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The humoral response and antibodies against SARS-CoV-2 infection

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Two and a half years into the COVID-19 pandemic, we have gained many insights into the human antibody response to the causative SARS-CoV-2 virus. In this Review, we summarize key observations of humoral immune responses in people with COVID-19, discuss key features of infection- and vaccine-induced neutralizing antibodies, and consider vaccine designs for inducing antibodies that are broadly protective against different variants of the SARS-CoV-2 virus.

Since its initial outbreak at the end of 2019, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across every continent. By the end of February 2022, there were more than 400 million confirmed cases and the disease had claimed more than 5.9 million lives worldwide (World Health Organization COVID-19 dashboard; https://covid19.who.int). The world has seen development of highly efficacious COVID-19 vaccines and promising antiviral small-molecule and antibody drugs with an unprecedented speed[1]. From a clinical perspective, while completely asymptomatic SARS-CoV-2 infection is not uncommon, 30–50% of infected individuals show progressive respiratory involvement, including interstitial pneumonia[2,3]. In a subset of infected individuals, acute respiratory distress syndrome (ARDS) and severe inflammatory response syndrome (SIRS) develop, potentially accompanied by microvascular and macrovascular thrombosis that may eventually lead to death[4–6]. While pneumonia is largely a consequence of cytopathic injury by the virus[7], inappropriate and exaggerated host responses to the virus contribute to ARDS and SIRS[5,8]. As COVID-19 has become the single most studied human disease in history, unprecedented global efforts are being devoted to understanding how the host develops innate and adaptive immune responses to the SARS-CoV-2 virus and how the immune system helps control infection and transmission or, in certain cases, becomes dysregulated, causing tissue damage, organ failure, or death of the host. These efforts not only help to identify immunological correlates of infection- and vaccine-induced protection, but also facilitate development of treatment strategies for severe COVID-19 immunopathology.

The antibody response is an important arm of adaptive immunity against viral infection. On the basis of predominant isotypes and the profiles of somatic hypermutations of the resulting antibodies, the humoral immune response to viral infection or vaccines can be broadly divided into two phases. In the extrafollicular (EF) phase, B cells are activated to rapidly differentiate into plasma cells in foci outside of the follicle within a few days after infection[9], producing antibodies that contain few somatic hypermutations but that can nonetheless be of reasonably high affinities and able to neutralize the virus[10]. These EF plasma cells are predominantly of the IgM isotype following protein-antigen immunization, but they can be IgG- or IgA-switched, particularly in response to viral infections. In either case, EF plasma cells are thought to be relatively short-lived. In the germinal center (GC) phase, which takes several days to a week to begin but can last for months, antigen-specific B cells undergo somatic hypermutation and affinity-based selection to give rise to predominantly isotype-switched and high-affinity plasma cells that establish a long-lived compartment localized in the bone marrow. Both EF and GC responses produce antigen-specific memory B cells that may persist long after primary infection is cleared[11].

Almost everyone with SARS-CoV-2 infection seroconverts within 2 weeks post-symptom onset (PSO), producing IgM and IgG antibodies that predominantly recognize the viral spike and nucleocapsid proteins[12–15]. However, high serum titers of total or neutralizing antibodies against SARS-CoV-2 are more frequently found in severe cases of COVID-19 and do not necessarily correlate with better disease outcomes of the primary infection[16–18]. Transfusion of convalescent plasma was initially reported to be able to reduce the mortality rate of people hospitalized with COVID-19 (refs. [19,20]), although increased survival was not replicated in a subsequent large controlled trial[21]. Neutralizing antibodies that block angiotensin-converting enzyme 2 (ACE2)-dependent viral entry into host cells correlate well with efficacy of prophylactic vaccines[22]. Serum levels of neutralizing antibodies to SARS-CoV-2 peak within the first few weeks after infection or vaccination and decline subsequently[23–28], leading to reduced protection and an increased risk of re-infection by the original strain or newly emerging variants of concern or interest (VOCs or VOIs). Vaccine booster shots can induce broader and more potent neutralizing antibodies in patients convalescing from COVID-19 compared with previously uninfected individuals[29]. Antibodies that are cross-reactive because of previous exposure to other pathogenic and seasonal coronaviruses may affect the development of SARS-CoV-2-specific neutralizing antibodies as well[30–32]. What emerges from these and other studies of humoral immunity to SARS-CoV-2 is the importance of the timing and context in which B cell activation and antibody responses are initiated and maintained (Fig. 1).

The serum antibody response in SARS-CoV-2 infection

Similar to other respiratory infections, SARS-CoV-2 infection stimulates rapid production of IgM, IgG and IgA antibodies, which are measurable in the sera as early as a week PSO, including those that bind to nucleocapsid and the spike protein[12–15,24,25]. The rapidity

