics of immune memory generated to natural SARS-CoV-2 infection and to COVID-19 vaccination, how these facets of immunity can be examined, and how studying immune memory has already provided new insights into protection against variants of concern (VoC) and the potential need to update vaccine formulations.

2 | THE TECHNOLOGIES FOR DETECTION OF SARS-COV-2-SPECIFIC IMMUNE MEMORY CELLS

The adaptive immune system is able to respond to a vast array of pathogens with remarkable specificity. The challenge in studying adaptive immune cells (B and T cells) recognizing SARS-CoV-2 antigens lies in the fact that these are by definition rare events and need to be identified on the basis of binding a viral antigen. This is achieved by V(D)J recombination of antigen receptor genes during precursor-B and precursor-T-cell development. Through random

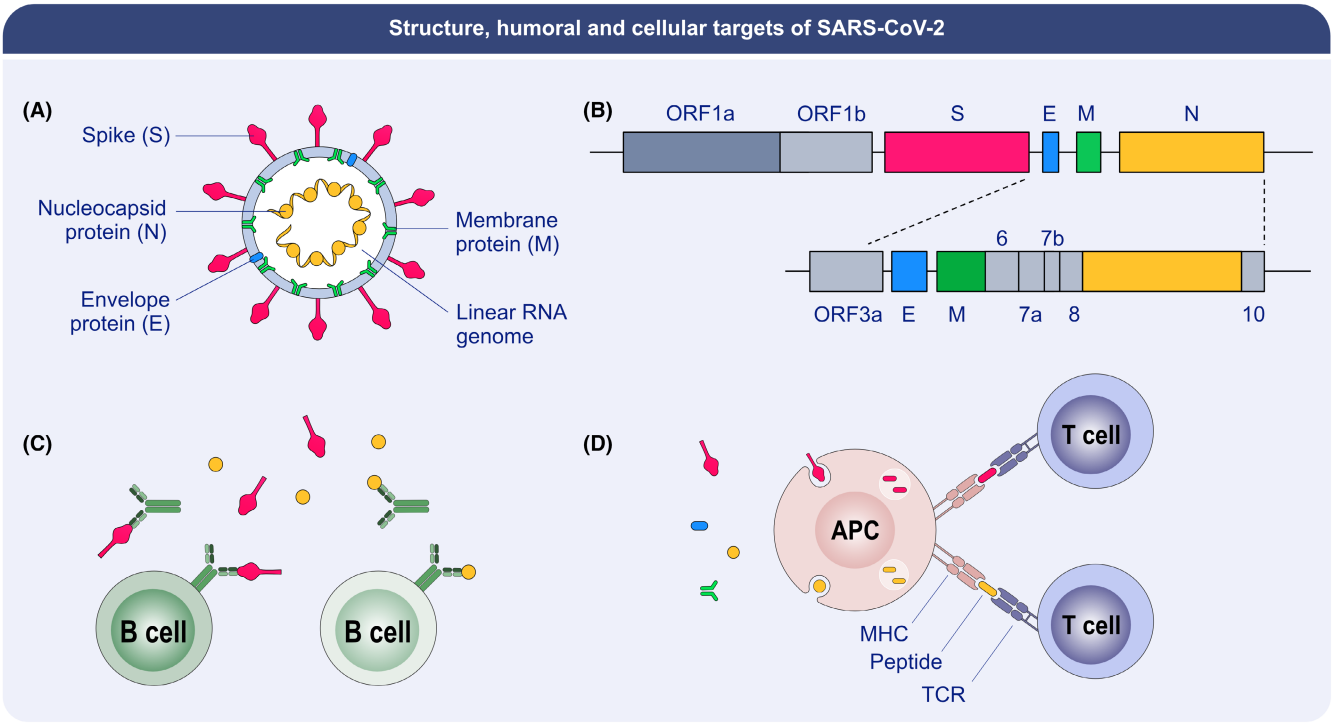

FIGURE 1 The SARS-CoV-2 particle and its recognition by adaptive immune cells. (A) SARS-CoV-2 is an enveloped virus with a linear RNA genome and four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). (B) The SARS-CoV-2 genome also encodes several non-structural proteins: open reading frames (ORFs) 1a, 1b, 3a, 6, 7a, 7b, 8, and 10. (C) Antibody and memory B-cell (Bmem) responses are predominantly directed toward the SARS-CoV-2 spike and nucleocapsid proteins. (D) $CD4^+$ and $CD8^+$ T-cell responses are directed against a larger array of proteins including the structural and ORF proteins, which are processed and presented in the context of MHC by antigen-presenting cells (APC).

genomic rearrangements, each naive B and T cell will carry an antigen receptor with a unique specificity, thereby combined having a repertoire of over tens of millions of different specificities.[38,39]

Following infection or vaccination, only those B and T cells that can specifically recognize the invasive pathogen will respond, proliferate, and differentiate. Long-lived memory in the form of antibodies, Bmem, and Tmem ensures a rapid response upon subsequent encounter with the same pathogen. Upon primary exposure, Bmem and antibody-producing plasma cells are formed predominantly from T-cell-dependent responses in the germinal center (GC). These structures in secondary lymphoid tissues facilitate antigen-presentation by follicular dendritic cells and helper T cells to drive B-cell proliferation and the induction of genomic changes in the immunoglobulin genes. These include somatic hypermutation (SHM) of the variable domains followed by selection for antigen-binding driving affinity maturation, as well as Ig class switch recombination (CSR) from IgM to either IgG, IgA, or IgE to change the antibody effector function.[40–42] IgG responses, especially involving the IgG1 subclass, dominate viral infection or vaccination responses, mediating potent effector functions through engagement of the Fc region of the antibody and activating the classical complement pathway.[43–45] Dimeric IgA can bind the polymeric Ig receptor allowing transportation across the epithelium to make IgA available at mucosal sites such as in the lung, the site of SARS-CoV-2 infection.[46,47]

