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Antibody and B Cell Responses to SARS-CoV-2 Infection and Vaccination: The End of the Beginning

Katharina Röltgen[1,2] and Scott D. Boyd[3,4]

[1]Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Allschwil, Switzerland

[2]University of Basel, Basel, Switzerland

[3]Department of Pathology, Stanford University School of Medicine, Stanford, California, USA; email: publications_scott_boyd@stanford.edu

[4]Sean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine, Stanford, California, USA

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Abstract

As the COVID-19 pandemic has evolved during the past years, interactions between human immune systems, rapidly mutating and selected SARS-CoV-2 viral variants, and effective vaccines have complicated the landscape of individual immunological histories. Here, we review some key findings for antibody and B cell–mediated immunity, including responses to the highly mutated omicron variants; immunological imprinting and other impacts of successive viral antigenic variant exposures on antibody and B cell memory; responses in secondary lymphoid and mucosal tissues and non-neutralizing antibody-mediated immunity; responses in populations vulnerable to severe disease such as those with cancer, immunodeficiencies, and other comorbidities, as well as populations showing apparent resistance to severe disease such as many African populations; and evidence of antibody involvement in postacute sequelae of infection or long COVID. Despite the initial phase of the pandemic ending, human populations will continue to face challenges presented by this unpredictable virus.

1. ANTIBODY AND B CELL RESPONSE FINDINGS EARLY IN THE SARS-COV-2 PANDEMIC

Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2 (CoV-2)] represents the third zoonotic spillover of a coronavirus (CoV) into human populations causing large disease outbreaks in the first two decades of the twenty-first century (1–3). Despite having lower virulence than the earlier SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus) outbreaks, the highly infectious CoV-2 and its viral variants have generated a far more devastating pandemic estimated to have caused more than 1.1 million deaths in the United States and 6.88 million deaths worldwide since January 2020 and up to March 2023 when the Johns Hopkins University stopped round-the-clock tracking of coronavirus disease 2019 (COVID-19) data (**https://coronavirus.jhu.edu/map.html**). The scale of societal disruption caused by CoV-2 echoes that of the 1918 influenza pandemic in the previous century. Fortunately, rapid efforts by the global scientific, biotechnology, and pharmaceutical communities to analyze CoV-2 and human immune system responses to it, and to develop effective vaccines and therapeutics, have yielded a trove of new scientific insights and products that have saved many lives. Here we assess main advances in the past two years in our understanding of humoral immunity to CoV-2 infection or vaccination, continuing threads of antibody and B cell responses that we and others have explored in reviews after the first year of the pandemic (4, 5). We regret that the vast number of publications on these topics (more than 26,000 nonpreprint papers with search terms "COVID-19" and "antibody" in PubMed from December 2019 to April 2023) sharply limits our ability to include many important contributions to the global scientific effort during the pandemic.

Extensive cooperation between researchers and sharing of key data such as viral sequences, as well as assay protocols and reagents, together with rapid distribution of research results in preprint servers and journals in 2020 had begun to answer key questions about COVID-19 and human immune responses to CoV-2. It was clear that most COVID-19 patients made antibody responses to CoV-2 surface proteins such as the spike protein (S protein) and its receptor-binding domain (RBD) that mediates binding to the host cell receptor, angiotensin-converting enzyme II (ACE2) (6). Antibodies to the spike, particularly those binding to RBD and preventing interaction with ACE2 but also a subset of antibodies that bind the spike N-terminal domain (NTD) and rarer antibodies that target the spike S2 stem domain, could neutralize CoV-2. The concentration of immunoglobulin G (IgG) binding to spike or RBD and the titer of neutralizing antibodies to CoV-2 were identified early as correlates of protection from COVID-19 (7). It was also becoming apparent that the concentrations of serum antibodies targeting CoV-2 proteins showed kinetics similar to those against the four endemic human CoVs (HCoVs) OC43, HKU1, NL63, and 229E (8), decreasing relatively quickly in the months following infection, with half-lives estimated as 126, 102, and 60 days for IgG against spike, RBD and the nucleocapsid antigens, respectively, and even shorter half-lives for IgM and IgA responses (9, 10). Many studies isolating monoclonal antibodies (mAbs) from individual B cells of individuals following either infection with CoV-2 or vaccination generated panels of neutralizing antibodies and characterized these structurally with cryo-electron microscopy or X-ray crystallography, defining major epitope regions on the spike RBD associated with neutralization of the virus and providing examples of the molecular basis for neutralizing activity in polyclonal plasmas (11–13).

Initial fears that replication of the RNA genome of CoV-2 could lead to mutational variants and opportunities for immune evasion due to altered amino acid sequences in spike were confirmed by the appearance and efficient spread of viral variants in human populations (14–16). Viral variants with modest numbers of mutations in spike and RBD that led to escape from antibody binding and neutralization caused successive waves of renewed infections across the United States and

internationally. CoV-2-neutralizing mAb cocktails targeting the spike RBD were developed with remarkable speed by several companies, tested in patients, and given emergency use authorization (EUA) by the US Food and Drug Administration (FDA). Unfortunately, the pace of mAb development was matched by the continuous emergence of viral variants that altered the epitopes bound by these antibodies, eventually rendering them ineffective (17).

The accelerated development of several different types of vaccines for CoV-2, perhaps most notably the novel mRNA-lipid nanoparticle vaccines produced by Pfizer-BioNTech and Moderna, was a remarkable achievement. These vaccines provided highly effective protection against severe disease or death, and reduction in symptomatic illness, before a full year had passed from the beginning of the pandemic, at least in those countries where vaccine supplies were adequate. Unfortunately, proposed systems for vaccine distribution to a broader range of countries were not well supported, resulting in most vaccine doses being used in higher income countries initially (18, 19). The emergence of viral variants with mutations in spike and RBD soon led to lower vaccine efficacy, although protection against severe disease or death remained robust. Investigations comparing the antibody and B cell responses stimulated by CoV-2 infection to those from the mRNA vaccines as well as other vaccine modalities such as the adenoviral-vectored AstraZeneca, Janssen, and Sputnik V vaccines and the inactivated viral vaccine from the Chinese manufacturer Sinopharm had begun, but many key questions such as the duration of vaccine-stimulated immunity were not yet answered (20, 21).

These earliest investigations of antibody and B cell immunity to CoV-2 infection and vaccination were critically important for informing initial responses to the pandemic. They also benefitted from a relatively simple initial immunological landscape when no one had been previously infected or vaccinated with CoV-2. The past two years have seen progressively increasing complexity in human populations, as individuals develop immunological histories of prior infection with different viral variants, with or without vaccination with the various vaccines (**Figure 1*a***). These changes have raised fascinating immunological questions that we now address here, including the extent to which more drastically divergent viral variants such as the omicron-derived variants (**Figure 1*b***) can escape from prior humoral immunity; how successive exposures to different CoV-2 antigens shape an individual's B cell memory and antibody-secreting plasma cell populations; the effects of infection and vaccination on mucosal antibody responses and responses in other tissues (**Figure 1*c***); the roles of non-neutralizing antibodies in contributing to protection against infection or severe disease; the nature of antibody and B cell responses and potential immunological resistance mechanisms in populations that appear to have been more impervious to severe COVID-19, such as African populations (**Figure 1*d***), and those who have been more vulnerable, such as patients with cancer, immunodeficiency states, and other comorbidities (**Figure 1*e***); and the evidence for antibody-mediated mechanisms contributing to the lingering symptoms of long COVID or postacute sequelae of COVID-19 (**Figure 1*f***). We conclude with a consideration of lessons learned in the COVID-19 pandemic that could help in responses to future pandemics and ongoing efforts to improve preparedness.

2. RESPONSES TO OMICRON-DERIVED COV-2 VARIANTS

The sudden emergence and global dominance of the CoV-2 omicron variant first detected in South Africa and Botswana in November 2021 brought a new phase in the COVID-19 pandemic. While previous variants of concern had a small number of amino acid changes in the S protein, the acquisition of more than 30 amino acid changes in the omicron (BA.1.1.529) spike and 15 amino acid changes in the RBD was an alarming development, because it provided much more extensive evasion of humoral immunity than earlier variants. The details of the origin of