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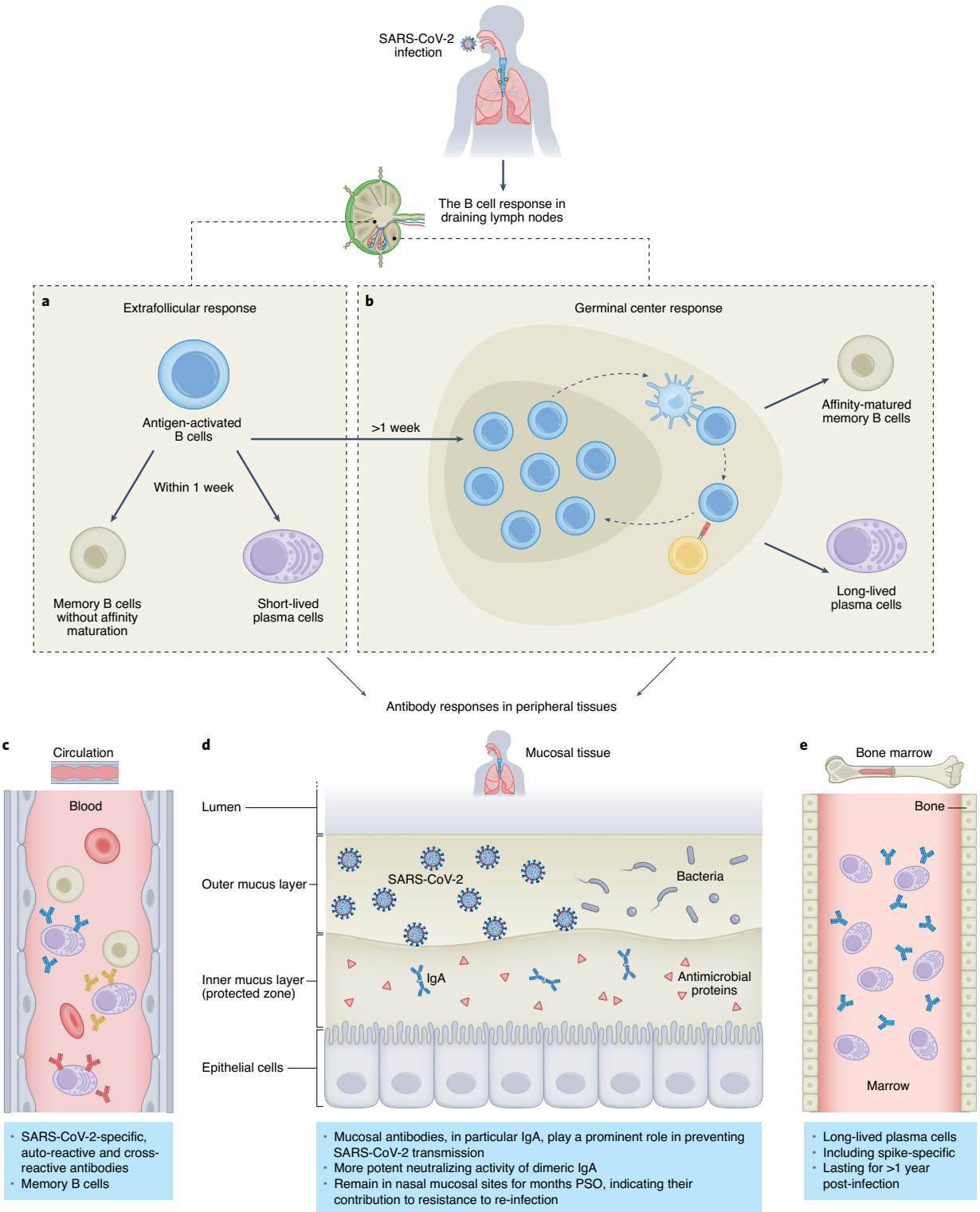

Fig. 1 | The B cell and antibody response against SARS-CoV-2 infection. Overview of the B cell and antibody response to SAR2-CoV-2 infection in the human system. **a**, Once activated, the extrafollicular (EF) response is rapidly launched. Some B cells differentiate into either short-lived plasma cells to serve as pioneers fighting against SARS-CoV-2 infection or memory B cells with few mutations, or they participate in the germinal center (GC) reaction. **b**, Through the GC response, B cells gain affinity-increasing immunoglobulin (Ig) gene mutations and potentially differentiate into either long-lived plasma cells to secrete high-affinity neutralizing antibodies and help maintain anti-SARS-CoV-2 antibody levels in serum or memory B cells with higher mutation frequencies and increased longevity. These differentiated B cells and plasmablasts migrate to different inflammatory sites to function (**c**–**e**). **c**, In blood vessels, memory B cells join the circulation system in surveillance, and plasma cells migrate to inflammatory sites to fight against infection. Other antibodies, like cross-reactive antibodies secreted by other viral-infection-induced plasma cells, contribute to the clearance of SARS-CoV-2. Auto-reactive antibodies may increase following SARS-CoV-2 infection in blood and potentially harm other healthy tissues by inducing autoimmune diseases. **d**, In mucosal sites, especially in nasal tissues, dimeric IgA protects from SARS-CoV-2 invasion and re-infection. **e**, In the bone marrow, long-lived plasma cells reside and help maintain anti-SARS-CoV-2 antibody levels in the host.

of such responses suggests that the antibodies have an EF origin[33]. Neutralizing activities toward pseudotyped or live SARS-CoV-2 also appear rapidly in these antibodies; this activity is readily detected in convalescent sera, although levels of neutralization achievable vary greatly among individuals[16,23,27,34]. This variability may partly explain why plasma therapy attempted early in the pandemic produces mixed results[1].

Cross-section and longitudinal studies indicate that ELISA titers and neutralizing antibodies against SARS-CoV-2 peak in 3 to 4 weeks PSO[23,24]. While levels of these serum antibodies do decay[25–28], they can be relatively stable for months, with IgG being more stable than IgM and IgA antibodies[18,23,24]. These kinetic features are consistent with a gradually increasing contribution by a more long-lasting plasma-cell compartment beyond continuous recruitment of EF plasma cells.

While COVID-19 severity varies greatly among individuals following SARS-CoV-2 infection, higher titers of ELISA and neutralizing antibodies are found in individuals with severe COVID-19 than in those with mild disease[18,28,35] or those without symptoms[36]. Because severe disease is more likely to start with a high viral load, as suggested by a survey of studies involving more than 10,000 participants in total[37], the elevated level of antibodies in severe cases probably results from much stronger antigen-driven EF response[33].

Mucosal antibodies in SARS-CoV-2 infection

Plasma neutralizing antibodies are the best predictor of vaccine-induced protection from infection[22]. However, although antibodies in circulation or tissues help control viral spread within the body, mucosal antibodies, and particularly secretory IgA, in the respiratory tract may play a more prominent role in preventing transmission of SARS-CoV-2 through the airway[38]. This protection is based on strategic tissue distribution and the more potent neutralizing activity of dimeric secretory IgA than monomeric serum IgA and antibodies of other isotypes[39]. Indeed, virus-specific IgA is detected in saliva from infected individuals[24]. Neutralizing IgA antibodies in nasal fluids have been found in seronegative healthcare workers, suggesting a strictly local response in the nasopharynx-associated lymphoid tissue[40]. Significant levels of SARS-CoV-2 antibodies, including neutralizing IgA, remain in nasal fluids for months PSO[41,42]. Presumably, these antibodies contribute to reduction or resistance to re-infection.