In humans, Bmem can be defined on the basis of CD27 expression and/or the expression of IgG, IgA, or IgE. All Bmem display molecular signs of antigen exposure, including SHM in their Ig genes, an extensive replication history and upregulation of activation markers (e.g., CD80 and TACI).[40,46,48,49] $CD27^+IgM^+IgD^+$ Bmem, as well as $CD27^-IgA^+$ subsets, can be formed without cognate T-cell help.[46,49] In contrast, $CD27^+IgM^+IgD^-$ and $CD27^-IgG^+$ Bmem subsets are formed from primary GC reactions, whereas $CD27^+IgG^+$ and $CD27^+IgA^+$ Bmem display molecular signs of secondary GC reactions.[40,48] The molecular changes in Ig genes and the pre-activated cellular phenotypes ensure that upon reactivation these "experienced" cells respond rapidly through proliferation, differentiation into plasma cells that produce high-affinity antibody, and re-entry into a GC.[50] These antibodies can then opsonize the virus, or activate other effector cells to clear the virus through Fc receptor engagement.[44,51]

Follicular helper T(fh) cells, a specialized subset of T cells, are required for GC induction and, therefore, the production of high-affinity antibody, long-lived plasma cells, and Bmem cells.[52] Tfh are defined by the expression of CXCR5, the receptor for CXCL13, which acts as a chemoattractant for the B-cell zone of secondary lymphoid tissues. In peripheral blood, circulating (c)Tfh can be identified which express dim levels of CXCR5.[53,54] B cells engage cognate Tfh support through presentation of viral peptides on their surface MHC. Other $CD4^+$ helper T-cell (Th) subsets contribute to viral responses including through the production of anti-viral cytokines, such as IFN-γ, and co-stimulation of $CD8^+$ T cells. Upon recognition of cognate peptide presented on MHC class I, activated $CD8^+$ T cells also produce anti-viral cytokines but can additionally directly kill virally infected cells, via the release of cytotoxic granules such as perforin and granzymes.[55–57]

Thus, Bmem, $CD4^+$ Tmem, and $CD8^+$ Tmem are formed following infection or vaccination. However, these antigen-specific cells are only a small fraction within the vast population of immune memory cells, requiring specialized and highly sensitive techniques to accurately identify these cells within peripheral blood or tissue samples.

2.1 | Detection of SARS-CoV-2-specific B cells

Traditionally, antigen-specific plasma cells or Bmem are detected using enzyme-linked immunosorbent spot (ELISPOT). This involves incubation of cells on a plate that is coated with the antigen of interest. Plasmablasts will spontaneously secrete antibodies, which will directly bind to the antigen close to where they were secreted by the cell. A labeled secondary antibody is then added allowing the detection of the antigen-specific antibodies secreted by the plasma cells. Subsequently, by counting the number of "spots" created, one can infer the original number of antigen-specific plasmablasts in the sample.[33] Similarly, antigen-specific Bmem can be detected following in vitro stimulation to drive differentiation and secretion of antibodies. The ELISPOT technique is extremely sensitive and relatively quick, but has some disadvantages. The cells used in the ELISPOT assay cannot be used in further downstream analysis, nor is there any information obtained from the B cells that do not recognize the antigen of interest.[33]

There are also procedures to immortalize B-cell clones to enable further assessment of their antigen reactivity.[58] This approach can enable function assessment of the antibodies produced by a single B-cell clone. However, the procedure is labor intensive and can be time consuming, especially when 10s-100s of clones per donor will be evaluated. An alternative approach for detection of antigen-specific B cells would be to label the antigen of interest (ie. fluorescent protein tetramer) and probe for the cells that bind these with their antigen-specific surface expressed Ig (Figure 2A).[33–35] Fluorescently tagged antigens of interest can be combined with antibodies against B-cell surface markers, thereby enabling in-depth examination of the immunophenotype of antigen-specific B cells. The advantages of this approach are multi-fold: inclusion of multiple protein targets for examination of multiple Bmem specificities in a single tube,[53,59,60] assessment of B cells that do not recognize the antigens, and collection of cells for downstream molecular analysis of Ig genes and/or gene expression profiles. A potential caveat of using fluorochrome-coupled antigens is the fact that large protein-based fluorescent dyes such as PE or APC can be recognized by surface Ig on small populations of B cells.[61–63] Therefore, care is required when selecting the fluorochrome for tetramer conjugation. As a solution, double discrimination can be applied whereby two different fluorescent conjugates of the same protein tetramer are used for detection of antigen-specific Bmem (double positive), enabling exclusion of fluorochrome-specific Bmem (single positive) (Figure 2B).[34,59,60,64–66]