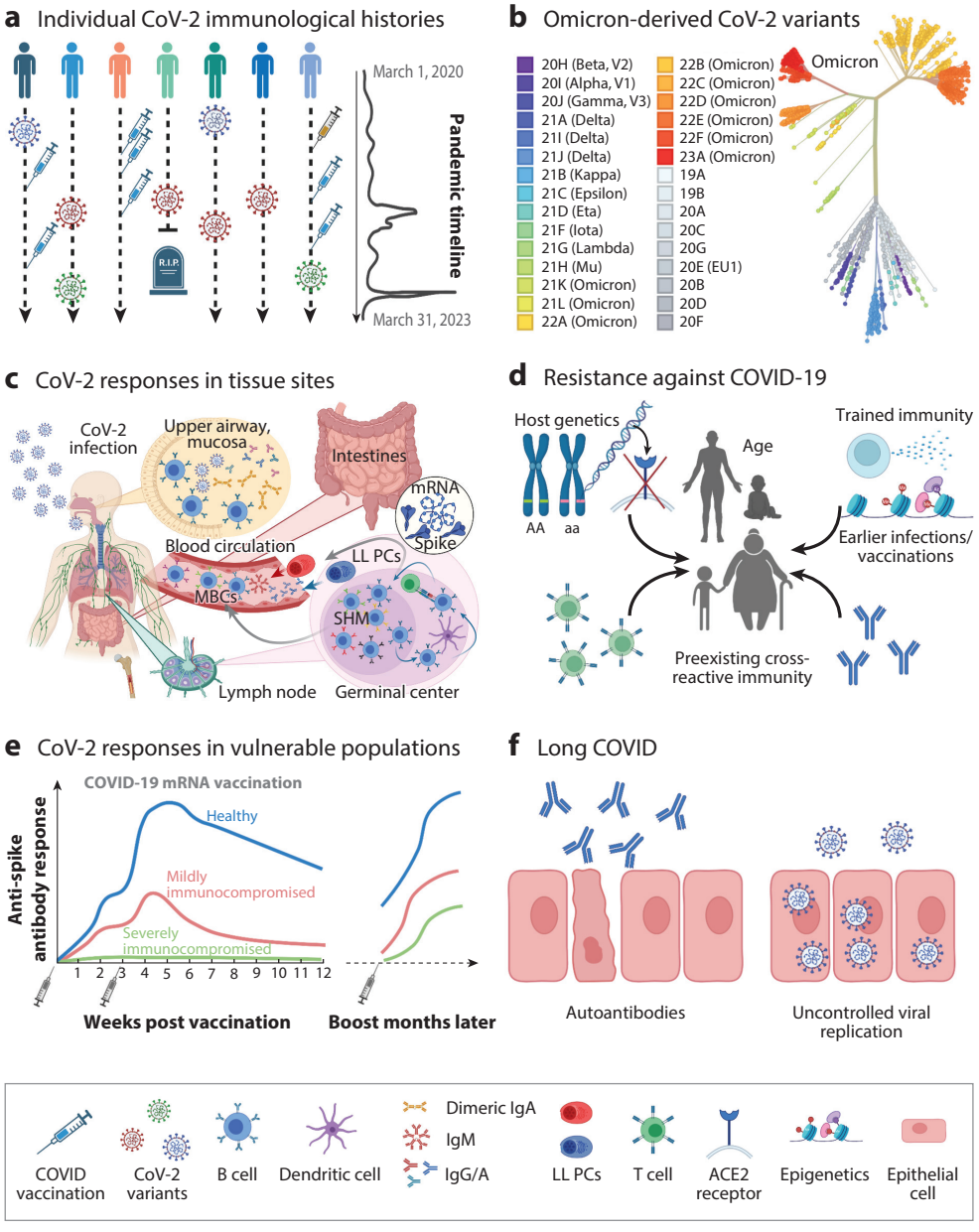

Figure 1

Advances in understanding interactions between human B cell and antibody responses and CoV-2. (*a*) Diverse CoV-2 infection and vaccination histories during the COVID-19 pandemic leading to development of (hybrid) immunity. (*b*) Unrooted phylogram of CoV-2 genomes isolated from infected individuals worldwide between December 2019 and March 2023. Panel adapted from **https://nextstrain.org** (CC BY 4.0). (*c*) Overview of the humoral immune response to CoV-2. Panel adapted from Reference 4 with permission from Elsevier. (*d*) Overview of proposed resistance factors against COVID-19. Panel adapted from Reference 22 with permission from Elsevier. (*e*) Antibody responses to repeated CoV-2 vaccination in healthy and immunocompromised individuals. (*f*) Proposed immune mechanisms involved in long COVID pathologies. Figure adapted from images created with BioRender.com. Abbreviations: ACE2, angiotensin-converting enzyme II; CoV-2, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); COVID-19, coronavirus disease 2019; Ig, immunoglobulin; LL PC, long-lived plasma cell; MBC, memory B cell; SHM, somatic hypermutation.

omicron are unknown, but it appears likely that the extensive accumulation of mutations and selection for evasion of antibody responses occurred during prolonged infection in an individual with impaired immunity, as has been documented in patients immunosuppressed due to organ transplantation, hematologic malignancy, or human immunodeficiency virus (HIV) infection (23–26). By December 2021, several research groups had documented omicron's greater escape from vaccine or prior infection–derived humoral immunity, compared with even the most evasive prior variant, beta (B.1.351). Neutralizing antibody titers for omicron were decreased by at least 15- to 20-fold compared with titers for ancestral CoV-2 in individuals with either prior infection or prior mRNA vaccination (27, 28). Notably, smaller decreases in neutralizing titers for omicron were seen in individuals who had histories of both prior infection and vaccination, suggesting that hybrid immunity from those different exposures had increased the breadth of the antibody response so that it could recognize more divergent viruses such as omicron (29). A similar effect of hybrid immunity was seen in vaccinated individuals who had subsequent omicron breakthrough infection; their plasma had better neutralization of other variants such as delta (B.1.617.2) as well as omicron, compared with the plasma of unvaccinated patients who had only been infected with omicron (30). Individuals vaccinated and boosted with ancestral D614G-encoding mRNA vaccines who had received a third vaccine dose also showed greater omicron neutralization, suggesting that repeated exposures, even to the ancestral CoV-2 spike antigen, can stimulate progressively better antibodies to divergent variants (31, 32). Titers of IgG binding to omicron spike or RBD in previously infected or vaccinated individuals were closer to the titers for binding to other variants than were the neutralizing titers to omicron compared with other variants, leaving open the possibility that non-neutralizing, potentially protective antibody effector mechanisms against omicron could be less affected than the neutralizing responses (28). Not unexpectedly, neutralizing mAbs, including commercialized therapeutic antibodies derived from patients with earlier exposures, were also rendered ineffective by the extensive mutations in the RBD of omicron and the additional variants derived from omicron (17, 31).

Beyond the evidence of the omicron spike's escape from binding or neutralization by antibodies stimulated by earlier variants, there are some interesting data supporting the idea that the selection processes that gave rise to omicron have also made it inherently less immunogenic (less stimulatory of B cell and antibody responses) than earlier variants (33). CoV-2 naive mice immunized with the RBD of omicron raise low titers of antibodies to the RBDs of other earlier variants but also show low titers for omicron itself, compared with the titers against the ancestral Wuhan-Hu-1-like RBD in mice immunized with that antigen. Similarly, humans without prior CoV-2 infection or vaccination who become infected with omicron raise relatively low titers of anti-omicron neutralizing antibodies and even lower neutralizing titers against other variants (34). These findings could also help to explain why there is only a marginally better boost of omicron-specific antibodies in recipients of bivalent omicron and ancestral D614G-encoding mRNA booster vaccines, compared with individuals boosted with an ancestral D614G-only vaccine (35).

While the escape from neutralizing and binding antibodies by omicron CoV-2 is evident, there are other immune responses stimulated by vaccination, such as T cell responses. How do clinical estimates of vaccine efficacy against omicron viruses compare with the antibody data? Ancestral CoV-2 mRNA vaccine efficacy was 93% for delta compared with 70% for omicron in preventing hospitalization with COVID-19 in an early study from South Africa (36). A study from Qatar gave a similar result, with more than 70% protection from severe, critical, or fatal COVID-19 due to the BA.2 variant in individuals who had either had prior CoV-2 infection, vaccination with BNT162b2 or mRNA-1273 COVID-19 mRNA vaccines, or a combination of vaccination and infection (37). Protection against infection rather than severe disease was, however, weaker, with protection after primary mRNA vaccination series plus one booster dose

or prior infection and two-dose vaccination providing 52% and 55% effectiveness of protection, respectively (37). Stronger protection against omicron infection conferred by hybrid immunity was reported in a study of English adolescents, in which prior infection and two-dose vaccination gave more than 96% protection against omicron infection within 6 months of the second vaccine dose (38). Across these and other studies of antibodies and omicron, it has been reported that prior infection, vaccination, or both are protective against severe disease due to omicron, but less so against infection, and that hybrid immunity from a combination of infection and vaccination provides greater protection than either exposure type alone.

All current circulating CoV-2 viruses are derived from omicron-like viruses, and the third year of the pandemic has documented numerous new variants (among them, BA.2.75.2, BQ.1, BQ.1.1, and XBB) with additional mutational diversification or evidence of recombination between different omicron-derived viruses. The mutations in these new omicron sublineages confer additional loss of binding and neutralization by mAbs elicited by earlier variants and have rendered all prior therapeutic neutralizing mAbs ineffective (39). For example, of the commercial therapeutic mAbs that had retained activity against earlier BA.2 and BA.5 omicron viruses, cilgavimab no longer neutralizes BA.2.75, BQ.1, BQ.1.1, or XBB, while sotrovimab is impaired in neutralizing BQ.1.1 and bebtelovimab fails to neutralize BQ or XBB variants (39).