Cross-reactive antibodies

SARS-CoV-2 shares 79% and 50% genome sequence identity with SARS-CoV and MERS-CoV, respectively, including the coding sequence for the receptor-binding domain (RBD), the main target of neutralizing antibodies[43,44]. Sequence homology between SARS-CoV-2 and other human coronavirus is lower, but remains immunologically relevant. In principle, recall of cross-reactive memory B cells that are produced during prior coronavirus infections may contribute to the rapid EF antibody response (IgG and IgA in particular) following primary SARS-CoV-2 infection[45]. Previously, SARS-CoV-specific antibodies isolated from people with SARS have been found to cross-react with human coronaviruses 229E and OC43 (ref. [46]). Antibodies that can cross-react or cross-neutralize SARS-CoV and SARS-CoV-2 have been observed[47–49]. IgG antibodies that bind to SARS-CoV-2 spike proteins have been detected in blood drawn from healthy donors before the COVID-19 pandemic[50,51], probably due to cross-reactivity to the human coronavirus (hCoV) that causes common cold[52]. Indeed, studies of uninfected cohorts in Canada have uncovered antibodies that are cross-reactive to SARS-CoV-2 spike and spike proteins from hCoV HKU1, NL63 and 229E, but not OC43 (ref. [53]). In sub-Saharan Africa, pre-existing serological cross-reactivity to SARS-CoV-2 spike and nucleocapsid has likely resulted from exposure to hCoV NL63 and 229E[54]. These cross-reactivities are likely due to antibodies targeting to the highly conserved S2 domain of the spike protein, as the S1 domain is much less conserved in comparison, likely owing to strong selective pressure exerted by the immune system[30–32]. High levels of pre-existing cross-reactive antibodies tend to correlate with milder clinical manifestations after SARS-CoV-2 infection in some studies[50,51,55], but not others[52]. Interestingly, people who show seroreactivity to hCoV OC43 spike protein do not have detectable cross-neutralizing antibodies against SARS-CoV-2 (ref. [56]). Given the fact that pre-existing cross-reactive T cells are prevalent among people who have not been exposed to SARS-CoV-2 (refs. [57,58]), the impact of cross-reactive cells is likely a significant variable in shaping the clinical outcome of SARS-CoV-2 infection[59].

Auto-reactive antibodies in SARS-CoV-2 infection

It is not uncommon for viral infections to lead to increased generation of autoantibodies, in part because of inflammation, cell-death-related autoantigen release, and molecular mimicry[60,61], although overt autoimmune disease does not necessarily ensue. SARS-CoV-2 infection leads to a marked increase in circulating autoantibodies targeting a wide range of autoantigens, including complement proteins, cytokines, chemokines and surface proteins[62]. Autoantibodies that recognize, and even neutralize, type I interferons, the very cytokines critical for orchestrating antiviral defense, have been identified in some people with COVID-19 and are strongly implicated in promoting life-threatening disease[63,64], because severe COVID-19 is often characterized by diminished interferon production[65–67].

Independent studies have also revealed a spectrum of antibody-driven autoimmune conditions following SARS-CoV-2 infection, including systemic lupus erythematosus[68], Guillain–Barre syndrome[69,70], and cold agglutinin syndrome[71,72], pointing to a likely scenario that de novo autoimmunity is a significant contributor to severe COVID-19 (ref. [73]).

The GC response in SARS-CoV-2 infection

Whereas the EF response gives rise to neutralizing antibodies, it is probably not sufficient for controlling SARS-CoV-2 infection[33]. Furthermore, prevention of re-infection depends on persistent neutralizing antibodies with increased affinity and long-lasting humoral memory in the form of memory B cells and long-lived plasma cells, which all require robust primary GC responses. However, the virus-specific GC response is difficult to assess directly in people, except for during autopsies of the deceased. Initial observations from autopsies of deceased people with COVID-19 show a surprising lack of anatomically identifiable GCs in lymph nodes or spleen[74,75]. Severe COVID-19 can be accompanied by severe lymphopenia[76–78]. It is likely that severe disruption of immune functions abrogates the GC response in those cases.

In people with non-severe COVID-19, analyses of antibodies, memory B cells and plasma cells over a period of months after infection revealed classical GC-dependent features. Although antibodies expressed by memory B cells isolated early after infection may carry relatively few mutations[79–81], the spike- or RBD-specific memory compartment continues to evolve and turn over in the subsequent months, after which antibodies are expressed that show greater somatic hypermutation[82,83] and increased neutralizing potency and breadth[84–86]. Spike-specific plasma cells have been found in bone marrow aspirates a year after SARS-CoV-2 infection, and their abundance correlates with serum spike-specific antibody titers[87], indicating formation of a long-lived plasma-cell compartment. SARS-CoV-2 infection induces robust T cell responses, including spike-specific $CD4^+$ T cells of the follicular helper phenotype that is capable of promoting antibody response[57,88–90]. In a rhesus macaque (*Macaca mulatta*) model of SARS-CoV-2 infection that recapitulates moderate disease in humans, primary infection clearly triggers GC formation, leading to protection from re-infection[91,92]. Finally, in

a rare analysis of SARS-CoV-2-seropositive organ donors, virus-specific GCs have actually been found in the lung-associated lymph nodes 6 months after infection[93]. In combination, these studies indicate that SARS-CoV-2 infection induces functionally robust GC responses that may last for months, potentially owing to antigen persistence[82]. In addition to de novo GC responses from naive B cells, it is likely that cross-reactive memory B cells generated during previous exposure to seasonal coronaviruses are recruited to participate in the GC response to SARS-CoV-2. This possibility is supported by the fact that antibodies against S2, highly conserved among human coronaviruses, tend to have higher levels of somatic hypermutation than contemporary RBD-specific antibodies following SARS-CoV-2 infection[31].

Although a persistent GC response may not be essential for controlling primary infection, with its continuous output of memory and plasma cells of increasing affinity and neutralization breadth and potency against SARS-CoV-2, it is a required component of, and arguably the best correlate for, a good prophylactic vaccine strategy.

