



# The germinal centre B cell response to SARS-CoV-2

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**Abstract** | The germinal centre (GC) response is critical for the generation of affinity-matured plasma cells and memory B cells capable of mediating long-term protective immunity. Understanding whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or vaccination elicits a GC response has profound implications for the capacity of responding B cells to contribute to protection against infection. However, direct assessment of the GC response in humans remains a major challenge. Here we summarize emerging evidence for the importance of the GC response in the establishment of durable and broad immunity against SARS-CoV-2 and discuss new approaches to modulate the GC response to better protect against newly emerging SARS-CoV-2 variants. We also discuss new findings showing that the GC B cell response persists in the draining lymph nodes for at least 6 months in some individuals following vaccination with SARS-CoV-2 mRNA-based vaccines.

During an immune response, B cells that encounter their cognate antigen become activated and migrate to the centre of the B cell follicle, where they form structures known as germinal centres (GCs)<sup>1</sup>. Within the GC, B cells compete for a limiting amount of T cell-derived signals, such as cytokines and CD40 ligand, that promote their migration from the light zone to the dark zone<sup>2</sup>. The magnitude of T cell help received by a B cell in the light zone dictates the extent of cell division and somatic hypermutation that occurs within the dark zone<sup>3,4</sup>. B cells that accrue productive mutations within their B cell receptor preferentially capture and present antigens to T cells upon their return to the light zone, facilitating their eventual differentiation into memory B cells or plasma cells<sup>2,5,6</sup>.

Data generated in mouse models suggest that memory B cells tend to emerge from the GC before plasma cells and, accordingly, display reduced levels of somatic hypermutation<sup>7–9</sup>. Memory B cells persist for years to decades and rapidly differentiate into antibody-secreting cells upon antigen re-encounter<sup>10,11</sup>. Following antigen re-encounter, memory B cells can also re-enter the GC, where they undergo further affinity maturation<sup>11</sup>. The reduced mutational load of memory B cells could facilitate their ability to recognize and respond to viral variants, with the memory B cell population in humans containing clones that are broadly reactive to several pathogens, including influenza virus and HIV<sup>12,13</sup>. By contrast, plasma cells are a terminally differentiated population of cells that tend to be specific for the subtype of virus previously encountered. Plasma cells persist in sites such as the bone marrow and serve as a first line of

defence against pathogen reinfection through constitutive secretion of antibodies<sup>14–16</sup>. In this manner, memory B cells and plasma cells cooperate to provide overlapping layers of protection against reinfection by the pathogen or related variants.

The quality of the B cell response following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection determines the duration and breadth of protective immunity. While SARS-CoV-2 infection induces a durable B cell response, antibody levels decay over time, raising the risk that immunity may wane as the neutralizing antibody titre decreases below the threshold needed to protect against reinfection<sup>17–21</sup>. SARS-CoV-2 reinfection has been observed among some previously infected individuals, raising the possibility that infection-induced immunity against SARS-CoV-2 may be short-lived, as is the case for seasonal coronaviruses<sup>22–28</sup>. However, it is not yet clear whether the dynamics of immunity to SARS-CoV-2 will follow the same patterns reported for other coronaviruses.

Additionally, the development and widespread use of mRNA-based and vector-based vaccines against SARS-CoV-2 is likely to profoundly impact the duration of protective immunity<sup>29–32</sup>. It is particularly important to determine the B cell response following mRNA-based and adenovirus vector-based vaccinations considering that these platforms have not previously been widely used in humans<sup>33</sup> (BOX 1). mRNA-based vaccines against SARS-CoV-2 have shown 94–95% efficacy against symptomatic disease and 90% efficacy in preventing asymptomatic infection at 12 weeks after vaccination<sup>29,30,34–37</sup>. While total SARS-CoV-2-specific antibody titres wane