3. CURRENT UNDERSTANDING OF ANTIBODY CORRELATES OF PROTECTION FROM COVID-19

The identification of easily measurable immunological markers that can reliably predict the level of protection from symptomatic or asymptomatic CoV-2 infection is pivotal for gauging the susceptibility of individuals or populations to vaccine breakthrough or reinfection with CoV-2 and for assessing the efficacy of existing and new vaccines. Correlates of protection from CoV-2 infection and disease will only be useful if assays to measure those markers are standardizable across different laboratories and adaptable to current and future CoV-2 variants. While multiple components of the immune system contribute to protection, antibodies that block viral entry into host cells and can be measured in blood and mucosa against different viral variant antigens are obvious candidates for the establishment of robust immune correlates and have been used as such for the assessment of levels of protection after vaccination against many other pathogens (40).

3.1. Antibody Binding and Neutralization as Correlates of Protection

To evaluate antibody binding and/or pseudovirus or live virus neutralization levels as correlates of protection from COVID-19, a number of clinical efficacy studies compared anti-CoV-2 spike antibody binding and/or neutralization titers in individuals who received different COVID-19 vaccines, such as mRNA-1273, adenoviral Ad26.COV2.S and ChAdOx1-S, and protein nanoparticle-based NVX-CoV2373, and subsequently did or did not get infected with CoV-2. All studies agreed in that higher levels of anti-CoV-2 spike IgG binding as well as virus neutralization were strongly correlated with protection from symptomatic CoV-2 infection during short-term follow-up of several months after vaccination (7, 41–43). Normalization of binding and neutralization antibody titers of vaccinees to those of convalescent COVID-19 patients enrolled in the same studies confirmed the strong correlation of antibody titers and vaccine efficacy across several vaccine platforms (44, 45). Of note, one of the studies found no significant association between antibody titers and protection against asymptomatic infection (7), highlighting the need to assess correlates on the basis of well-defined end points, that is, protection from disease, severe disease, or mortality. A reduced risk of CoV-2 reinfection (symptomatic and asymptomatic cases combined) with increasing anti-spike binding antibodies and pseudovirus or live virus

neutralization has also been reported after prior infection and before vaccination (46). Neutralizing antibody titers remained strongly correlated with protection from infection with CoV-2 variants of concern including alpha, beta, gamma, delta, and omicron (47, 48).

Agreement of data across vaccine platforms as well as after infection supports the usefulness of antibodies as markers for protection from COVID-19. However, efforts to define thresholds of antibody levels required for protection are complicated by differences between individuals in their virus exposure and nonimmunological host factors that alter susceptibility to COVID-19 as well as by the lack of standardized antibody measurements across studies, particularly for the assessment of neutralizing antibody levels. In addition to the normalization of antibody measurements based on convalescent patient titers, standardization was attempted by using the World Health Organization (WHO) standard polyclonal antibody to convert antibody levels into international units (49). This allowed studies to estimate antibody thresholds required for a certain percentage of protection, albeit with a wide reported range of international units of antibody neutralization between studies (7, 41), indicating that differences in the assays used to measure antibodies may account at least partly for those discrepancies. Moreover, due to the overlap of antibody levels between individuals with or without breakthrough infections, it was not possible to determine a definite antibody threshold, and instead a gradient of vaccine efficacy that increases with neutralization was observed. Standardization of IgG binding antibody levels is certainly more attainable, and several studies have reported an even higher statistical correlation of binding compared with neutralizing antibody titers with protection (41, 45), suggesting a role of non-neutralizing vaccine-induced antibodies and their crystallizable fragment (Fc) effector functions in protection.

3.2. Roles of Non-Neutralizing Antibody Effector Functions

In addition to the neutralization of viral particles, antibodies can also orchestrate cellular mechanism of antiviral defense via antibody Fc region–mediated recruitment of complement and/or Fc receptor (FcR)-expressing immune cells. These antibody-dependent effector functions include positive mechanisms such as antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity resulting in the clearance of virus and/or infected cells but can also have detrimental effects such as aberrant inflammatory immune responses. There is no doubt that Fc-dependent antibody functions play a role in shaping the outcome of infection with CoV-2, but the framework for understanding their relative contributions is limited. Fc-mediated effector functions against CoV-2 have on the one hand been linked to protection from fatal COVID-19 (50, 51); on the other hand, they have been implicated in excessive inflammation associated with tissue damage and worsening clinical status of COVID-19 patients (52).

Unlike neutralizing antibodies that must bind to the S protein at specific epitopes interacting with the ACE2 receptor to prevent the virus from entering cells, antibodies that elicit Fc effector functions may target any epitope on any CoV-2 antigen. Infection or vaccination-elicited Fc effector functions are therefore less affected by the emergence of viral variants. Major determinants of the type and response of FcRs engaged by Fcs are antibody isotype, subclass, and posttranslational modifications such as glycosylation. Even minor changes in the composition of Fc-associated glycans can significantly alter the conformation of the Fc region, changing its interaction with members of the Fc gamma receptor (FcγR) family expressed on immune cells. Elevated concentrations of anti-CoV-2 IgG1 Fc, lacking core fucose residues on N-linked glycans, were observed in patients with severe COVID-19 but not in those with mild symptoms (53, 54). Such afucosylated IgG1 responses are characterized by increased binding affinity to the activating FcγRIIIa/CD16a found on immune cells including subsets of natural killer cells, monocytes, and macrophages, potentially promoting cytokine storms and immune-mediated

pathologies associated with severe COVID-19 (54). The reasons for production of higher levels of afucosylated IgG in some individuals remain unknown. In contrast, antibodies that are elicited by mRNA vaccines are highly fucosylated and enriched in sialylation, both modifications that reduce the inflammatory potential of IgG (55). Differences between vaccine types have also been reported in that increased class-switching toward noninflammatory spike-binding IgG4 antibodies has been observed with time and/or repeated doses of mRNA but not adenoviral vaccines (56, 57). This class switch results in a reduced capacity of the spike-specific antibodies to mediate effector functions such as ADCP but is unlikely to compromise immunity in vaccinated individuals, as IgG4 antibodies usually have higher affinity and may form small immune complexes or larger, mixed immune complexes with IgG1 to enable efficient viral neutralization. Future research is required to evaluate the effectiveness of repeated vaccine boosters as well as potential benefits of heterologous vaccination regimens and/or spreading out boosters over longer time periods to optimally involve cellular and humoral mechanisms of the immune system, including both the variable and constant regions of antigen-specific antibodies (58).

4. HUMORAL IMMUNE MEMORY AND IMPRINTING FROM SEQUENTIAL INFECTION OR VACCINATION

4.1. Prior Endemic Human CoV Exposures

Given the homology of CoV-2 with endemic HCoVs including the human betacoronaviruses (beta-HCoVs) OC43 and HKU1 and the human alphacoronaviruses (alpha-HCoVs) 229E and NL63, it is possible that these viruses are a source of CoV-2 cross-reactive immune responses. All four HCoVs are highly prevalent worldwide, causing common respiratory infections. Protective immunity against reinfection with any of the four HCoVs is short-lived, and reinfection can occur within a year (8). It is still not fully clear to what extent HCoV cross-reactive antibodies have CoV-2 neutralization potential and whether recent HCoV infection may provide a certain degree of protection against CoV-2 infection and/or COVID-19 pathology.

While the CoV-2 RBD region has relatively low homology with other CoV RBDs, the N-terminal region of the nucleocapsid protein and the S2 fusion domain of spike are highly conserved among CoVs. The RBD region contains the most neutralizing antibody-binding sites, but some anti-S2 antibodies have also been shown to prevent CoV-2 cell entry. Although anti-nucleocapsid antibodies are unlikely to be neutralizing, their Fc region may elicit antibody effector functions. Testing of prepandemic serum from US individuals revealed that approximately 4% and 16% of samples contained IgG antibodies cross-reacting with the CoV-2 spike and nucleocapsid antigens, respectively (59). Less than 1% of prepandemic serum samples contained antibodies reacting with RBD, and none of the samples had CoV-2 neutralizing activity assessed in pseudovirus neutralization assays (59). Similar proportions of prepandemic antibodies have been reported in serum from Canadians, with an overall prevalence of anti-spike and anti-nucleocapsid IgG of 5% and 11%, respectively. This second study reported a higher prevalence of prepandemic anti-RBD antibodies of 4.6% and moderate inhibition of spike-ACE2 interaction in some sera as measured in a surrogate blocking enzyme-linked immunoassay (60). Conversely, it has also been shown that infection with CoV-2 boosts anti-spike IgG antibodies cross-reactive with other HCoVs, particularly the beta-HCoVs OC43 and HKU1 (59, 61). In line with this, highly mutated, preexisting beta-HCoV cross-reactive memory B cells (MBCs) have been shown to expand in the early response to CoV-2 infection (62). However, their frequency decreases over time, suggesting that CoV-2 infection provides only a temporary expansion of these members of the MBC pool.