Features of S glycoprotein and antibody neutralization

Spike proteins on the surface of SARS-CoV-2 viral particles and infected cells are the major target of neutralizing antibodies. Each matured SARS-CoV-2 virion contains, on average, 26 ± 15 (mean ± s.d.) spike trimers, covered extensively by glycans and randomly distributed on the surface[94]. For each monomeric S glycoprotein, there are two functional subunits: the S1 subunit, for binding to the receptor ACE2, and the S2 subunit, for mediating fusion of viral and cellular membranes (Fig. 2a). The S1 subunit folds into four major structural domains, the amino-terminal domain (NTD), the RBD, and two carboxy-terminal domains (CTDs), which wrap around and protect the inner S2 subunit. Antibodies predominantly neutralize the virus by blocking S protein from binding to its receptor ACE2 and interfering with the subsequent steps that are required for membrane fusion. Many RBD-binding antibodies can trigger S1 shedding, suggesting that they also neutralize the virus by mimicking ACE2 to induce premature conversion to the post-fusion conformation[95]. Cryo-electron microscopy and crystal-structure analyses have revealed that the RBD undergoes spontaneous structural fluctuation between an 'up' and a 'down' conformation. Only the up conformation enables the exposure of the receptor-binding motif (RBM) of the RBD, which can then become accessible and bind the host receptor ACE2. The up conformation is believed to be less stable, potentially explaining why the dominant trimer state has only one of the three RBDs standing up[96,97]. Although all these domains are susceptible to antibody binding, the RBD is the predominant target of neutralizing antibodies, followed by the NTD. S2-binding antibodies are poorly neutralizing, although some react broadly against many members of the sarbecovirus subgenus[30,31]. Such a pattern of antibody recognition is seen in naturally infected and vaccinated individuals[98,99], indicating that the S glycoprotein expressed through vaccines resembles those on the infectious particles.

S protein demonstrates a high degree of variability among different virus strains or circulating VOCs, particularly in the RBD and NTD domains, in part due to continuous pressure exerted by the human immune system. The most mutated VOC — Omicron, with its BA.1 and BA.2 subvariants — has approximately 35 mutations in the S protein compared with the prototype strain initially found in Wuhan, China. At least 15 of the 35 mutations are located in the RBD and 8 mutations in the NTD[100,101], making Omicron BA.1 and BA.2 the most distinct in antigenic properties. Such antigenic variability affords this VOC a significantly increased chance of escaping from neutralization by antibody treatment and vaccine protection[64,102–104].

RBD-directed neutralizing antibodies

The landscape of neutralizing epitopes on the spike trimer of SARS-CoV-2 has been mapped by a total of seven core 'communities' of antibodies (RBD-1 to RBD-7; Fig. 2b)[105]. These antibodies target three major surfaces on RBD, namely the top RBM face, the solvent-exposed outer face, and the cryptic inner face. The correspondence of this community-based classification and previous classification based on germline usage and structural information[106,107] is provided in Table 1.

RBM-face-targeting antibodies are among the most potent neutralizing antibodies against SARS-CoV-2, exemplified by RBD-1, RBD-2 and RBD-3 (ref. [105]). While overlapping extensively in their binding sites on the RBM surface, each community demonstrates a somewhat unique binding pose and specificity. RBD-1 binds to the center of the ACE2 binding site, whereas RBD-2 shifts to the 'peak' and RBD-3 toward the flat surface 'mesa.' Many antibodies to RBD-2 overlap with those previously categorized in class 1 (see Table 1 for definition), such as C102, C105, P2C-1F11, CB6 and REGN10933 (refs. [16,79,80,106,108]). These antibodies preferentially use heavy chain germline variable (V_H) segment *IGHV3-53*/*IGHV3-66* and have limited somatic hypermutation and relatively short complementarity-determining region CDR3 loops (<15 residues). Two signature motifs, NY at V_H residues 32 and 33 in the CDR1 and an SGGS motif at V_H residues 53 to 56 in the CDR2, are crucial for RBM binding[109–111]. Furthermore, a substantial portion of RBD-2 antibodies, such as COV2-2196, S2E12 and A23-58.1, prefer to use *IGHV1-58* and are therefore named *IGHV1-58* supersite antibodies[112,113]. Such common features suggest that the *IGHV3-53*/*IGHV3-66* and *IGHV1-58*-encoded antibodies possess unique biochemical and structural features that render them naturally strong in binding and highly complementary in shape to the RBM surface. However, such specific and strong binding is also associated with VOC escape. For example, RBD-2 and RBD-3 antibodies are severely affected by the p.K417N/T, p.E484K/A and p.N501Y mutations found in Alpha, Beta, Gamma and the Omicron subvariants BA.1 and BA.2 (refs. [102,114,115]).

Outer-face-targeting antibodies are among the most broad and potent neutralizing antibodies against SARS-CoV-2 VOCs and are attributed to the RBD-4 and RBD-5 communities[105]. Their footprints on the RBD are solvent-exposed, accessible in both the up and down conformations, and largely overlap with those previously categorized in class 2 and class 3 (ref. [106]; see Table 1). Members of the RBD-4 community bind toward the outer edge of the RBM and block ACE2, exemplified by antibodies C002, A19-46.1, BD-368-2, COV2-2130 and P2B-2F6 (refs. [79,106,116,117]). Those in the RBD-5 community, however, do not block ACE2, as they bind away from the

Fig. 2 | SARS-CoV-2 spike-directed neutralizing antibodies. a, Spike protein of SARS-CoV-2. Top, schematic diagram of the domain organization. SD1, subdomain 1; SD2, subdomain 2; FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; TM, transmembrane domain. S1/S2 and S2 are two protease cleavage sites. Left, closed state of the spike trimer with three down RBDs; right, open state of the spike trimer with two down RBDs and one up RBD. The spike is presented as a gray cartoon, with the RBD highlighted in cyan. The structures were published in ref. [97]. **b**, RBD-directed neutralizing antibodies. For each antibody community (RBD-1 to RBD-7), the footprint of a representative antibody on the RBD is shown. The highly conserved N343 glycosylation site on the outer face is colored in deep blue. The RBM is outlined in light coral. See Table 1 for corresponding references. **c**, NTD-directed neutralizing antibodies. For each antibody community (NTD-1 to NTD-3), a representative complex structure of the spike trimer bound by the antibody is shown. The spike trimer and antibody are both presented as surface, with RBD colored in cyan, NTD in purple and S2 in gray.