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## Box 1 | mRNA-based vaccines

mRNA-based vaccines use lipid nanoparticles to transport mRNA encoding viral proteins to the cell membrane of host cells<sup>123</sup>. The nanoparticles are then endocytosed into the cell, where they subsequently escape the endosome and release the enclosed mRNA into the cytoplasm to be subsequently translated into antigenic protein (for example, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein). Exogenous mRNA is inherently immunostimulatory and is recognized by numerous pattern recognition receptors expressed in different locations in the cell<sup>173</sup>. This allows mRNA-based vaccines to induce a robust T cell and B cell response against the viral protein without requiring additional adjuvants. The lipid nanoparticles used in mRNA-based vaccines are conjugated to several lipids, including polyethylene glycol, to increase their stability and lifespan. The mRNA transcribed by the vaccine has a short half-life and remains in human tissues for only a few days<sup>174</sup>. While the half-life of the viral protein produced by mRNA-based vaccines is unclear, the persistence of the germinal centre response following vaccination suggests that viral antigen is present for at least 30 weeks after vaccination in some individuals<sup>99</sup>. mRNA-based vaccines are easily modifiable, allowing rapid production of vaccines containing mRNA encoding proteins expressed by viral variants.

over time following vaccination, neutralizing antibody titres and protection against hospitalization and death persist at high levels for at least 6 months<sup>38,39</sup>. However, key questions remain regarding the duration of protective immunity following mRNA-based vaccination and whether antibodies induced by vaccination will protect against reinfection by SARS-CoV-2 variants.

Considerable progress has been made in elucidating the B cell response following SARS-CoV-2 infection and vaccination. Here we examine emerging evidence that establishment of a robust GC response is critical for the induction of durable protective immunity. We also summarize new data showing that SARS-CoV-2 vaccination induces a GC B cell response that persists for at least 6 months in some individuals. Finally, we discuss the importance of the memory B cell response in protecting against newly emerging viral variants and examine how the GC response can be modulated to induce a more broadly protective B cell response.

### B cell response to SARS-CoV-2 infection

SARS-CoV-2 infection induces a robust humoral immune response in most individuals<sup>17,40,41</sup>. While the magnitude of the serum antibody response against SARS-CoV-2 is heterogeneous, it generally declines rapidly over the first 4 months after infection, with a more gradual decline evident from that point onwards<sup>17–19,40,42–48</sup>. Conversely, the SARS-CoV-2-specific memory B cell response increases over the first 4–5 months after infection before plateauing<sup>17,40,49</sup>. We found that SARS-CoV-2-specific plasma cells are stably maintained in the bone marrow between 7 and 11 months after infection, consistent with a model in which long-lived bone marrow plasma cells maintain serum antibody levels at later time points<sup>39,42</sup>.

Severe SARS-CoV-2 infection is associated with an elevated antibody and memory B cell response compared with milder infections<sup>17,50,51</sup> (FIG. 1a). This could be explained by the fact that severely ill individuals generate a robust extrafollicular B cell response that correlates with an increase in proinflammatory cytokine levels and neutralizing antibody titres<sup>52</sup>. Severely ill individuals may also be failing to form functional GCs as evidenced

by the marked decrease in the number of T follicular helper T (T<sub>FH</sub> cells) present in the draining lymph nodes and spleen<sup>53</sup>. The low levels of somatic hypermutation among responding B cells following severe infection is consistent with an impaired GC response and may lead to the production of antibodies that are unable to mediate disease resolution. However, a robust circulating T<sub>FH</sub> cell response is detectable in the blood of many severely infected individuals, suggesting that the GC response is not defective in all cases<sup>54–56</sup>. Impaired disease resolution in severely infected individuals may also be caused in part by impaired T cell-mediated clearance of virally infected cells<sup>19,52,57–60</sup>.

Mild SARS-CoV-2 infection also induces an early extrafollicular response in which naive and seasonal coronavirus-specific memory B cells differentiate into activated B cells and short-lived plasmablasts<sup>61,62</sup> (FIG. 1b). While early SARS-CoV-2-specific memory B cells have near germ line sequences, these cells progressively accrue somatic mutations in their V<sub>H</sub> genes, suggesting that they are a product of an ongoing GC response<sup>40,41,61,63</sup>. SARS-CoV-2 nucleic acids have been detected in the intestine of some individuals for at least 3 months after mild infection and may fuel an ongoing GC response<sup>40</sup>. The presence of long-lived plasma cells in the bone marrow of SARS-CoV-2-infected individuals further supports this model, as high-affinity plasma cells are predominantly derived from GCs<sup>42,64</sup>. Indeed, a robust GC and T<sub>FH</sub> cell response that persists for up to 6 months has been identified in humans and rhesus macaques following SARS-CoV-2 infection<sup>65,66</sup>.