Informative studies tackling the question of cross-protective effects of prior HCoV infection on CoV-2 infections have assessed baseline anti-HCoV antibodies of individuals who

subsequently did or did not become infected with CoV-2. A common trend toward higher preexisting anti-HCoV nucleocapsid IgA and IgG levels was observed in subsequently CoV-2 seroconverted asymptomatic health-care workers compared with symptomatic health-care workers, although statistical significance was reached only for anti-OC43 nucleocapsid IgA (63). Similarly, in a second study, health-care workers with high compared with lower IgG antibody levels to the OC43 nucleocapsid C-terminal domain were less likely to become CoV-2 seropositive, while no significant association was found between anti-spike antibody levels and incidence of CoV-2 infection (64). A third study found that baseline anti-HCoV spike IgG, IgM, and IgA antibody levels did not differ between individuals who did or did not become infected with CoV-2 (65). Moreover, no significant difference between baseline anti-HCoV spike antibody levels and COVID-19 disease severity was found (65). The use of different CoV-2 antigens (spike versus nucleocapsid) for measuring preexisting HCoV antibody levels may have contributed to these discordant results. The C-terminal domain of the nucleocapsid protein is well preserved within, but less conserved between, HCoV species, allowing for a specific association of detected antibodies with exposure to certain HCoV types. Parts of the S protein (in particular the S2 region) are known to be highly conserved among HCoVs, giving rise to HCoV cross-reactive responses that cannot be associated with exposure to specific HCoV types. One epidemiological study based on electronic health records found that recent prior infection with HCoVs was associated with less severe COVID-19 illness (66), while another found no significant difference in COVID-19 severity regardless of recent HCoV infection (67). Taken together, these data suggest that if prior HCoV infection does have an effect on COVID-19 disease course, it is likely to be small.

4.2. Immunological Imprinting of B Cell Responses to Successive CoV-2 Variant Antigens

The successive waves of CoV-2 viral variant infections that have moved through human populations in the past three years, as well as varying vaccination and boosting choices and timing, have given rise to many different kinds of individual immunological histories of CoV-2 antigen exposures. The concept of immunological imprinting in antibody and B cell responses reflects prior evidence, particularly from influenza virus studies, that prior exposures to particular viral variant antigens can shape future responses to other viral variants and affect clinical outcomes. For example, the effects of differing childhood influenza virus infections depending on birth year have been proposed as an explanation for different age-related rates of mortality in individuals who become infected with H5N1 or H7N9 avian influenza (68). The primary mechanistic candidate for antibody response imprinting is the formation of MBC populations during initial antigen exposures that then influence which epitopes of future antigenic variants will give rise to dominant responses. At this point in the CoV-2 pandemic, what is the evidence for imprinting effects of prior CoV-2 variant exposures from infection or vaccination on subsequent responses and on clinical outcomes of CoV-2 infection?

Data from polyclonal antibody serological studies revealed major differences in the relative amount of binding to RBD antigens from different CoV-2 variants in individuals who had been infected by each variant; individuals whose first CoV-2 exposure was infection by alpha or delta variants had plasma IgG that preferentially bound the alpha or delta RBDs, respectively (61). In contrast, IgG from individuals who were first vaccinated with mRNA vaccines expressing Wuhan-Hu-1-like spike followed by infection with alpha or delta variants showed preferential binding to the Wuhan-Hu-1 RBD even after the variant virus infections. Similar effects of preferential binding of the first viral variant encountered have been reported for other variants, including omicron (34). Does an individual's history of prior exposures affect their susceptibility to infection by new variants? Epidemiological studies from Qatar found that among unvaccinated individuals, those

who had been infected with a pre-omicron viral variant followed by BA.1 or BA.2 omicron variants had lower rates of infection by BA.4 or BA.5 omicron or other later variants, compared with individuals who had only had prior omicron infection, suggesting that the combined pre-omicron and omicron infections may have provided MBCs and plasma antibodies with greater breadth, conferring more protection against later omicron variants (69). Complementing this result, but showing the complexity of imprinting effects, Tan et al. (70) found in vaccinated and boosted Singapore residents that prior infection with BA.2 was associated with protection against BA.4 or BA.5 variants but less so against the later XBB variant that had further diverged in sequence. In a study of vaccinated and boosted individuals in London, omicron (B.1.1.529) infection was also associated with increased protection from later omicron variant infection, but this extra protection was not observed if the individual had also been infected by Wuhan-Hu-1 virus in the initial infection wave (71). The contrast between this result and that from the Qatar study could be related to the differences in vaccination status in the two cohorts. A reassuringly consistent finding in these and most other studies is that hybrid immunological experience by vaccination and infection, or vaccination and boosting alone, is associated with protection from severe COVID-19 and death.

5. MECHANISMS IN B CELL RESPONSES TO COV-2 EXPOSURES

Studies of the serological responses to CoV-2 infection and vaccination naturally lead to many questions about the B cells and plasma cells producing the antibodies, the MBCs that enable faster responses to subsequent exposures, and the changes in these populations after repeated encounters with antigenic variants.

5.1. B Cell Mechanisms of Imprinting

Studies probing the mechanistic basis for imprinting effects have found, for the most part, that the B cell responses to successive different CoV-2 variants stimulate B cell clones that recognize epitopes shared between the variant antigens, with few clones that bind only the second antigen encountered (72–74). One study adds the additional result that small numbers of clones that are not cross-reactive and appear to be newly stimulated by the second antigen, as judged by low rates of somatic mutation in the antibody genes, can also be detected (75). The cross-reactive RBD epitopes targeted in vaccinated individuals who have breakthrough infections with BA.1, BA.4, or BA.5 differ from the most prominent neutralizing, ACE2-blocking sites targeted during primary Wuhan-Hu-1-like infection or vaccination (73). The fact that hybrid immunity has been found to be quite protective against severe disease and death even later in the omicron wave may suggest that antibodies against these other epitopes, together with other branches of immunity such as T cell responses, may contribute to the less severe disease manifestations.

A less thoroughly studied aspect of imprinting mechanisms is the effect of the amount of time that passes between antigen exposures on the imprinting result. Since affinity maturation of B cell clones seems to continue for months after infection or vaccination (62, 76–78) and alters the affinity and breadth of B cell binding to CoV-2 antigens, it is possible that two different antigen exposures separated by a greater length of time could give rise to differences in variant antigen epitope binding and breadth.

5.2. Evolution of B Cell Responses and B Cell Memory Over Time in Blood and Lymphoid Tissues

Primary exposure to CoV-2, which is increasingly rare but has been extensively studied early in the COVID-19 pandemic, is characterized by an initial burst of highly polyclonal B cell populations that show near germline sequences (79) with limited contribution from highly mutated MBCs

likely derived from prior exposure to beta-HCoVs (62). The apparent lack of somatic mutations in antibody genes points to naive B cells rapidly differentiating into short-lived antibody-secreting cells. Longer-term immunity relies on germinal center (GC) responses in secondary lymphoid tissues, where B cells undergo somatic diversification and affinity-driven selection of B cells with the highest-affinity receptors, resulting in the differentiation into long-lived plasma cells and MBCs. Indirect evidence for GC responses in CoV-2 infection has been found in longitudinal flow cytometry and B cell receptor (BCR) analyses of blood samples from convalescing individuals showing that circulating spike- and RBD-binding MBCs progressively accumulate somatic mutations in their V genes. Increasing frequencies of these antigen-binding cells measured in the initial months postinfection (62, 76, 77) may at least in part be explained by improved antigen-binding affinity. Groups of clonally related RBD-specific antibodies isolated from some of the individuals shortly after CoV-2 infection and later in convalescence revealed that in addition to the acquisition of somatic mutations in the months after infection, antibodies had greater neutralization potency and breadth (80). Of note, for some antibodies, affinity maturation enabled neutralization of CoV-2 variants and heterologous sarbecoviruses, indicating that increasing antibody diversity may improve protection against diversifying CoV-2 populations (80). This finding is also supported by analysis of the polyclonal serum response in convalescent individuals, which shows a significant improvement of variant-binding breadth over time (61, 81). Breadth of CoV-2 variant RBD binding was, however, consistently lower at early time points in convalescent individuals compared with individuals after mRNA vaccination (61), suggesting that mechanisms of humoral responses and their interactions with viral/vaccine antigens in secondary lymphoid tissues may differ between infection and vaccination.

BNT162b2 and mRNA-1273 vaccination also induce robust spike- and RBD-specific B cell responses. Similar to what has been reported after CoV-2 infection, the frequency of circulating CoV-2-binding MBCs in the blood continued to increase for up to 6 months (21, 78) and remained stable up to 9 months postvaccination (32). This included MBCs that cross-recognized several CoV-2 variants including alpha, beta, and delta at higher frequencies than mild CoV-2 infection (78). Analysis of clonally related Wuhan-Hu-1 only and variant cross-binding RBD-specific MBCs, revealing higher somatic hypermutation (SHM) in variant cross-binding clones, suggests that variant binding capacity can evolve from clones that initially bound only to Wuhan-Hu-1 RBD (78). Of note, two doses of mRNA vaccination also generated an MBC response against the omicron variant, with 40–50% of RBD-binding MBCs able to cross-bind omicron (32), at least to some degree. A third vaccine dose efficiently recruited MBCs with cross-reactivity to multiple CoV-2 variants (32).