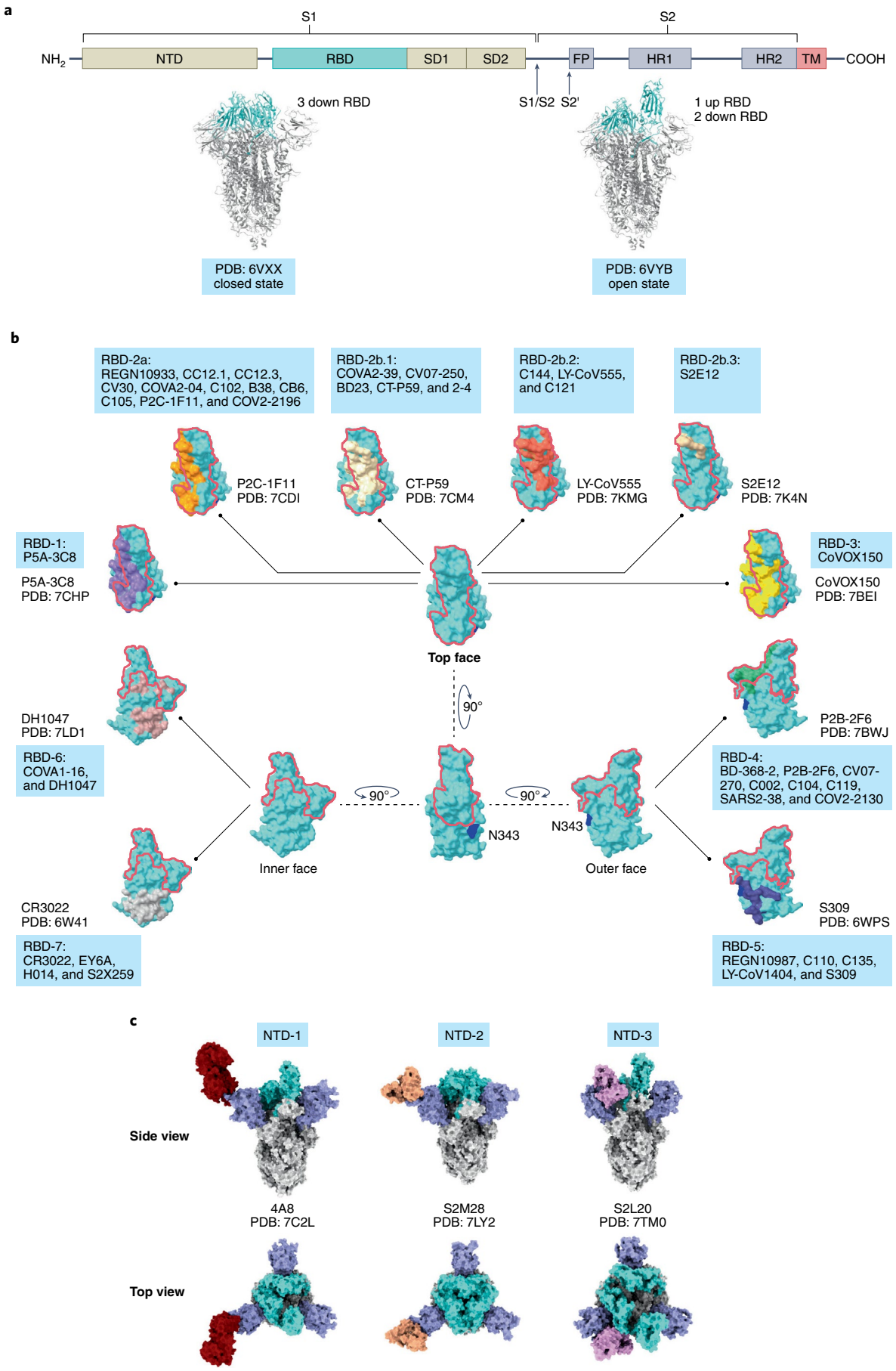
a
S1
S2
NH2
NTD
RBD
SD1
SD2
FP
HR1
HR2
TM
COOH
S1/S2
S2'
3 down RBD
1 up RBD
2 down RBD
PDB: 6VXX
closed state
PDB: 6VYB
open state
b
RBD-2a:
REGN10933, CC12.1, CC12.3, CV30, COVA2-04, C102, B38, CB6, C105, P2C-1F11, and COV2-2196
RBD-2b.1:
COVA2-39, CV07-250, BD23, CT-P59, and 2-4
RBD-2b.2:
C144, LY-CoV555, and C121
RBD-2b.3:
S2E12
P2C-1F11
PDB: 7CDI
CT-P59
PDB: 7CM4
LY-CoV555
PDB: 7KMG
S2E12
PDB: 7K4N
RBD-1:
P5A-3C8
P5A-3C8
PDB: 7CHP
RBD-3:
CoVOX150
CoVOX150
PDB: 7BEI
Top face
90°
DH1047
PDB: 7LD1
RBD-6:
COVA1-16, and DH1047
P2B-2F6
PDB: 7BWJ
RBD-4:
BD-368-2, P2B-2F6, CV07-270, C002, C104, C119, SARS2-38, and COV2-2130
90°
90°
N343
N343
Inner face
Outer face
CR3022
PDB: 6W41
RBD-7:
CR3022, EY6A, H014, and S2X259
S309
PDB: 6WPS
RBD-5:
REGN10987, C110, C135, LY-CoV1404, and S309
c
NTD-1
NTD-2
NTD-3
Side view
4A8
PDB: 7C2L
S2M28
PDB: 7LY2
S2L20
PDB: 7TM0
Top view