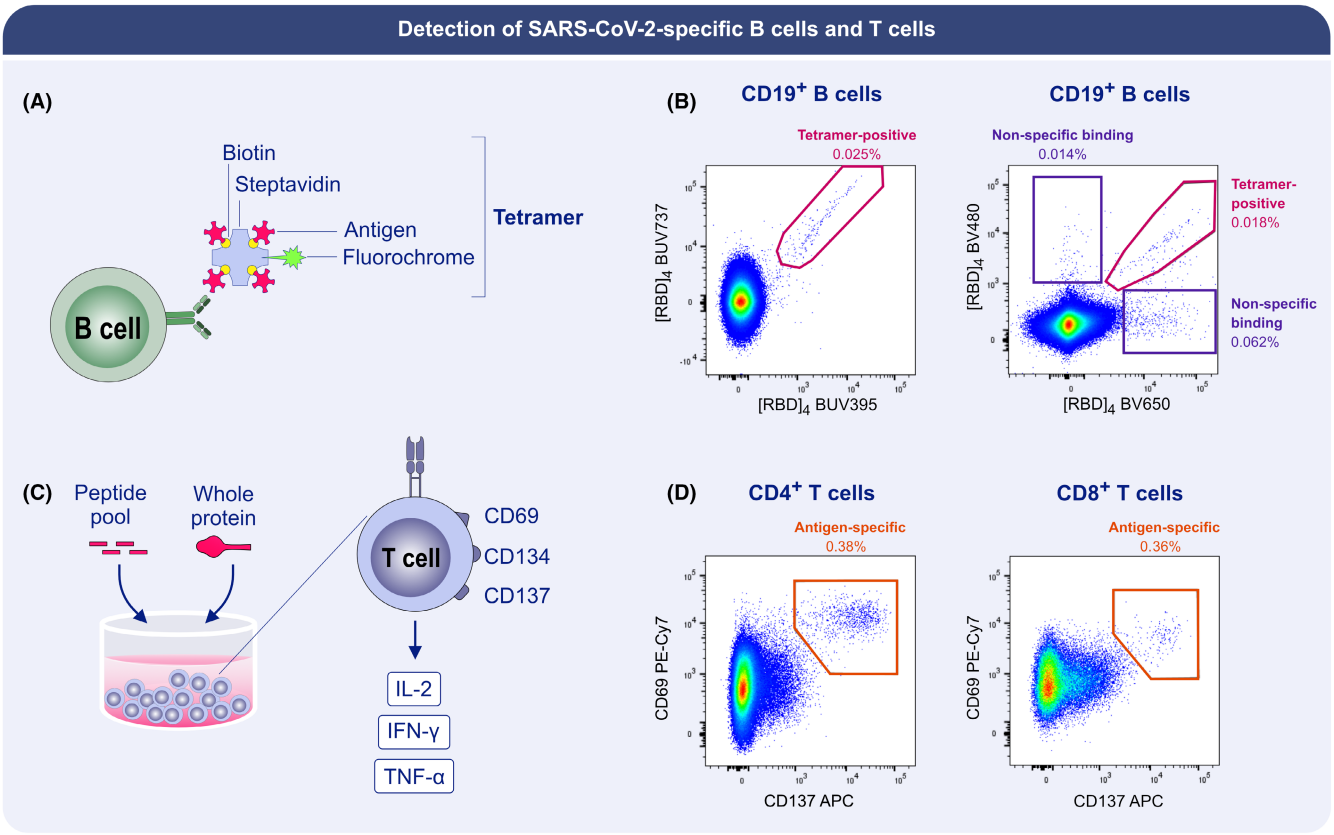

FIGURE 2 Detection of SARS-CoV-2-specific B and T cells. (A) Antigen-specific B cells can be identified using fluorescently labeled protein tetramers. (B) Through double discrimination with two antigen tetramers conjugated to distinct fluorochromes, B cells binding protein-based fluorochromes (e.g., BV650, a tandem of BV421) can be excluded. (C) SARS-CoV-2-specific T cells can be detected with the activation-induced marker (AIM) assay. PBMC are stimulated with whole SARS-CoV-2 protein or overlapping peptide pools. (D) After incubation, SARS-CoV-2-specific T cells are activated and be identified by AIM, such as CD69 and CD137, and assayed for anti-viral cytokine production (e.g., IFN-γ, TNF-α, and IL-2).

2.2 | Detection of SARS-CoV-2-specific T cells

The detection of SARS-CoV-2-specific T cells is somewhat less straightforward than for B cells, because T cells recognize a peptide fragment of the original antigen presented in the context of MHC. Recombinant MHC molecules can be produced, tetramerized with fluorescent streptavidin conjugates, and loaded with the peptide of choice. This approach has been very successful for detection of antigen-specific $CD8^+$ (MHCI tetramers) and $CD4^+$ T cells (MHCII tetramers) for a wide range of infectious diseases, including COVID-19.[67,68] Similar to the detection of antigen-specific B cells, this technique takes advantage of the unique TCR expressed by each T cell. There are several limitations, the most prominent being the availability of a limited set of MHC tetramers representing the most frequent HLA alleles, the need for HLA typing of the individual being tested, and epitope mapping to identify the immunodominant peptides.

Alternatively, antigen-specific T cells can be identified by stimulating PBMCs with either whole protein antigens,[69] or overlapping peptide pools, followed by detection of antigen-specific T cells through detection of activation markers (Figure 2C).[70–75] These can either be intracellular cytokines (IFN-γ, IL-2, TNF-α) or activation-induced markers (AIM) on the cell surface. Typically, a combination of two surface markers is used for detection of antigen-specific $CD4^+$ T cells (CD25, CD69, CD137, CD154, and/or CD134) and $CD8^+$ T cells (CD25, CD69, CD107a, CD137, and/or CD134) (Figure 2D).[70–75] This method is more amenable to high-throughput screening because there is no need for HLA typing as antigen-presenting cells from the PBMC fraction are used for peptide presentation, and a combination of peptides can be pooled to assess a larger fraction of cells recognizing epitopes from one or more proteins.