Hybrid immunity after vaccination plus infection results in a substantial increase in circulating spike- and RBD-specific MBC frequencies (78, 82, 83); these, however, decline to levels similar to those seen after two doses of mRNA vaccination after 6 months (78). In hybrid immunity, the RBD-binding MBCs have substantially more SHM and affinity maturation than after vaccination alone (78, 82, 83). Functionally this aligns with the significantly higher potency and variant breadth of neutralizing antibodies from MBCs in people with hybrid immunity compared with vaccination or infection alone (82, 83).

While initial investigations of B cell responses to CoV-2 infection and COVID-19 vaccination mostly focused on easily obtainable B cells that have entered the blood, few studies have examined responses in lymph nodes (LNs), spleen, or other organizing sites of adaptive immunity. Sampling approaches such as fine-needle aspiration (FNA) enable isolation and analysis of cells from lymphoid organs of healthy human subjects (84), providing the first direct insights into GC reactions that are critical for generating high-affinity MBCs and long-lived bone marrow plasma cells (BMPCs).

Analysis of FNAs from LNs has revealed that COVID-19 mRNA vaccination elicits potent spike- and RBD-specific GC B cell and plasma cell responses in vaccine-draining but not contralateral LNs, with sustained GCs detected in most individuals for at least 6 months after the booster immunization (85, 86). GC B cell responses were associated with a robust induction of T follicular helper (Tfh) cells, class-switched RBD-specific MBCs, and neutralizing antibodies (85). Valuable insights into the maturation of these antigen-specific B cell responses in different tissues after mRNA vaccination have been provided in one of the most comprehensive investigations of blood, LN, and bone marrow B cells analyzed in the same vaccinees by Kim et al. (86). In this study, analysis of FNAs from draining axillary LNs after the primary mRNA vaccination schedule enabled the identification of spike-specific GC B cells that were sustained in LNs in most study participants for at least 29 weeks (86). A 3.5-fold increase in SHM frequency was observed among all spike-binding GC B cells between weeks 4 and 29. Analysis of clonal relationships of BCRs revealed significantly higher levels of SHM in spike-binding GC B cells at week 29 compared with clonally related circulating plasmablasts at week 4 and slightly higher SHM levels compared with clonally related blood MBCs at week 29 after vaccination. SHM frequencies of spike-binding GC B cells and LN plasma cells increased over time at a similar rate with a high degree of overlap between the two compartments. Spike-binding BMPCs from aspirates collected 29 and 40 weeks after vaccination exhibited a degree of SHM that was similar to that of LN plasma cells at 15 and 29 weeks after vaccination. BMPC-derived mAbs detected 6 months after vaccination showed increased affinity compared with the corresponding plasmablast-derived mAbs from week 4 postvaccination (86). These data demonstrate that mRNA vaccines induce robust and persistent GC reactions generating affinity matured MBC and BMPC populations in healthy individuals. However, the relatively short half-life of plasma antibody titers against CoV-2 spike following mRNA vaccination suggests that the specific BMPC populations may not be as long-lived as those generated by some other vaccines such as those for vaccinia, measles, or mumps (87). Notably, a marked impairment of GC B cell responses in LNs associated with a nearly abolished RBD-specific MBC response in LNs and blood and reduced capacity of serum antibodies to neutralize CoV-2 was found in kidney transplant recipients receiving mRNA vaccines (85).

While FNA samples can provide information on the presence of immune cells in the sampled lymphoid organs, lymphoid tissue core needle biopsies obtained with larger gauge needles offer a unique opportunity to study GC architecture. We used this approach to examine GC formation and composition in mRNA vaccinees compared with tissues obtained from deceased COVID-19 patients. We detected fully developed GCs, including $BCL6^+$ GC B cells, $PD\text{-}1^+$ Tfh cells, and extensive $CD21^+$ follicular dendritic cell networks in ipsilateral axillary LN biopsies from mRNA vaccinees (61). On the contrary, GCs were poorly formed in severely ill COVID-19 patient LNs and spleen, with disrupted follicular dendritic cell networks and decreased GC B cells and Tfh cells (61, 88). These observations indicate impaired GC function and thus potential impairment of formation of long-lived MBCs and plasma cells in the most severe cases of COVID-19. Whether patients with mild COVID-19 exhibit similar impairment of GC structures or functions is an important question as yet unanswered.

An additional question of interest for GC reactions in CoV-2 infection and vaccination responses is the quantity, localization, and persistence of CoV-2 antigens in GCs and other sites in the body. It has recently been shown that viral proteins can persist in the gut of CoV-2 convalescent individuals for at least 4 months (76). Analysis of resected peribronchial LNs from COVID-19 patients who died within 1 to 3 weeks of onset of symptoms detected nucleocapsid protein in GCs in most patients, and spike in one of seven. In core needle biopsies of LNs from mRNA-vaccinated individuals, S protein could be detected in GCs for up to 2 months (61), indicating that antigen to fuel GC reactions and affinity maturation can persist for extended periods of time in relevant

tissue sites. Addressing the degree to which spike antigen concentrations and persistence in GCs differ between vaccination and infection, or in patients with different disease severity, will require further study.

5.3. B Cell Phenotypes in Response to Infection and Vaccination

A complicating feature of the analysis of specific B cells involved in immune responses to CoV-2 exposures is the use of different combinations of surface markers or transcriptional features to define B cell subsets in various studies. B cells that circulate in the peripheral blood, and, in particular, antigen-specific MBCs that undergo phenotypic and functional changes over time following antigen exposure, are highly heterogeneous, and several partially overlapping subsets of activated nonplasmablast vaccine- or infection-stimulated B cells have only recently been recognized, on the basis of surface marker characteristics such as low CD21 and upregulated CD71 (89, 90). In addition to these subsets, a variety of atypical B cell subsets have been defined with different combinations of surface markers, for example, CD11c, other markers such as FcRL5, and lack of CD27 expression. Both CoV-2 infection and vaccination induce robust class-switched plasmablast- and nonplasmablast-activated MBC responses that are further increased after secondary exposures.

In analyzing responses to CoV-2 infection, several groups have provided detailed descriptions of the B cell populations that appear in the blood with characteristic timing. Sokal et al. (62) report that in the initial weeks of COVID-19, patients show circulating antibody-secreting cells (ASCs) designated as plasmablasts expressing markers of proliferation, as well as nondividing plasma cells, and in addition have three nonplasmablast B cell phenotypes in the blood: $CD21^{low}CD27^{+}CD38^{+}CD71^{+}$ activated B cells (ABCs), $CD21^{low}CD27^{low}CD38^{-}CD71^{low}CD11c^{+}FcRL5^{+}$ cells that have similarity to subsets previously designated as atypical memory or double negative 2 (DN2) in the literature (91), and an intermediate phenotype of activated cells with $CD21^{+}CD27^{int/+}CD38^{-}CD71^{low}CD95^{+}$. At later times after infection, the antibody-secreting plasmablast and plasma cell types are largely absent, and resting memory B cells compose most of the antigen-specific B cells, with progressively fewer cells showing the other activated phenotypes. The largest clones of ASCs had shared clones with the ABC populations, suggesting that they share a common precursor or phenotype. The bimodal distribution of SHM seen in the ASC immunoglobulin genes suggested that some clones were derived from prior MBCs, while others were newly drawn into the response, likely from naive B cells (62). Patients who had severe COVID-19 differed from those with mild disease in having higher frequencies of antigen-specific MBCs at 6 months postinfection. Somewhat surprisingly, $CD71^{+}$ ABC populations were still present in the blood at 6 months postacute illness, potentially indicating that antigen-driven stimulation persisted at least that long. The patients with severe illness had higher frequencies of $CD71^{+}$ ABCs in the initial weeks of infection, persisting to 6 months after infection. Other investigators have reported that severe COVID-19 disease was associated with higher frequencies of DN2 phenotype cells (those lacking IgD and CD27 expression, and with low CD21 but $CD11c^{+}$ expression) (91). One question that remains not fully answered is the extent to which the B cell clones observed in each of these activated non-ASC subsets contribute to long-lived BMPCs.

The B cells responding to mRNA vaccination have been particularly closely studied since these vaccines became authorized for use. Approximately 1 week after the second dose of mRNA vaccination, B cell responses develop from $CD27^{+}IgD^{+}IgM^{+}CXCR5^{+}$ cells to IgA^{+} or IgG^{+} plasmablasts ($CD27^{+}IgD^{-}CD38^{+}CXCR5^{-}CD11c^{+}$), with a somewhat later appearance of MBCs with a $CD27^{+}IgD^{-}CD38^{+}CXCR5^{+}CD24^{+}CD11c^{-}$ phenotype (92). Several antigen-specific MBC populations emerged after vaccination, including conventional phenotype resting memory cells ($CD27^{+}CD20^{+}CD21^{+}$) further defined by their isotype expression, as well as

activated memory cells similar to those seen after infection ($CD27^+CD20^{++}CD21^{lo}CD11c^+$). Spike-specific cells were most enriched in the IgG^+ and IgA^+ plasmablasts, as well as the activated MBCs with a $CD21^{lo}CD11c^+$ phenotype (93).