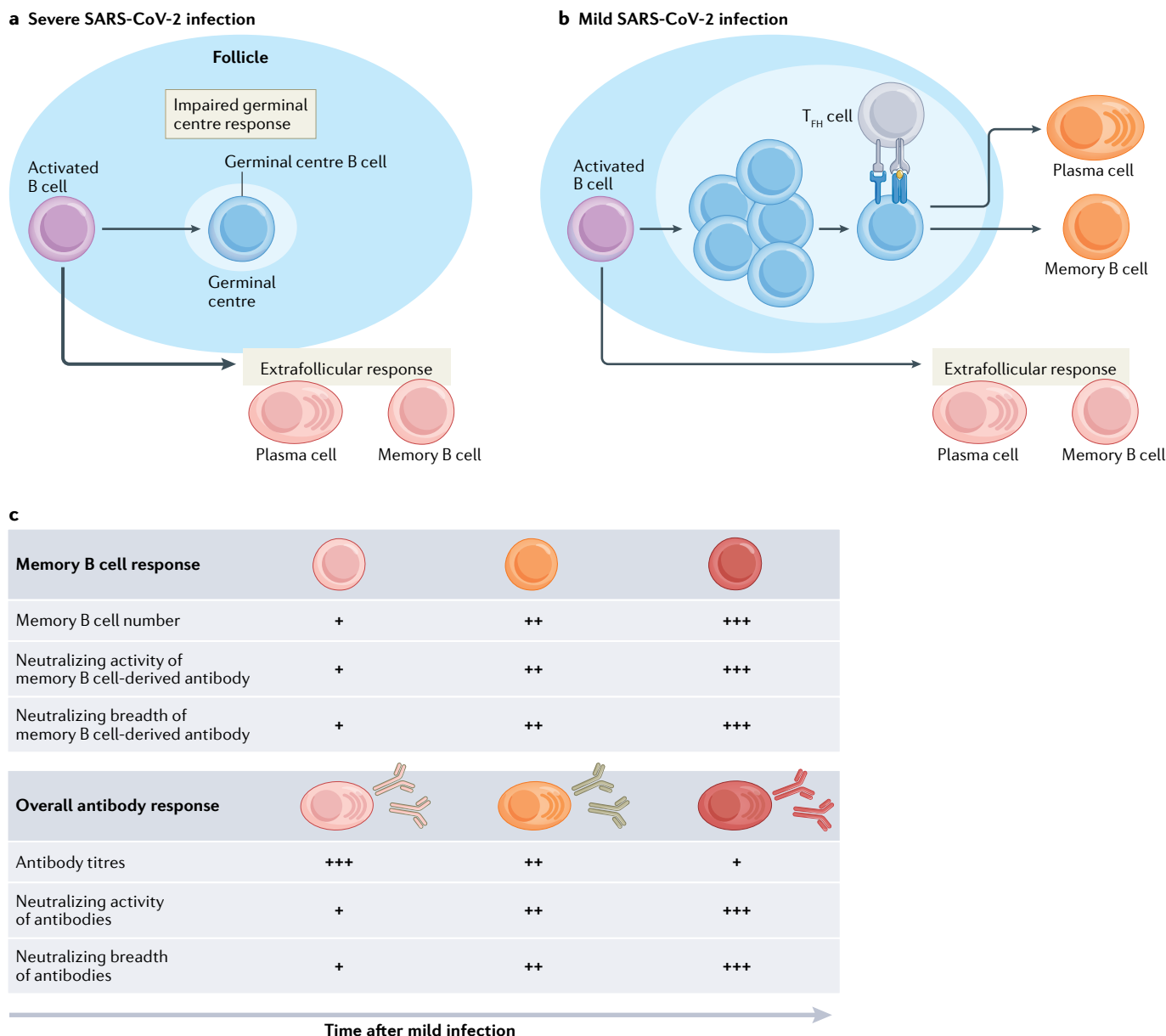
Antibodies expressed from somatically mutated SARS-CoV-2-specific memory B cells display enhanced antigen binding, neutralizing potency and neutralizing breadth relative to those from memory B cells present at earlier time points<sup>40,61,63,67</sup>. B cells encoding SARS-CoV-2-specific antibodies that fail to neutralize the virus, including those that cross-react with seasonal coronaviruses, are less detectable at later time points<sup>40,41,48,61,68,69</sup>. Somatic mutations of the V<sub>H</sub> genes in memory B cells are associated with a sustained antibody response and rapid recovery from SARS-CoV-2 infection<sup>40,46</sup>. Additionally, SARS-CoV-2-specific antibodies in the serum at 10 months after infection display enhanced neutralizing activity and breadth<sup>48</sup>. Together, these data suggest that the GC response, which is necessary for the development of affinity-matured memory cells and plasma cells, is important for the development of B cells capable of protecting against SARS-CoV-2 infection<sup>70–72</sup> (FIG. 1c).