Table 1 | Summary of SARS-CoV-2 antibodies

Epitope						Antibodies	PDB	Heavy chain gene	Light chain gene	Ref. Number
RBD class 1	Neutralizing antibodies encoded by the *VH3-53* gene segment, with short CDRH3 loops that block ACE2 and bind only to up RBDs.	RBS-A	Antibodies are encoded by germline genes *IGHV3-53* and *IGHV3-66*. Similar to the ACE2-binding site, the RBS-A epitope is accessible only when the RBD is in the up conformation.	RBD-1	Contains hACE2-derived molecules and IgGs that largely overlap with the RBM.	P5A-3C8	7CHP	*IGHV3-53*	*IGKV1-9*	109
				RBD-2a	Bind toward the inner face of the RBD, and its binding area overlaps highly with that of the therapeutic antibody REGN10933.	REGN10933 (Casirivimab)	6XDG	*IGHV3-11*	*IGKV1D-33*	108
						CC12.1	6XC2	*IGHV3-53*	*IGKV1-9*	111
						CC12.3	6XC4	*IGHV3-53*	*IGKV3-20*	111
						CV30	6XE1	*IGHV3-53*	*IGKV3-20*	176
						COVA2-04	7JMO	*IGHV3-53*	*IGKV3-20*	81
						C102	7K8M	*IGHV3-53*	*IGKV3-20*	106
						B38	7BZ5	*IGHV3-66*	*IGKV1-9*	177
						CB6 (LY-CoV016; Etesevimab)	7C01	*IGHV3-66*	*IGKV1-39*	80
						C105	6XCM	*IGHV3-53*	*IGLV2-8*	110
						P2C-1F11 (BRII-196)	7CDI	*IGHV3-66*	*IGKV3-20*	95
						COV2-2196 (Tixagevimab)	n/a	*IGHV1-58*	*IGKV3-20*	178
				RBD-2b.3	Bind to the peak of the RBD, similar to antibody S2E12.	S2E12	7K4N	*IGHV1-58*	*IGKV3-20*	179
RBD class 2	ACE2-blocking neutralizing antibodies that bind both up and down RBDs and can contact adjacent RBDs, including a VH3-53 antibody that uses a long CDRH3 with a hydrophobic tip to bridge between adjacent down RBDs, thereby locking the spike into a closed conformation.	RBS-B	Antibodies bind at a different angle and straddle the RBS ridge, where RBD Phe486 inserts into a pocket between the light and heavy chains of the Fab on the paratope surface.	RBD-2b.1	Bind toward the outer face of the RBD, similar to antibody COVA2-39.	COVA2-39	7JMP	*IGHV3-53*	*IGLV2-23*	180
						CV07-250	6XKQ	*IGHV1-18*	*IGLV2-8*	181
						BD23	7BYR	*IGHV7-4-1*	*IGKV1-5*	116
						CT-P59 (Regdanvimab)	7CM4	*IGHV2-70*	*IGLV1-51*	182
						2-4	6XEY	*IGHV1-2*	*IGLV2-8*	183
		RBS-C	These antibodies target the back side of the RBS on the opposite side of the RBS ridge, at a different angle of approach from those that target RBS-A and RBS-B. These antibodies have fewer clashes with ACE2 binding to the RBD and can bind both up and down RBD conformations.	RBD-2b.2	Bind toward the outer face of the RBD, similar to antibody C144.	C144	7K90	*IGHV3-53*	*IGLV2-14*	106
						LY-CoV555 (Bamlanivimab)	7KMG	*IGHV1-69*	*IGKV1-39*	112
						C121	7K8X	*IGHV1-2*	*IGLV2-23*	106
				RBD-4	Bind toward the outer edge of the RBM and can block ACE2, bind up and down RBD, similar to antibody C002.	BD-368-2	7CHC	*IGHV3-23*	*IGKV2-28*	184
						P2B-2F6	7BWJ	*IGHV4-38-2*	*IGLV2-8*	79
						CV07-270	6XKP	*IGHV3-11*	*IGLV2-14*	181
						C002	7K8S	*IGVH3-30*	*IGVK1-39*	106
						C104	7K8U	*IGHV1-46*	*IGLV2-14*	106
						C119	7K8W	*IGHV4-34*	*IGKV3-20*	106
						SARS2-38	7MKM	*IGHV2-9*	*IGKV5-44*	185
						COV2-2130 (Cilgavimab)	n/a	*IGHV3-15*	*IGKV4-1*	178

Continued

Table 1 | Summary of SARS-CoV-2 antibodies (continued)

Epitope						Antibodies	PDB	Heavy chain gene	Light chain gene	Ref. Number
RBD class 3	Neutralizing antibodies that bind outside the ACE2 site and recognize both up and down RBDs.	RBS-D		RBD-5	Bind away from the RBM, toward the S309 site, and do not block ACE2. Bind up and down RBD, similar to REGN10987. Inter-spike cross-linking.	REGN10987 (Imdevimab)	6XDG	*IGHV3-30*	*IGLV2-14*	108
						C110	7K8V	*IGVH5-51*	*IGVK1-5*	106
						C135	7K8Z	*IGHV3-30*	*IGKV1-5*	106
						LY-CoV1404 (Bebtelovimab)	7MMO	*IGHV2-5*	*IGLV2-14*	126
						BRII-198	n/a	n/a	n/a	102
		S309 proteoglycan	Bind N343 glycan and can bind in up and down RBD.			S309 (Sotrovimab)	6WPS	*IGHV1-18*	*IGKV3-20*	47
RBD class 4	Do not block ACE2 and bind only to up RBDs.	CR3022 cryptic	CR3022 site has been found to be a target of cross-neutralizing antibodies against SARS-CoV-2.	RBD-3	Bind down from the center of the ACE2 binding site toward the RBD mesa, similar to antibody ADI-56046.	ADI-56046	n/a	n/a	n/a	186
				RBD-6	Bind to the inner face of the RBD and require two RBDs to be in the up configuration. Block ACE2 and compete with RBD-2a antibodies.	COVA1-16	7JMW	*IGHV1-46*	*IGKV1D-33*	187
						DH1047	7LD1	*IGHV1-46*	*IGKV4-1*	188
				RBD-7	Bind to the inner face of the RBD and require two RBDs to be in the up configuration. Downward shift of the RBD-7 footprint allows simultaneous binding of RBD-2a antibodies with RBD-7.	CR3022	6W41	*IGHV5-51*	*IGKV4-1*	189
						EY6A	6ZCZ	*IGHV3-30-3*	*IGKV1-39*	190
						H014	7CAI	*IGHV1-69-2*	*IGKV6-21*	191
						S2X259	7RA8	*IGHV1-69*	*IGLV1-40*	129
NTD				NTD-1	Bind from the top side of the NTD to cover the NTD N terminus and residue Y144. Epitope overlaps with that of monoclonal antibody 4A8 and other 'supersite' binders.	4A8	7C2L	*IGHV1-24*	*IGKV2-24*	128
						4-8	7LQV	*IGHV1-69*	*IGLV3-1*	183