6. RESPONSES IN MUCOSAL TISSUE SITES

One of the fundamental questions in CoV immunology is why infection with these viruses does not elicit more complete and longer-lasting protection against reinfection. The development of viral variants and immune evasion only partly explains this circumstance, considering that infection with seasonal HCoVs recurs frequently, even within a year and with an identical strain (8, 94). Answers may be found by examining interactions of the viruses with defense mechanisms in different compartments of the human immune system.

6.1. Early Interaction of CoVs with the Immune System

Mucosal surfaces of the respiratory tract represent the primary route of entry and early local replication of respiratory viruses, such as CoVs. These viruses have adapted over thousands of years to tolerize host immune responses, enabling infection and replication in mucosal sites well before systemic adaptive immune mechanisms set in to control them (95). Consequently, CoV-2 as well as other HCoVs tend to repeatedly reinfect people without eliciting durable sterilizing protection. Of note, although CoV-2 RNA has been detected in plasma of patients with severe disease, no study has yet demonstrated the presence of infectious virus in blood (95–98), suggesting that viruses may encounter fully effective adaptive immune responses only after viral replication in the mucosa and onward transmission to others. In contrast, life-long immunity after infection with, for example, polio, variola, or measles virus is associated with significant viremia leading to a direct contact of large numbers of infectious virions with multiple immune compartments (99). The development of future sterilizing vaccines against CoV-2 constitutes a major challenge, if not even infection can elicit durable protective immunity.

6.2. Stimulation and Effects of Mucosal Antibody Responses

CoV-2 initially infects and replicates within epithelial cells of the upper airway mucosa, especially the nasal cavity. These tissues are rich in lymphoid cells that are organized into nasopharynx-associated lymphoid tissues. Once an infection in the upper respiratory tract has been established, CoV-2 may disseminate systemically and progress to other epithelial cells such as those in the lower respiratory tract, where broncho-associated lymphoid tissues are present. Mucosal sites can mount robust local adaptive responses, comprising tissue-resident memory T and B cells and localized antibodies, which are key effector molecules at mucosal sites. Mucosal antibodies have two major sources: local production of IgA and translocation of circulating antibodies to the mucosa. Given that viral loads decrease rapidly after symptom onset and that most infections are asymptomatic or mild, mucosal immune responses are likely to play a key role in viral clearance. Dimeric secretory IgA (sIgA) is the principal antibody isotype in mucosal tissues and is crucial for the protection of mucosal surfaces. Characterized by high avidity, sIgA is significantly more potent in neutralizing CoV-2 than monomeric plasma IgA (100).

Analysis of paired samples of blood and saliva in COVID-19 patients has shown positive correlations for anti-CoV-2 spike and RBD IgM, IgG, and, to a lesser extent, IgA (101), although saliva antibody levels were significantly lower than corresponding blood antibody levels (102), reflecting that IgM and IgG antibodies mainly enter from the blood via transudation through the gingival crevicular fluid, and are thus highly diluted, while sIgA is produced by local plasma cells. Salivary IgG antibodies are detected in convalescing mild COVID-19 patients for up to 9 months

after infection (103), while IgA and IgM antibody levels rapidly decay (101, 103). In more severely affected, hospitalized COVID-19 patients, nasal anti-nucleocapsid and anti-spike IgG responses have been detected for up to 12 months after infection, while antigen-specific nasal IgA waned after 9 months (104). Interestingly, antibody affinity against CoV-2 spike in nasal washes was significantly higher in asymptomatic individuals compared with symptomatic COVID-19 patients (105). Nasal wash samples from subjects with severe disease exhibited little to no viral neutralization capacity, whereas individuals with mild symptoms had elevated mucosal neutralization activity (106). Higher nasal RBD- and spike-specific antibody levels at study enrollment were associated with lower viral load (107).

Of note, mRNA vaccinees elicited significantly lower levels of anti-spike IgA antibodies as well as neutralizing activity against different CoV-2 variants in the bronchoalveolar lavage (BAL) fluid compared with COVID-19 convalescents. In addition, mRNA vaccines did not appear to induce significant BAL tissue-resident CoV-2-specific B and T cell memory, unlike that seen in COVID-19 convalescent patients (108). The lack of notable IgA production in BAL appeared in contrast with the detection of moderate but significant anti-spike IgG and IgA responses in saliva after mRNA vaccination, with IgG levels similar to, and IgA levels lower than, those of COVID-19 convalescent patients. Anti-spike and anti-RBD IgG and IgA, but not IgM, were detected in the saliva of most vaccinees after one dose of mRNA vaccination. IgA antibodies in saliva were found to associate with the secretory component, indicating their mucosal, transcytotic origin and polymeric multivalent nature. Three months after the first vaccine dose, the median level of salivary anti-spike/RBD antibodies had diminished nearly to baseline. Administration of a second dose boosted IgG, but not IgA, responses. A strong concentration-dependent neutralizing activity of vaccinee saliva was found and attributed to IgA, as depletion of IgA, but not IgG, from the samples resulted in the loss of neutralization capacity. Antibody levels and neutralization capacity of saliva significantly declined to baseline levels over a period of 6 months (109, 110).

Currently available injectable systemic COVID-19 vaccines have been highly effective in reducing the risk of severe disease, hospitalization, and death. Nasal vaccines, on the other hand, could potentially achieve mucosal immunity, complementing and likely bolstering the systemic immune response by inhibiting infection and preventing viral transmission to others. At the end of 2022, at least 100 mucosal COVID-19 vaccines were in development and 20 in clinical trials (111). A combination of intramuscular mRNA vaccination and subsequent intranasal spike subunit protein vaccination, called prime and spike, showed proof of concept in the mouse model, eliciting strong protective mucosal immunity (112).

7. DEMOGRAPHICALLY OR CLINICALLY DISTINCT POPULATION RESPONSES TO COV-2 INFECTION AND VACCINATION

Evidence is accumulating that not everyone is equally susceptible to CoV-2 infection and that different mechanisms of natural resistance may be at play, as has been reported for many other human infections (113, 114). Immunological mechanisms conferring resistance include preexisting adaptive immunity and enhanced (trained) innate immunity potentially mediated through long-lasting epigenetic and metabolic rewiring of myeloid cells in response to earlier vaccination or infection (22), as discussed in the following paragraphs in the context of diverse outcomes of the COVID-19 pandemic on different continents and in different population groups. In contrast, other groups of patients such as those with malignancies, immunodeficiency conditions, and other comorbidities may have increased susceptibility to severe COVID-19, and extra effort needs to be spent in finding optimal prevention and treatment strategies for these vulnerable individuals, particularly now that all of the previously authorized mAb therapies have lost effectiveness against recent omicron-derived variants.

7.1. CoV-2 Immunity in African Populations

In contrast to expectations that existing socioeconomic challenges and the fragile, overburdened health infrastructure in West, Central, and East Africa would exacerbate consequences of the COVID-19 pandemic, significantly fewer CoV-2 infections and less COVID-19-related morbidity and mortality have been reported compared with figures from other continents (**https://coronavirus.jhu.edu/map.html**). Apart from likely underreporting of COVID-19 cases and the young population age structure in Africa, hypotheses to explain lower disease burden in certain countries include differential protective mechanisms of the human immune system in different populations, such as cross-reactive immunity after previous infection with other HCoVs or a more stimulated, trained immune system due to widespread use of live attenuated vaccines such as bacille Calmette–Guérin and/or exposure to many other pathogens prevalent in Africa (22). Trained immunity is characterized by nonspecific increased responsiveness, mediated by metabolic and epigenetic reprogramming in myeloid and lymphoid cells (115).

Serological surveys for exposure to CoV-2 in different African countries have indeed revealed vast underreporting of CoV-2 infections. In a meta-analysis of population-based studies to estimate CoV-2 seroprevalence in Africa including 43% of WHO African continent member states, sharp increases in pooled seroprevalence from 3% (95% CI, 1%–9.2%) across Africa in Q2 2020 to 70% (95% CI, 65%–75%) in Eastern Africa, 56% (95% CI, 45%–67%) in Southern Africa, 73% (95% CI, 64%–81%) in Western Africa, and 76% (95% CI, 72%–78%) in Central Africa as of Q3 2021 have been reported (116). High seroprevalence even before the omicron variant circulation that started in Q4 2021 suggests much greater population exposure compared with reported numbers of CoV-2 infections and therefore lower susceptibility to severe disease in these populations, considering the relatively low numbers of COVID-19-related deaths reported in Africa. With a median age of approximately 20 years, Africa has by far the youngest population compared with other continents and hence a lower burden of noncommunicable disease comorbidities that are known risk factors for severe COVID-19. Infectious diseases, on the other hand, that are highly prevalent in Africa, such as HIV/AIDS and tuberculosis, also pose significant risk factors for severe COVID-19 (117, 118). Similar median population age combined with much lower COVID-19 mortality rates in India compared with those in Brazil argue against age being sufficient by itself to explain the outcome of the pandemic on different continents.