Numerous monoclonal antibodies have been derived from responding B cells in convalescent patients that are capable of neutralizing SARS-CoV-2, with some of these monoclonal antibodies already being used therapeutically to resolve SARS-CoV-2 infection. An antibody titre of 20% of the mean convalescent level has been proposed as sufficient for 50% protection against detectable SARS-CoV-2 infection, while only 3% is necessary for 50% protection from severe infection<sup>73</sup>. Therefore, an individual who starts with 80% protection against mild disease will have more than 50% protection against severe infection with an antigenically similar strain of SARS-CoV-2 for at least 3 years<sup>73</sup>. However,

the widespread emergence of viral variants that evade neutralization by preformed antibodies present in convalescent serum will likely significantly decrease the duration of antibody-mediated immunity elicited by SARS-CoV-2 infection<sup>74,75</sup>. In these cases, protection against severe disease will be reliant on the reactivation of somatically mutated memory B cells that recognize antigenically distinct viral variants, which is discussed further in the next section<sup>40,76,77</sup>.

**B cell response to SARS-CoV-2 vaccination**

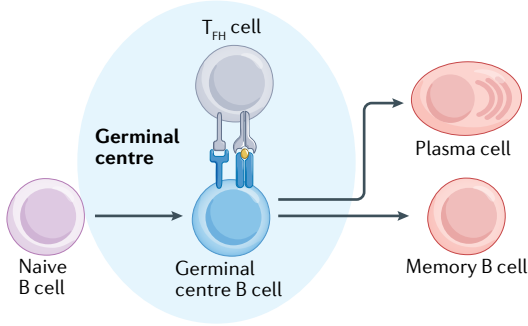
There are several dozen SARS-CoV-2 vaccines that are in use globally. Currently, only the mRNA-based Pfizer–BioNTech and Moderna vaccines and the viral vector-based Johnson & Johnson Janssen vaccine are authorized for use in the United States. mRNA-based vaccination induces a robust SARS-CoV-2-specific antibody response that is strongly enhanced upon administration of a second dose in individuals who were not



**Fig. 1 | B cell response to SARS-CoV-2 infection. a** | Severe infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces a robust extrafollicular response but an impaired germinal centre (GC) B cell response in some individuals. Antigen-engaged B cells differentiate into memory B cells and short-lived plasmablasts that give rise to antibodies with a low level of somatic hypermutation. **b** | Mild SARS-CoV-2 infection induces both an extrafollicular response and GC B cell response. The GC B cell response gives rise to affinity-matured memory B cells and long-lived plasma cells. **c** | There is an increase in the number of SARS-CoV-2-specific memory B cells over time following mild infection. Memory B cells derived