2.3 | Antigenic targets of SARS-CoV-2

The abovementioned technological advances have facilitated detection of SARS-CoV-2-induced immune responses at the cellular level (Bmem and Tmem) immediately from the start of the pandemic.[59,60,73] SARS-CoV-2 contains four main structural proteins that are all targets of the immune system: spike, envelope, membrane, and nucleocapsid (Figure 1A).[3] In addition, the viral genome also encodes several non-structural proteins, especially open reading frames (ORFs) 1a, 1b, 3, 6, 7a, 7b, 8, and 10 (Figure 1B).[3] The

SARS-CoV outbreak in the early 2000s was found to induce strong antibody responses to the spike and nucleocapsid proteins.[76,77] These two proteins were also identified as the major targets early in the COVID-19 outbreak with 90% of SARS-CoV-2-infected people generating antibodies to these structural proteins.[59,60,78] Antibodies that target the RBD of the spike protein have the capacity to prevent target cell adhesion, thereby neutralizing the virus providing protective immunity to SARS-CoV-2 (Figure 1C).[79–82] Still, antibodies and immune cells targeting other viral antigens can play an important role in viral clearance and generation of cellular immunity. SARS-CoV-2 T-cell responses also mainly target the spike and nucleocapsid proteins, although most infected individuals also generate responses toward the membrane, envelope, and ORF3a, 6, 7a, and 8 proteins (Figure 1D).[3,67,71,72,74]

3 | ANTIBODY RESPONSES AND IMMUNE MEMORY FOLLOWING SARS-COV-2 INFECTION

3.1 | Antibody responses

Antibodies are the gold standard target for detection of previous viral infection, especially for cytomegalovirus, hepatitis B, and Epstein–Barr virus,[83–85] as well as for evaluation of vaccine responses.[86] Early during SARS-CoV-2 infection, activated B cells differentiate into plasmablasts within 7–10 days after infection, and produce high amounts of antibody to clear the pathogen.[87,88] These plasmablasts rapidly decline after viral clearance as soon as 20 days after infection.[60,89] Similarly, serum antibodies targeting both the spike and nucleocapsid proteins reach peak levels at around 20 days post-infection, followed by a decline in the contraction phase of the immune response.[60,64,69,75,90–93] pike-specific antibodies that target the RBD can compete with ACE2 binding and thereby inhibiting cell entry. Sufficiently high levels of these antibodies have a virus-neutralizing effect that varies greatly between individuals.[53,94] Following contraction of the response, SARS-CoV-2-specific antibody levels remain quantitatively stable from 3 months up to 8–15 months.[59,60,64,69,75,87,90,94,95] These durable SARS-CoV-2-specific antibody levels are the result of continuous production by long-lived plasma cells in the bone marrow.[95]

3.2 | Memory B cells

In parallel to plasma cells, circulating immune memory cells formed after an infection can be very durable, as has been demonstrated for small pox-specific B cells that were detected 60 years post-infection, and T cells that have a half-life of 14 years.[96] Furthermore, influenza-specific Bmem have also been isolated from individuals nearly 90 years after surviving the 1918 pandemic,[97] demonstrating that this cell population may provide long-term immunity, regardless of the level of antibody.

Multiple research groups have consistently demonstrated the presence of SARS-CoV-2-specific Bmem in patients with COVID-19. Early after infection, a large proportion of these cells display an "atypical" memory phenotype ($CD21^{lo}CD27^{-}$), indicative of recent activation. This atypical population begins to contract after 14 days with a shift toward $CD21^{+}$ Bmem.[50,69,98,99] Early in COVID-19 convalescence, the majority of Bmem are unswitched, expressing IgM, with the proportion of IgG-switched Bmem increasing up to 11 months post-infection.[59,60,64,75,95] Beyond 1 to 2 months after infection, spike- and nucleocapsid-specific Bmem exhibit a classical memory phenotype (i.e., Ig class switched, $CD27^{+}$, $CD71^{-}$),[53,59,60,69,99] and these are present in stable numbers for >12 months post-infection.[59,60,64,69,75,95,100–103] It remains unclear whether the durability of Bmem is due to longevity of individual cells, or if these are continuously formed due to persistent antigen exposure. Examination of intestinal biopsies by Gaebler and colleagues revealed the presence of SARS-CoV-2 antigens 4 months after infection.[64] This could indicate a mucosal reservoir that provides the GC with a continuous supply of antigen, thereby prolonging its activity and formation of Bmem. This ongoing activity could also explain their observations that absolute numbers of SARS-CoV-2-specific B cells continue to rise beyond 4 months after infection with more SHM observed.[59,60,64]

3.3 | Memory T cells

Alongside Bmem, diverse subsets of SARS-CoV-2-specific T cells have been extensively characterized, including Tfh and $CD4^{+}$ and $CD8^{+}$ effector and memory subsets. SARS-CoV-2-specific $CD4^{+}$ T cells are detected in over 90% of patients from 1 month after infection.[59,71–73] Following in vitro stimulation with SARS-CoV-2 proteins or peptides, antigen-specific $CD4^{+}$ T cells predominantly express IFN-γ, IL-2 and TNF-α, and very little IL-17, fitting with a Th1 profile.[53,69–71,73,74] Phenotypically, these SARS-CoV-2-specific $CD4^{+}$ T cells are enriched for $CCR7^{+}CD45RA^{-}$ central memory (Tcm) and $CCR7^{-}CD45RA^{-}$ effector memory (Tem) cells.[59]

A robust Tfh response has been observed following SARS-CoV-2 infection with numbers peaking after approximately 4 weeks, and displaying an enrichment in $CCR6^{+}CXCR3^{-}$ Tfh17 cells.[53,59] These cTfh17 cells were previously shown to be superior to other cTfh subsets in providing help to B cells.[52,104,105] However, this is contradicted by other studies suggesting that CCR6 upregulation aids in homing to mucosal tissues such as the lung.[73,106]

Unlike $CD4^{+}$ T cells, SARS-CoV-2-specific $CD8^{+}$ T cells are detectable in about 70-80% of convalescent patients at 1 month after infection,[59,71,73] with responses being lower in patients with severe COVID-19.[72,73] Upon in vitro stimulation, $CD8^{+}$ T cells predominantly produce IFN-γ and TNF-α, with co-expression of granzyme B, perforin, and CD107a, indicating cytotoxic capacity.[69,71,73,74] Phenotypically, SARS-CoV-2-specific $CD8^{+}$ T cells are enriched for Tem and $CCR7^{-}CD45RA^{+}$ effector memory (TemRA) populations.[59]