The jury is still out on levels of preexisting immunity to CoV-2 in African versus other populations, as data on molecular and epidemiological profiles of HCoVs in Africa are scarce. It has been reported that all four seasonal HCoVs (229E, HKU1, NL63, and OC43) that are endemic in other parts of the world are also circulating in Africa (119–121), but the frequency and antigenic types of HCoV exposure in different African populations compared with other populations are unclear. One active surveillance study in rural Kenya for the presence of respiratory disease–causing viruses found a high prevalence of often asymptomatic infection with 229E, NL63, and OC43, with 72% of study participants experiencing at least one HCoV infection episode over the 6-month study period (120). No additional HCoVs have so far been identified in Africa. In principle, seroepidemiological studies have the potential to assess preexisting cross-reactive antibody responses to CoV-2, but one of the challenges in directly comparing levels of pathogen-specific antibodies in sera from African versus other populations has been the generally higher serological assay background signals in a large proportion of African plasma samples that has been reported not only for CoV-2 (122) but also for other pathogens such as HIV (123) or ZIKA virus (122). While the mechanisms behind this phenomenon have not been fully elucidated, hypergammaglobulinemia resulting from polyclonal B cell activation induced by pathogens such as *Plasmodium* is suspected to lead to higher antibody cross-reactivity. Whether such cross-reactive antibodies provide any

protective advantage is not clear. Comparison of prepandemic samples from Central Africa, Europe, South America, and North America revealed low to undetectable levels of antibodies against the S protein. A higher prevalence of N-binding antibodies in the Central African participant samples was detected, but these antibodies failed to neutralize CoV-2 in vitro as well as in a mouse model (124). Of note, Fc-mediated antibody functions as well as cross-reactive T cells against the CoV-2 nucleocapsid protein or other antigens have not been assessed in the Central African participant samples and may play a role in potential protection. Increased prepandemic anti-CoV-2 nucleocapsid levels have also been reported in West and East African countries compared with samples from other continents, while IgG antibodies binding to other HCoVs were found in samples from all regions (125). Higher prevalence of prepandemic anti-nucleocapsid levels in Africa compared with other regions may indicate either the presence of CoV-unrelated cross-reactive antibodies or possibly the circulation of as-yet-unrecognized HCoVs with homologous nucleocapsid proteins.

Overall, more data are needed to fully assess immune responses of African populations after SARS-CoV-2 infection and to further explore potential reasons for the low disease severity in these groups. Systematic analyses of the nature and longevity of immune responses to different COVID-19 vaccines in West, Central, and East Africa are urgently required.

7.2. Pediatric Responses to CoV-2

Age at the time of primary CoV-2 infection has been one of the most notable determinants of COVID-19 outcome, with children generally experiencing a milder course of COVID-19 than adults. The fact that children under 5 years of age have the highest prevalence of infection with other HCoVs while people over the age of 65 years have lower overall HCoV prevalence (126) has prompted assumptions that recent HCoV infection might provide cross-reactive protection to children against CoV-2. In line with this, CoV-2 cross-reactive neutralizing antibodies that were predominantly of the IgG isotype and targeted the S2 subunit of the S protein have been detected in a much higher percentage of CoV-2-uninfected children than adults (127). Moreover, CoV-2 infection in children caused a twofold increase in antibody titers against all four HCoVs, while titer increases were modest in adults. Preabsorption of plasma samples with CoV-2 S1 or S2 domains before assessment of antibody binding to the four HCoV subtypes revealed that most of these antibodies cross-reacted with the more conserved S2 domain of the two more closely related beta-HCoVs, HKU1 and OC43. However, CoV-2 infection in children also boosted alpha-HCoV-specific antibody responses that were not preabsorbed, potentially generated by weakly cross-reactive B cell clones (128). Accordingly, prepandemic children also had higher frequencies of class-switched convergent B cell clones to CoV-2 and HCoVs, while adults displayed only a few such clones (129). Comparison of antibody concentrations to CoV-2 spike, RBD, NTD, and nucleocapsid antigens in seropositive children and adults with asymptomatic infection or mild COVID-19 revealed robust responses, broadly similar in magnitude. Older adults who are at higher risk of developing severe COVID-19 are therefore also more likely to develop higher antibody responses to CoV-2. Only a small percentage of children (~0.03%) develop severe disease in the form of a multisystem inflammatory syndrome (MIS-C) (130). Children with and without MIS-C exhibit similar anti-spike and anti-nucleocapsid antibody profiles, with more IgG antibodies specific for the S protein over the nucleocapsid protein, compared with adults (131). Children also had enhanced binding of antibodies to viral variant spike and RBD but displayed similar neutralizing ability compared with adults, indicating that increased antibody responses in children likely result from antibodies targeting non-neutralizing epitopes, which may still be important for other effector functions. Spike-specific T cell responses were more than twice as

high in children compared with adults and were also detected in many seronegative children, further speaking for preexisting cross-reactive responses to seasonal CoVs (128).

Upon vaccination, children produce an IgG-dominant antibody response, with a higher titer than adults after receiving a 100-μg adult dose and a titer more similar to adults following a 50-μg pediatric dose. Antibodies in vaccinated children have enhanced Fc receptor binding capacity compared with vaccinated adults or after CoV-2 infection. Vaccine-induced antibody binding and neutralization titers in children at the 100-μg dose group were higher compared with those observed in exposed children with or without MIS-C (132). Due to immunosenescence, immune function declines with age resulting in reduced diversity and memory of T and B cells (133). COVID-19 mRNA vaccine antibody responses and neutralizing titers in older adults are generally lower (including a number of nonresponders) compared with younger adults, but responses can usually be rescued after a third booster dose (134, 135).

7.3. Immunocompromised Populations

Immunocompromised patients have borne a disproportionate burden during the pandemic, facing a higher risk of prolonged CoV-2 infection, viral shedding, viral evolution, severe COVID-19 illness, and death. A recent meta-analysis found lower IgG antibody levels in immunocompromised patients with solid organ transplant, malignant diseases, and inflammatory rheumatic diseases compared with control individuals. Analysis of such patients is critically important, to guide vaccination or other prophylactic strategies and to help improve their outcomes if they become infected with CoV-2. Valuable insights about the relative importance of different branches of immune responses to CoV-2 can also be gained by studying patients with different immunological impairments.

Patients with cancer diagnoses are a large and diverse group, differing in their clinical conditions and treatments that may affect immune system function. Current evidence suggests that cancer patients are at greater risk of severe COVID-19 or death than others (136), although a meta-analysis highlighted risk of bias in the results of almost all studies of this topic (137). Patients with hematological malignancies have been particularly heavily affected, as supported by analysis of US-based electronic health record systems covering millions of patients (136) that showed these patients as having an odds ratio of 11.9 of primary CoV-2 infection compared with individuals without cancer and increased rates of hospitalization and death. A smaller but still elevated risk of breakthrough infection after vaccination (odds ratio 1.2) was also seen in these patients compared with controls without cancer. Patients with acute lymphoid leukemias were at the greatest risk within the hematologic disease categories. Patients with lung cancer are another group reported to have increased CoV-2 infection rates, hospitalization, and death (138). A recent study of 176 lung cancer mRNA-vaccinated patients documented that most had neutralizing antibody titers and spike-binding antibody titers similar to controls, but a small subset (5%) of patients had very low levels (139). The study also demonstrated that additional booster mRNA vaccine doses could improve the antibody responses in most patients, but a small subset did not respond well. No particular cancer treatment regimen was significantly associated with worse serological responses, but the authors plan to study this topic more extensively in a larger ongoing cohort. The clear clinical guidance from the study is to encourage booster doses for these patients.

The CoV-2 pandemic has also raised concerns for patients with autoimmune diseases, due to fears that their underlying disorders or immunosuppressive treatments would increase the risk of contracting CoV-2 infection and worsen COVID-19 outcomes. An additional concern has been that health-care disruptions would affect autoimmune condition management. It has been difficult

to answer COVID-19 prevalence and outcome questions in these patient populations definitively on the basis of the many hundreds of small epidemiological studies that have been published, and due to the challenges of adjusting results for comorbidities in rheumatic disease patients and controls. A recent systematic review and meta-analysis from the COVID-19 Global Rheumatology Alliance found that the prevalence of CoV-2 infection in patients with rheumatic diseases was significantly increased relative to controls [relative risk 1.53 (95% CI, 1.16–2.01)] while hospitalization, intensive care unit admission, and ventilator use did not differ significantly, but the mortality rate was elevated in the rheumatic disease patients, with an odds ratio of 1.74 (95% CI, 1.08–2.80) (140). Some medications used in treating a subset of autoimmune disease patients, such as B cell–depleting mAbs, are likely to contribute to poorer outcomes in COVID-19 and may interfere with vaccine responses (141), indicating that management of these diseases while protecting patients from CoV-2 will remain challenging. Many other patient groups, such as individuals who have had organ or stem cell transplants, or those with primary immunodeficiencies, are also at risk for more severe disease and worse outcomes with COVID-19, as well as impaired vaccine responses, and must not be forgotten as many countries attempt to return to normality and declare the end of the pandemic.