RBM and toward sites recognized by S309, REGN10987, P36-5D2, LY-CoV1404, C110 and C135 (refs. [47,106,108,118]). RBD-4 antibodies, like those in class 2, appear to interact with residues F486 and Q493 in the RBM, which distinguish SARS-CoV-2 from SARS-CoV-1 and are thought to enhance the RBD of SARS-CoV-2 for binding to ACE2 (ref. [106]). Interaction between RBD-4 antibodies and F486 mimics the interaction between that residue and ACE2: F486 buries into a hydrophobic pocket between the light and heavy chains of the antibodies. Another common interaction is with E484, mediated through either the heavy or the light chain. However, the p.E484K/A mutation has recently been found in Beta, Gamma, Omicron BA.1 and BA.2, Mu, Eta and Lota; this mutation markedly reduces, or even completely abrogates, the neutralizing activity of many antibodies in RBD-4 community. Interestingly, a combination of COV2-2196 (RBD-2) and COV2-2130 (RBD-4), when used in the therapeutic mode as Tixagevimab–Cilgavimab, manufactured by AstraZeneca, achieves good neutralization against Omicron BA.1 and BA.2, despite each of the two therapies individually having reduced or lost neutralizing activity[119,120]. The p.L452R mutation, primarily found in Delta, Epsilon and Kappa, also significantly reduces or completely abolishes neutralizing activity of RBD-4 antibodies[121–124]. However, the footprints of RBD-5 antibodies appear to center around the N343 glycan, highly conserved among SARS-CoV-2, SARS-CoV-1, and many bat and pangolin viruses that are considered high risks for potential outbreaks[47]. Representative antibodies REGN10987, LY-CoV1404 (the parental antibody of Bebtelovimab, manufactured by Eli Lilly), and C110 bind to regions between the outer edge of the RBM and N343 glycan[106,108], whereas the other representative antibodies S309 (the parental antibody of Sotrovimab, manufactured by GlaxoSmithKline/Vir Biotechnology) and C135 bind to regions containing the N343 glycan. Escape mutations from REGN10987 include those at positions N439, N440 and G446 (refs. [102,125]). Notably, LY-CoV1404 potently neutralizes Omicron BA.1 and BA.2 and has recently been approved by the US Food and Drug Administration (FDA) for emergency use[126]. Although S309 maintains its potency and breadth of neutralization against Omicron BA.1 and BA.2 in vitro, the FDA recently announced that the current 500 mg dose would not be effective against Omicron BA.2 infection. GlaxoSmithKline/Vir is preparing evidence in support of a higher dose for treating this subvariant. Lastly, like RBM face-targeting antibodies, the outer-face-targeting antibodies show low levels of somatic hypermutations without undergoing apparent maturation, indicating that they too exert timely and powerful antiviral functions during early infection. The relatively conserved nature of the outer surface could be explored more extensively for the development of antibody drugs and vaccines.

Inner-face-targeting antibodies belong to recently classified antibodies in the RBD-6 and RBD-7 communities. They are relatively smaller in number, weaker in neutralizing potency, and bind to cryptic epitopes opposite to the outer surface, accessible only when the RBD is in the up conformation. Some members require at least two or three RBDs in the up conformation for binding[127–129]. As the RBD can adopt a variety of conformations, such as tilting and turning when bound to various ligands compared with the ligand-free configuration, cryptic epitopes on the inner face can be transiently exposed and accessed by antibodies. Overall, the inner-face antibodies demonstrated stronger propensities to cross-link spike trimer than did the RBM antibodies, but their neutralizing potencies are generally weaker. This response is perhaps due to their transient nature and limited accessibility that adversely affects antibody recognition and penetration. Examples of such antibodies include S2X259, DH1047 and CR3022 (refs. [18,47,129]). However, recently emerged Omicron subvariants BA.1 and BA.2 have resulted in marked reduction in and complete loss of neutralizing activity of RBD-6 and RBD-7 antibodies, largely due to mutations at positions S371, S373 and S375 ([64,102]).

Of note, there are some antibodies that do not exactly fall into the existing classification systems, such as ADG-2 and S2H97. While the epitope of ADG-2 partially overlaps with those in class 1 and class 4, ADG-2 approaches its epitope from a distinct angle[130]. S2H97 binds to a cryptic epitope at the cliff region right below the peak of RBM. S2H97 binding requires more opening of the RBD than does binding by ACE2 or RBD-6 and RBD-7 antibodies. Like the antibodies that do not compete with ACE2, S2H97 likely neutralizes the virus by interfering with and interrupting post-ACE2-binding steps before viral entry[125].

NTD-directed neutralizing antibodies

These antibodies exhibit weaker neutralizing potency than that of antibodies to the RBD. They do not compete with ACE2 for binding to RBD, but may involve interference with conformational changes required for fusion or proposed interactions with attachment receptors, such as transmembrane lectins DC-SIGN, L-SIGN and SIGLEC1 (refs. [131,132]). Some studies indicate their critical role in Fc-mediated effector functions, both in vitro and in vivo[133]. NTD neutralizing antibodies are categorized into three major communities (NTD-1 to NTD-3) on the basis of their binding pose and specificity, which are largely convergent to the 'NTD supersite.' The supersite is made of N1 (residues 14–26), N3 (residues 141–156), and N5 (residues 246–260) loops that are positively charged and surrounded by glycans[105,131,134]. The NTD-1 antibodies bind from the top side of NTD, covering the N terminus and residue Y144. 4A8, the first NTD-directed antibody identified, is the representative of this antibody community[135]. The NTD-2 antibodies bind to the front side, whereas the NTD-3 antibodies bind to the left side of the NTD, close to the RBD of the adjacent protomer[105,131]. However, all these antibodies seem to be sensitive to mutations occurring both inside and outside of their discrete footprint, suggesting that NTD-directed antibodies are largely conformation-sensitive[136]. Surprisingly, many mutations found in circulating VOCs and VOIs are insertions and deletions, such as 69–70del, Y144del, 157–158del and 242–244del, as opposed to the point mutations found in the RBD[75,114,115,135]. Interestingly, Omicron BA.2 has relatively fewer mutations than BA.1 in the NTD, providing a potential explanation for its reduced serological escape compared with that of BA.1. Nevertheless, these results may indicate that the deleted residues, or perhaps the supersite, are not absolutely required for viral infections, although the relative fitness of these mutants is currently unknown. As NTD-directed antibodies are prone to viral escape, it is not surprising that no antibodies directed to this domain are under clinical development. The reduction of serum neutralizing activity against VOCs and VOIs found in infected and vaccinated individuals must therefore be in part due to the deletions found in the NTD. Design of vaccine candidates capable of minimizing or completely overcoming the mutational effect in the NTD domain is highly desired.