SARS-CoV-2-specific T cells remain at detectable levels up to 8 months post-infection.[59] In contrast to Bmem, Tmem numbers gradually decline over time. The half-life of $CD4^+$ T cells is approximately 94–119 days,[59,75] and $CD8^+$ T cells decline with a half-life of 225–650 days.[59,75] Although T cells recognize the diverse protein antigens of SARS-CoV-2, those targeting the spike protein are most numerous and have the longest half-life post-infection.[59,71] Potentially, the kinetics will not continue linearly over time, T: cells formed after SARS-CoV infection in the early 2000s have been detected up to 17 years after infection indicating that SARS-CoV-2 Tmem numbers may reach a plateau level.[107]

Overall, SARS-CoV-2 infection generates robust long-lived Bmem and Tmem compartments, which remain stable even after the contraction of the antibody response.

4 | RECENT INSIGHTS INTO DYNAMICS OF IMMUNE MEMORY TO COVID-19 VACCINATION

Following the COVID-19 pandemic outbreak, there has been an unprecedented response with rapid vaccine development and roll-out within 1 year, which has saved countless lives since early 2021. Taking advantage of recently developed, novel vaccine technologies, mRNA (BNT162b2, mRNA-1273) and adenoviral vector (ChAdOx1 nCoV-19, Ad26.COV2.S) based vaccines were rapidly approved in many Western countries globally. Both the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines are lipid nanoparticles containing an mRNA molecule encoding the SARS-CoV-2 spike protein in its stabilized pre-fusion form.[108–110] The ChAdOx1 nCoV-19 (AstraZeneca) and the Ad26.COV2.S (Johnson & Johnson) vaccines are replication-deficient adenoviral vector vaccines containing double-stranded DNA that encode the same full-length spike protein.[111–113] The initial dosing regimens for the mRNA vaccines (BNT162b2 and mRNA-1273) were 2 doses with an interval of 3 to 4 weeks, whereas the ChAdOx1 vector vaccines were given in 2 doses with a 12-week interval, and the Ad26.COV2.S was given as a single dose.[110,111,113] Both vaccine design platforms were novel in the sense that these trigger host cells to produce the SARS-CoV-2 spike protein, thereby generating both humoral (antibodies, Bmem) and cellular responses ($CD4^+$ and $CD8^+$ Tmem).[110,112] In addition to the abovementioned mRNA and adenoviral vaccines, which are administered intra-muscularly, mucosal administration of SARS-CoV-2 vaccines is considered.[114,115] Mucosal vaccines are designed to generate high amounts of mucosal IgA at the infection site and hence could provide better protection and potentially sterilizing immunity.[115] However, to date no candidate has been approved for use in humans.[115]

All four approved vaccines demonstrated high efficacy in clinical trials for protection from SARS-CoV-2 infection and reduction in severe disease.[109–112] However, some adverse events have been reported following COVID-19 vaccination. Polyethylene glycol (PEG) found in mRNA vaccinations can cause anaphylaxis in some individuals; however, with sufficient screening and risk management, a COVID-19 vaccine can still be administered.[116–120] Two other conditions of note are vaccine-induced thrombocytopenia and thrombosis (VITT) following ChAdOx1 nCoV-19 vaccination[121,122] and myocarditis following administration of BNT162b2 or mRNA-1273.[123,124] Each condition is extremely rare. VITT is more prevalent in older individuals, but the rate is very low at 1 in 100,000.[125] Myocarditis following mRNA vaccination is more prominent in young men with 1.7 in 100,000 affected.[123] Importantly, these complications are now well documented, and can be recognized and treated early to avoid long-term complications.[126–129]

Both mRNA and adenoviral vaccines induce high levels of antibodies within 4 weeks after administration. Two doses of an mRNA vaccine typically elicit higher levels of antibody than those observed after primary SARS-CoV-2 infection.[130,131] In previously infected individuals, antibodies are higher after the first dose compared to naive individuals indicating that the vaccine is boosting pre-existing memory.[132,133] Reports of antibody responses to adenoviral COVID-19 vaccination are limited; however, significantly lower levels of IgG and neutralizing antibodies are generated compared to mRNA vaccination.[134–136] Interestingly, individuals vaccinated with one dose of adenoviral vaccine and boosted with one dose of mRNA vaccine generate similar responses to those who received two mRNA doses.[137,138] mRNA vaccination generates peak antibody levels 15–20 days after vaccination and declines thereafter (Figure 3A,B).[101,130,139–141] Long-lived bone marrow plasma cells have been detected up to 7 months after mRNA vaccination.[142] Recovered COVID-19 patients who received a vaccination show marginally higher antibody levels, which declined at similar rates to uninfected individuals.[130,132,142] This suggests that plasma cell life spans are similar between the two groups, and vaccination does not further enhance the longevity of plasma cells in COVID-19 convalescent patients.[130,143] High levels of neutralizing antibodies strongly correlate with vaccine-induced protection against infection.[144] While protection against infection is short-lasting, vaccine-induced protection against severe disease lasts for up to 6 months.[145] These kinetics do not correlate with serum antibodies (Figure 3A), but rather with immune memory cells (Figure 3B).[73,146]

Spike-specific Bmem are generated after one dose of mRNA vaccination and frequencies peak approximately 1 month after the second dose (Figure 3B).[130,140] These include a large IgG-expressing population, which expands after the second dose at the expense of IgM-expressing Bmem (Figure 3B).[101,130,140] Interestingly, RBD-specific Bmem have fewer SHM in their Ig genes than Bmem directed to other regions of the spike protein.[130] Previously infected individuals generate more Bmem to the first vaccine dose than uninfected individuals, fitting with the presence of previously formed memory.[130] Irrespective of previous infection, double-dose vaccination induces durable spike-specific Bmem numbers up to 6 months post-vaccination (Figure 3B).[59] Bmem generated to adenoviral COVID-19 vaccination have not been characterized in great detail. Still, there is some evidence that the frequencies of spike-specific Bmem are lower than after mRNA vaccination, with similar durability.[131]