8. LONG COVID

Millions of people have died from CoV-2 infection, but for those who survive their illness, and even for those who have very mild symptoms, postacute sequelae of COVID-19, or long COVID, poses another risk to their health and quality of life. A recent comprehensive review of this topic (142) lays out the scope of the potential threat, with an estimated 10% of infected individuals suffering lingering symptoms affecting cardiac, vascular, and neural tissues among other organ systems, leading in some cases to long-term disability. The mechanisms implicated in long COVID are far from clear more than three years after the start of the pandemic, and major candidates include persistent CoV-2 virus in the body, altered immune function potentially including autoimmune mechanisms, damage to tissues derived from the initial infection, dysregulation of clotting systems in the blood, and reactivation of other latent viruses such as Epstein–Barr virus (EBV) (142). Clear definitions about long COVID phenotypes and subcategories will likely be important for making progress in understanding this disease. Published evidence linking antibody responses to the development of long COVID so far provide little clarity about whether antibody- or B cell–mediated effects contribute to this condition. A study from Su et al. (143) taking a systems immunology approach found evidence implicating EBV in long COVID, on the basis of detection of EBV viremia in patients, and reported several autoantibodies associated with the long COVID phenotype in some patients, including classic autoantibodies such as Ro (SS-A), La (SS-B), Jo-1, P1, and U1-snRNP and also antibodies targeting interferon alpha-2. Autoantibodies were usually seen in patients with lower titers of anti-CoV-2 antibodies. Other studies finding autoantibodies in long COVID have identified specificities for the ACE2 receptor (144) or G protein–coupled receptors that could contribute to the neurological phenotypes (145). There is not yet consensus about the presence of autoantibodies in long COVID, however. An additional recent study reported that autoantibodies against chemokines are common in COVID patients and correlate with better outcomes (146). In contrast, a preprint describing multimodal immune system monitoring in long COVID patients and control individuals (147) reports elevated anti-spike antibody concentrations and antibody binding to linear peptides associated with increased neutralizing activity in plasma in long COVID patients, without detection of autoantibodies with an assay including more than 6,000 human extracellular proteins. One common thread between this study and the EBV-related finding of Su et al. (143) is a finding of elevated antibody levels to herpesviruses including EBV

but with additional features of elevated antibodies against non-omicron CoV-2 and also against the herpesvirus varicella-zoster virus (147). The discordant results between these studies could potentially be further explored by head-to-head comparison of the results of different serological testing of shared samples from well-characterized patient cohorts. If the estimates of numbers of patients who will be affected by long COVID are accurate, the societal impact of this condition should drive expanded and ongoing research to define its causes and test therapeutics.

9. WHAT HAVE WE LEARNED TO HELP PREPARE FOR FUTURE PANDEMICS?

9.1. Rapid Assay Development, Rapid Vaccine Development

One silver lining to the COVID-19 pandemic has been the rapid mobilization of research capacity as well as multidisciplinary research collaborations such as the National Institutes of Health (NIH)/National Cancer Institute (NCI) SeroNet program and many other NIH initiatives (148) that shared goals of accelerating diagnostics, therapies, and vaccine development and of quickly advancing the science of CoV-2 and its interplay with the human immune system. With the end of the official public health emergency from the pandemic in the United States on May 11, 2023, it will be important to maintain the collaborative organizational networks that have developed during the pandemic, in a form that will enable an even faster response to the next pandemic that will undoubtedly occur in the future.

9.2. Role of Convalescent Plasma

In early 2020, before effective anti-CoV-2 mAbs and small-molecule antivirals had been identified, COVID-19 convalescent plasma (CCP) therapy, which is based on the passive transfer of specific antibodies from the plasma of recently recovered individuals to patients with COVID-19, was authorized by the FDA and was subsequently used to treat more than half a million hospitalized COVID-19 patients in the United States during the first year of the pandemic (149). Once logistical challenges such as dedicated collection of convalescent plasma (CP), determination of pathogen-specific antibody content, standardization of therapeutic doses, blood type matching, screening for blood-borne pathogens, and intravenous delivery are overcome, potential benefits of CP include availability as soon as there are survivors, affordability, and, due to the polyclonal properties, higher resistance to the emergence of viral escape variants compared with mAb therapy. While the protective effect of CP has mainly been attributed to antibody-mediated neutralization of pathogens, IgG Fc-dependent effector functions as well as other anti-inflammatory or immunomodulatory proteins may also play an important role (150).

As it turned out, the COVID-19 pandemic presented a unique opportunity to study mechanisms of action, safety, and efficacy of CP on a large scale. Investigations with large numbers of participants have determined that the use of CCP is relatively safe with a less than 1% incidence of serious adverse events and no evidence of antibody-mediated enhancement of disease severity (151). Numerous studies ranging from observational case series to randomized controlled trials have reported highly variable efficacy results for CCP therapy, which together with current WHO guidelines discouraging CCP usage and, on the other hand, expansion of the FDA EUA to include outpatient use of CCP created confusion about the use of CCP for health professionals and patients. Common themes in studies that did not find a mortality benefit by CCP usage are the use of plasma with variable or unknown anti-CoV-2 antibody levels as well as inclusion of patients with severe COVID-19 treated at late disease stages, when symptoms are mainly caused by inflammation-driven damage to multiple organs (152).

In a meta-analysis of 39 randomized clinical trials including 21,529 hospitalized COVID-19 patients and 70 matched cohort studies with 50,160 hospitalized COVID-19 patients, transfusion of CCP was associated with a 13% mortality benefit compared with standard of care. Meta-analysis of subgroups revealed that treatment with CCP earlier in the course of the disease was associated with a 37% decrease in mortality rates and that treatment with high-titer CCP was associated with a 15% decrease in mortality rates, while low-titer CP may not confer a clinically meaningful mortality benefit (153). In addition, two well-designed randomized controlled trials in outpatients demonstrated reduction in clinical deterioration (154, 155).

CCP may be particularly beneficial for immunosuppressed COVID-19 patients who fail to mount antibody responses to CoV-2 infection or vaccination and have an increased risk for morbidity and mortality. A systematic review of CCP use in patients with innate or acquired immunosuppression including three randomized clinical trials with 214 participants, five matched cohort studies with 1,560 participants, and 138 case reports or series including 623 individuals found an association between CCP use and a mortality benefit in hospitalized patients with COVID-19 (156).

Going forward, the use of CP for COVID-19 and future epidemics should abide by the most important principles, that is, high titer of transfused neutralizing antibodies and early onset of CP treatment.

9.3. Initiatives Preparing for Future Pandemics

Most contagious diseases that emerged in the past century had begun as viral infections of animals that spilled over to humans, including the Great Influenza in 1918, several other influenza outbreaks in later years (the 1957–1958 Asian flu, the 1968 Hong Kong flu, and the 2009 swine flu), SARS in 2002–2004, MERS in 2012, and COVID-19. Zoonotic viruses with properties leading to a short incubation period and rapid spread in humans through the respiratory pathway, such as influenza viruses and CoVs, are also likely candidates for the next pandemic threat. While spillover events are inevitable, pandemics are not (157). Starting points for pandemic prevention are animal disease monitoring (the close monitoring of unusual sickness in livestock or unexpected die-offs among wildlife) to detect viruses before they infect humans and broad molecular and serological surveillance of animals and humans. The advent of highly multiplexed protein arrays to detect antibodies to hundreds of thousands of potential pathogen epitopes using platforms commercially available via companies including VirScan and Luminex enables simultaneous testing for exposure of animal and human populations to a wide range of viral and other antigens. Utilizing this technology, Mina and colleagues (158) have suggested a new strategy to quickly track disease outbreaks by testing for antibodies to infectious agents in millions of anonymized blood samples (from blood banks, plasma collection centers, and heel needle sticks of newborns) per day through an effort presented as the Global Immunological Observatory. Questions of testing capacity and a paucity of historical and contemporary samples to define baseline signals will need to be addressed. Ideally, the effort should be complemented by parallel efforts surveilling and sequencing pathogens themselves. As humans have extensive and increasing contact with wildlife known to harbor vast numbers of viruses, wildlife should be included in surveillance efforts. This will require significant investments, which are, however, trivial compared with costs of future pandemics.

10. CONCLUSIONS

The COVID-19 pandemic has occurred at a time when human immunology and virology researchers were empowered by a host of experimental tools such as high-throughput DNA sequencing and single-cell transcriptomics that had become practical on a large scale only in the

previous one or two decades. While remaining a global catastrophe, the pandemic has also provided an unprecedented opportunity to learn more of the rules that determine the paths of human immune responses and immunological memory and has accelerated the use of other technologies such as mRNA vaccinations and other novel vaccine modalities that may offer better protection against historically difficult targets such as HIV, malaria, tuberculosis, and other pathogens. As one important example, insights from studies of immunological imprinting with CoV-2 variant antigens should help to inform future vaccine booster strategies. Keeping in mind the large numbers of individuals who are more vulnerable to CoV-2 infection due to immunodeficiency conditions, it would be a pity if no additional mAb or other passive immunotherapeutics were developed in the months and years ahead. The omicron viral variant and its offspring came as a big surprise after a series of much less divergent variants had appeared in the early months of the pandemic. It remains to be seen whether, after global populations have been heavily and repeatedly infected with omicron-derived variant viruses, a new highly divergent lineage might potentially appear, escaping the humoral immune responses elicited by omicron.

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