Fc-dependent antibody functions and non-neutralizing antibodies

By engaging different Fc receptors expressed on different cell types, antibodies exert multiple effector functions upon antigen binding. For neutralizing antibodies, FcR-dependent effector functions can contribute to the potency of neutralization, particularly evident when neutralizing antibodies are used in a therapeutic mode[137–139]. When effector functions of non-neutralizing antibodies are considered, the outcome can be more complex and nuanced. These antibodies may contribute to protection by mediating antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). However, they may contribute to disease exacerbation through antibody-dependent enhancement (ADE) of infection. ADE could occur when non-neutralizing or sub-neutralizing antibodies bind to and facilitate virus entry into

Fc-receptor-expressing cells, or when such antibodies cause excessive inflammation and immune pathology. Elevated serum ADCC activities have been seen in individuals with COVID-19, particularly those who are hospitalized[140,141]. Kinetically, serum ADCC activities generally follow overall antibody titers, peaking at 2–4 weeks following infection and gradually declining thereafter[142–144]. Definitive evidence for ADE in human SARS-CoV-2 infection is relatively thin, although a very recent study reports Fc-receptor-mediated entry of antibody-opsonized SARS-CoV-2 into monocytes, leading to inflammatory cell death that may exacerbate the COVID-19 disease[145]. More studies and continuous monitoring of ADE are warranted, because in principle cross-reactive antibodies from previous coronavirus infection could exacerbate SARS-CoV-2 infection and, as new VOCs continue to emerge, neutralizing antibodies against earlier strains may lose neutralizing potency and become capable of mediating ADE instead[146,147]. This latter point is important from a vaccination perspective, because vaccines appear to induce more binding antibodies than neutralizing antibodies, compared with natural infection[148].

Perspectives on SARS-CoV-2 vaccines

We have gained significant insights into the humoral immune response and antibody immunity following SARS-CoV-2 infection. Perhaps not surprisingly, the response to SARS-CoV-2 generally follows the same stereotypical pattern that is established in animal models and can be expected of acute viral infections. These insights help guide our design, implementation, and evaluation of prophylactic and therapeutic strategies.

Most current SARS-CoV-2 vaccines target the prototype SARS-CoV-2 strain identified during at the beginning of the pandemic[149–154]. Given the multiple waves of increased infection rates and breakthrough infections associated with escaping VOCs such as Alpha, Beta, Gamma, Delta and Omicron, broadly neutralizing vaccines are highly desirable. Interestingly, recent studies have identified potent, broadly neutralizing antibodies to the RBD that are capable of neutralizing all VOCs, including Omicron[119,155,156], suggesting the likely existence of highly conserved and vulnerable regions within the RBD, a notion underscored in recent structural analyses of antibodies capable of neutralizing Omicron[113]. Broad and potent neutralizing antibodies can be substantially boosted after a third vaccine shot, particularly in individuals convalescing from COVID-19[157,158], supporting a strategy to improve the neutralizing potency and breadth by a booster shot, potentially through heterologous vaccine modality. This notion is supported by an increasing number of clinical studies in which heterologous vaccine boosting has been found to be superior to homologous vaccine boosting[159–165]. Features of memory B cells that are activated by the boost, epitope specificities, and mechanisms of action of boosted antibodies are under investigation. Such results will inform on how to design and execute booster shots to maximize utility of the current vaccines.

Vaccines are also being developed to specifically target the S glycoprotein of emerging VOCs, similar to how flu vaccines are updated on an annual basis. Antigenically, the Omicron variant deviates the most from the prototype strain and is the most capable of escaping from vaccine protection[64,102–104,120,166], providing an impetus for creating Omicron-targeted vaccine. However, preliminary studies of Omicron-specific messenger-RNA vaccines have not demonstrated superiority in inducing high-level Omicron-specific neutralizing antibodies over the prototype vaccine, raising concerns about this vaccine strategy[167]. An important point to consider when targeting strain-specific RBD is the fact that, while high-affinity antibodies are generally desired, antibodies with the highest neutralizing potency also tend to have limited breadth against the spectrum of variants. For example, antibodies in the RBD-1, RBD-2, RBD-3 and RBD-4 communities are very sensitive to the p.K417N, p.L452R and p.E484K mutations found in the Beta, Gamma, Delta and Omicron variants. By contrast, antibodies with relatively moderate potency, such as those in RBD-5, RBD-6 and RBD-7, are largely able to cross-neutralize many variants and even some animal coronaviruses in wild bats and pangolins[105,127]. Striking a balance between potency and breadth of antibodies elicited by vaccination is certainly an issue to address on the road toward broadly neutralizing and universal vaccines.

To develop a universal vaccine capable of inducing broad and potent neutralizing against all VOCs, multiple antigens from different VOCs could be combined in the same vaccine. For example, nanoparticle vaccines derived from distinct and mosaic RBDs from various coronavirus strains represent a viable strategy in this direction[168–171]. This strategy is further supported by a preclinical study in which a recombinant RBD trimer vaccine induced robust, long-lasting and protective immunity against SARS-CoV-2 challenge in small animals and rhesus macaques without obvious lung-tissue pathology[170,172,173]. Monoclonal antibodies isolated from mice immunized with the RBD trimer are able to cross-neutralize various antigenically distinct variants, suggesting that the trimer formulation is particular apt at inducing broad antibodies against major variants[174]. Lastly, individuals infected with and recovered from SARS-CoV-1 infection 17 years ago can generate broad and potent neutralizing antibodies against a wide variety of SARS-CoV-2 VOCs and five bat and pangolin sarbecoviruses after being vaccinated with an mRNA vaccine against SARS-CoV-2 (ref. [175]). These results further highlight the possibility of a pan-coronavirus vaccine. Such broad protection implies the existence of long-lived memory B cells that recognize conserved features of these various related viruses. A deeper understanding of how such memory cells are induced, how they survive, and how they are recalled probably holds the key to designing broadly neutralizing vaccines that offer long-term protection.

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Competing interests

L.Z. has filed patent applications for BRII-196 and BRII-198 antibodies against SARS-CoV-2 and is a share holder of Tsb Therapeutics.

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