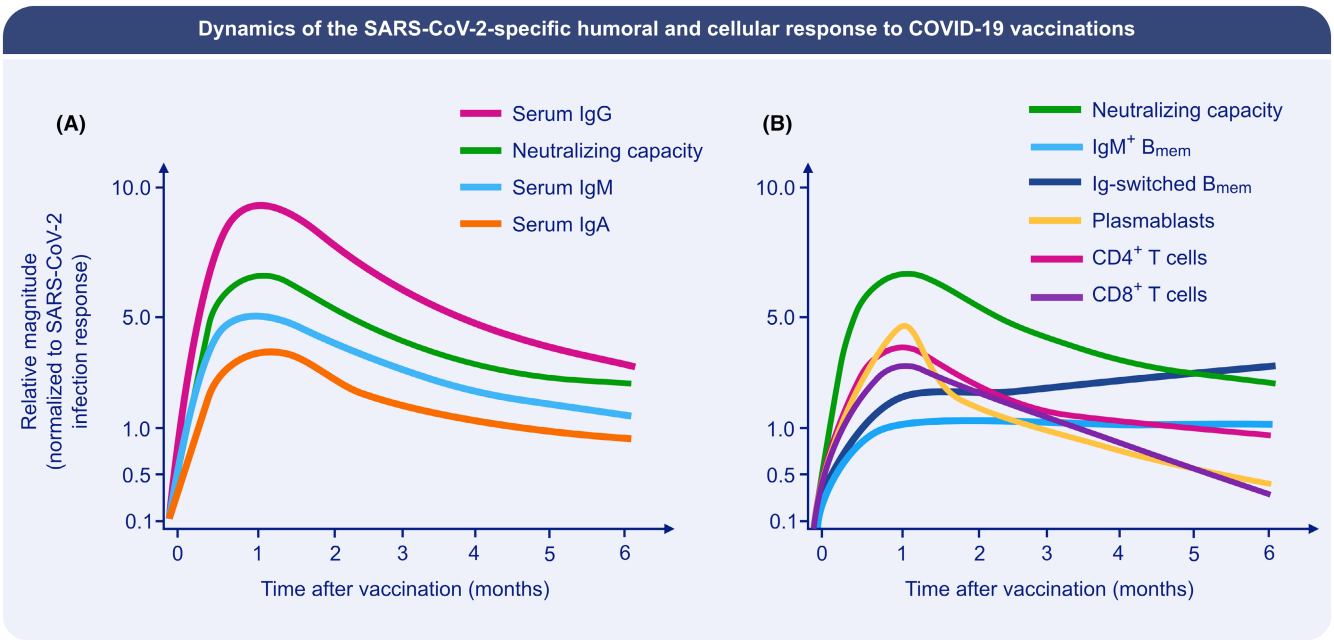

FIGURE 3 Dynamics of the SARS-CoV-2-specific humoral and cellular response to COVID-19 vaccinations. (A) Serological response to COVID-19 vaccines relative to neutralizing capacity (gray). Spike-specific antibodies are produced rapidly after vaccination and decline after approximately 3 months. (B) Immune memory generated to COVID-19 vaccines relative to neutralizing capacity (green). Plasmablasts are rapidly generated and produce high amounts of neutralizing antibody but the population begins to contract beyond 1 month post-vaccination. In contrast, SARS-CoV-2-specific memory B cell (Bmem) numbers remain stable for at least 6 months post-vaccination. In particular, the frequency of Ig-switched Bmem continue to increase up to 6 months post-vaccination. SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells show a strong initial response to the vaccination, followed by a gradual decline after 3 months post-vaccination. This decline is more profound for SARS-CoV-2-specific $CD8^+$ T cells than SARS-CoV-2-specific $CD4^+$ T cells. Data adapted from existing literature: antibodies,[130,140,185] Bmem and plasmablasts,[130,140] and Tmem.[130]

In addition to evaluation of circulating immune cells, several studies have examined these in tissue. Kim and colleagues sampled draining lymph nodes and bone marrow from vaccinated participants to examine the longevity of the GC response after mRNA vaccination.[142] spike-specific Bmem continued to acquire more SHM the longer they remained in the GC.[142] Furthermore, GC B cells displayed a higher level of clonal overlap with long-lived bone marrow plasma cells than with plasmablasts that were generated early in the response.[142] These results are in agreement with those from mouse models showing Bmem that are generated later in an immune response acquired more SHM and displayed a higher affinity to antigen.[147] This indicates that Bmem and long-lived plasma cells are a distinct end products of the GC, whereas plasmablasts exit earlier from the GC and have a lower affinity for antigen. Therefore, vaccinations that stimulate prolonged GC activity may produce more effective Bmem and long-lived plasma cells, thus providing better protection against disease.

Detailed evaluation with AIM assays showed rapid generation of spike-specific $CD4^+$ and $CD8^+$ T cells within the first 4 weeks after two-dose vaccination. spike-specific $CD4^+$ and $CD8^+$ T cells peak at around 1 month post-mRNA vaccination (Figure 3B), with spike-specific $CD4^+$ cTfh peaking 1 month post-vaccination followed by a rapid contraction. Non-cTfh $CD4^+$ cells directed against the spike protein are predominantly Th1/Th17 and Th1. While Th1/Th17 cells declined after 1 month post-vaccination, the Th1 population remain more stable.[130] spike-specific $CD4^+$ T cells generated exhibit a Tem or Tcm phenotype, with Tcm proportions declining over time while the Tem frequency remains more stable.[130] In contrast to the durable Bmem, spike-specific $CD4^+$ and $CD8^+$ T-cell numbers start to decline after 3 months with a shorter half-life time than after infection.[59,130] CD8+ T cells decline more rapidly with very few spike-specific cells detectable 6 months post-vaccination (Figure 3B).[130] Furthermore, spike-specific $CD4^+$ T cells have a similar half-life in infection and vaccination while spike-specific $CD8^+$ T-cell numbers decline more rapidly after vaccination compared to natural infection.[130] Initial reports documented a lower number of IFN-γ producing T cells after vaccination with adenoviral vectors than mRNA.[134] The durability of these cells has yet to be documented.

5 | RECENT INSIGHTS INTO IMMUNE PROTECTION FROM INFECTION WITH VARIANTS OF CONCERN

About 1 year into the pandemic, late 2020, the first SARS-CoV-2 variant was identified as being a variant of concern (VoC). VoC are determined by the World Health Organization (WHO) as variants that either increase transmission, lead to increased disease severity, or a decreased effectiveness of public health measures such as vaccination.[148] The first VoC, Alpha (B.1.1.7), was mutated at N501Y

in the spike RBD,[148] causing increased viral transmissibility by 43%–90% with minimal escape from antibody recognition.[149–151] Two subsequent VoC, Beta (B.1.351) and Gamma (P.1), shared the same 3 mutated residues in the spike RBD: K417N (Beta)/K417T (Gamma), E484K, and N501Y.[148] The E484K mutation affects one of the 3 epitopic regions within the RBD (RBD-2),[65] resulting in escape from antibody recognition.[152–157] This twofold to sixfold reduction in recognition from Wuhan-targeting antibodies resulted in their greater transmissibility.[154,158–160] While less data are available on the T-cell recognition of VoC, vaccine-induced $CD4^+$ Tmem were reported to recognize the Beta variant with a similar magnitude as the Wuhan strain.[108,161]

In May 2021, a fourth VoC emerged: Delta (B.1.617.2)[148] containing two spike RBD mutations (L452R and T478K), which both reside in the RBD-2 region, but did not impair antibody recognition as much as Beta and Gamma.[65,155,162,163] The Delta VoC was 60% more transmissible than Alpha and rapidly became the dominant strain globally.[162] These initial four SARS-CoV-2 variants only contained several mutations. In November 2021, this changed with the identification of Omicron (B.1.1.529).[148] The initial Omicron sublineage (BA.1) harbored 37 mutations in the spike protein, of which 15 are positioned in the RBD with one at E484 that mediates escape from vaccine-induced antibodies.[164–167] Omicron combined high transmissibility with escape from vaccine-induced antibodies as evidenced by its rapid predominance globally, and causing breakthrough infections in previously vaccinated individuals.[168] Despite the immune evasion and high transmissibility, Omicron infection in most individuals seemed restricted to the upper airways, causing less severe disease than other VoC.[169]

Considering that all circulating SARS-CoV-2 strains are now variants differing from the original Wuhan strain, it is critical to examine the antibodies and immune memory generated by a Wuhan-based vaccine, and whether these confer protection against severe disease from these VoC. It will be crucial to establish the absolute and relative amounts of antibodies and immune memory cells that can recognize each VoC. Moreover, durability of these variant-binding antibodies and memory cells will determine whether next-generation vaccines incorporating VoC are required to confer long-term protection.

To address the issue of decreased protection against VoC, and a waning antibody response, a third dose (booster) of SARS-CoV-2 vaccination is now recommended and administered 3–6 months after primary vaccination. In Australia and several European countries, even a fourth dose (i.e., second booster) is now recommended

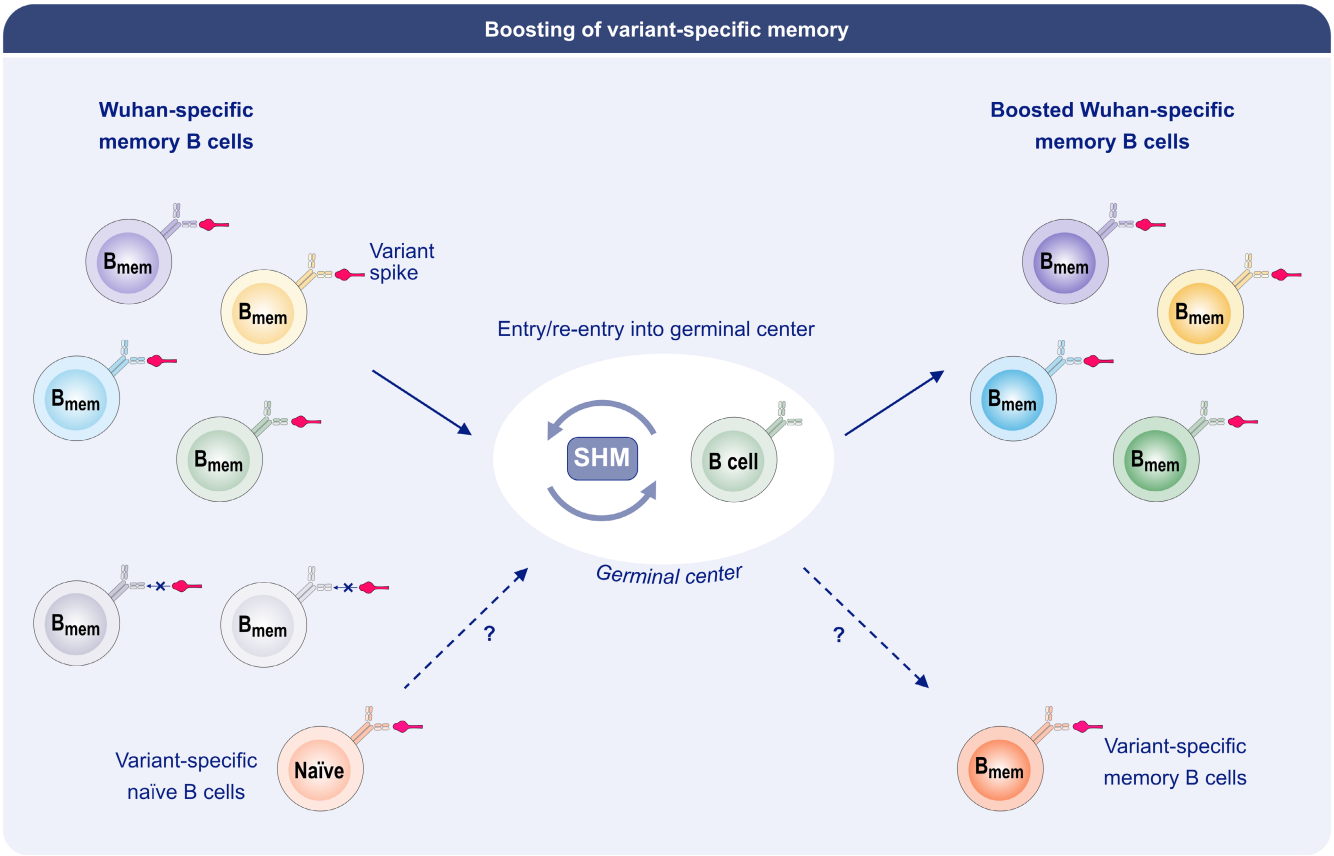

FIGURE 4 Germinal center reaction generated to SARS-CoV-2 vaccination SARS-CoV-2 vaccination generates a stable pool of Wuhan-specific memory B cells (Bmem). If a variant booster or breakthrough infection occurs, a portion of the pre-existing memory pool is reactivated. It is currently unknown if variant-specific naive B cells are engaged in this process or may take longer to enter the germinal center (GC). Without inclusion of naive B cells with new specificities, variant booster vaccines may limit the repertoire of SARS-CoV-2-specific Bmem, making a host potentially more vulnerable to future VoC.

for most adults.[170,171] Booster vaccination reactivates pre-existing Bmem resulting in an increase in antibody levels and subsequent rounds of SHM leading to further generation of "experienced" Bmem.[172–174] It is postulated that the booster vaccination drives further affinity maturation in pre-existing Bmem.[130] This increased affinity is likely the mechanism by which the booster dose increases the capacity of Bmem and antibodies to bind and neutralize Delta and Omicron VoC,[165,166,172,173,175,176] and reduce the severity of disease.[177–179] However, it remains unclear whether these effects are durable beyond 1 month post-boost.[166,180]

The high prevalence of breakthrough infections from Omicron variants poses the question whether the continual boosting with a Wuhan-based vaccine is the best method of reducing SARS-CoV-2 transmission and disease. Perhaps, a variant vaccine or a multivalent vaccine incorporating multiple variants (similar to seasonal influenza vaccinations) may be more effective. Furthermore, most current vaccines exclusively target the spike protein. If additional targets were included, these responses, although not neutralizing, may be less prone to viral escape, and thus could prevent severe disease. Recent studies indicate that Omicron infection in vaccinated individuals nearly exclusively triggers recall responses of pre-existing Bmem.[181–183] This suggests that if a variant booster vaccination or infection occurs, B-cell responses are dominated by Wuhan-specific Bmem with limited inclusion of new specificities from naive B cells (Figure 4). This concept of "original antigenic sin" may result in narrowing the Bmem repertoire with variant vaccine,[184] and would require strategies to boost inclusion of naive B cells into the response. Potentially, delayed booster vaccinations after 6–12 months would ensure a smaller circulating Bmem pool, allowing more naive B cells to respond.[130,166] This delayed boosting might also be beneficial to allow extra time for GC entry and affinity maturation of low-affinity Bmem capable of binding variants. These low-affinity cells could have more potential to undergo affinity maturation to the variant. Alternatively, Wuhan-specific epitopes of the vaccine could be masked, thereby promoting naive B-cell responses toward variant-specific epitopes.

6 | FUTURE PROSPECTS

Taken together, since 2020, there has been a massive effort by the medical and scientific community to better understand the SARS-CoV-2 virus, the generation and durability of immune memory to natural infection and vaccination. These insights will assist in future deployment of vaccines and design of therapies to treat vulnerable patients at risk of severe disease.

Despite recent developments, the technologies to quantify SARS-CoV-2-specific Bmem and Tmem responses are only available in specialized research laboratories. Moving forward, these technologies should be optimized for high-throughput applications in a diagnostic setting. In addition, development of clinical tests to identify Bmem and Tmem will allow these metrics to be incorporated into future vaccine clinical trials as a measure for vaccine efficacy. This will facilitate the measurement of a protective response, and identification of individuals who generate a sub-optimal response, thereby more accurately defining the timing or need for booster doses. How to identify the best biomarker for long-term immunity to SARS-CoV-2? This can be achieved through large scale long-term studies involving thousands of participants. Alternatively, by examining risk groups with defined immunological defects, we can examine which aspect of immunological memory is most critical for the reduction of infection and severe disease.

Finally, in the ever-changing landscape of the SARS-CoV-2 pandemic, further insights into the capacity of existing immune memory to recognize VoC, protect from infection, severe disease, and death will provide policy makers with key information required for the long-term management of this pandemic. These experimental data will provide the evidence base required for decisions on the frequency of booster vaccines, and the requirement for new generation vaccines for ongoing protection.

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CONFLICTS OF INTEREST

MCvZ and REO'H are inventors on a patent application related to this work. The other authors declare no conflict of interest.

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