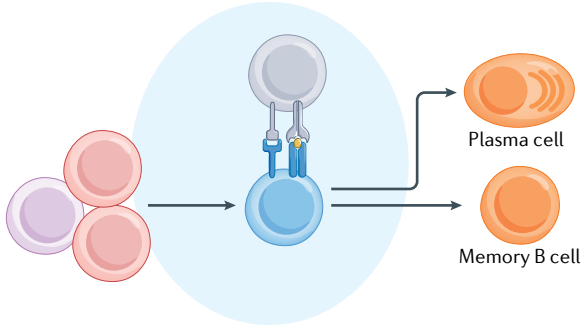
from the GC undergo continued clonal evolution for at least 1 year, with memory B cells found at later time points displaying increased levels of somatic hypermutation and encoding antibodies with enhanced neutralizing activity and breadth. The SARS-CoV-2-specific antibody titre decreases over the first 6 months following infection owing to the loss of antibodies derived from short-lived plasmablasts. The loss in protection attributable to this decrease in antibody titre is partially offset by a per antibody increase in neutralizing titre and breadth, likely owing the emergence of clonally evolved plasma cells from the GC. T<sub>FH</sub> cell, T follicular helper cell.

**a Uninfected individual dose 1**



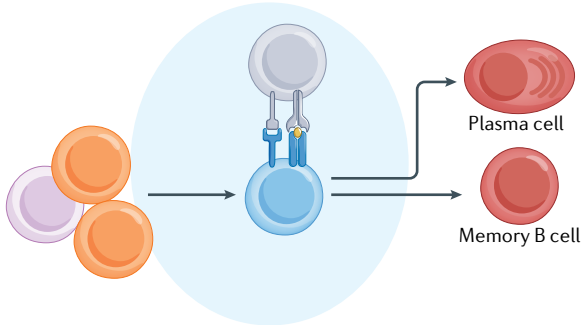
Response magnitude	++
Neutralizing activity	++
Neutralizing breadth	+

**b Uninfected individual dose 2**



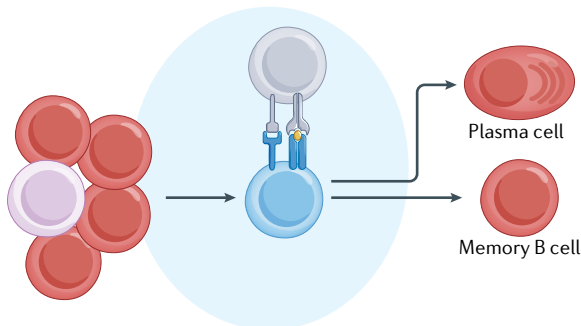
Response magnitude	+++
Neutralizing activity	+++
Neutralizing breadth	++

**c Previously infected individual dose 1**



Response magnitude	+++
Neutralizing activity	+++
Neutralizing breadth	+++

**d Previously infected individual dose 2**



Response magnitude	+++
Neutralizing activity	+++
Neutralizing breadth	+++

previously infected<sup>69,78–83</sup> (FIG. 2a). About half of vaccinated individuals develop neutralizing antibodies to SARS-CoV-2 after a single dose, with almost all individuals having neutralizing antibodies after the second dose<sup>78</sup>. mRNA-based vaccination also induces a robust memory B cell response that is further enhanced after the second dose<sup>69</sup>. There is an increase in the percentage of class-switched memory B cells following the second dose<sup>78</sup>.

**Fig. 2 | Germinal centre B cell response to SARS-CoV-2 vaccination.**

**a** | The first dose of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA-based vaccine induces a robust germinal centre response that gives rise to plasma cells and memory B cells in previously uninfected individuals. Primary immunization induces a significant increase in the number of SARS-CoV-2-specific antibodies, with about half of individuals developing neutralizing antibodies. However, these antibodies are largely unable to neutralize SARS-CoV-2 variants. **b** | The second dose of the SARS-CoV-2 mRNA-based vaccine induces a significant increase in the antibody response in previously uninfected individuals. Antibodies derived from the secondary immunization have robust neutralizing activity, although there is a decrease in the ability to neutralize SARS-CoV-2 variants compared with the wild-type (D614G) virus. **c** | The first dose of the SARS-CoV-2 mRNA-based vaccine induces a significant increase in the antibody response in individuals who have recovered from previous SARS-CoV-2 infection. Antibodies induced by primary immunization have robust neutralizing activity, with equivalent ability to neutralize wild-type and variant viruses. The number of pre-existing SARS-CoV-2-specific memory B cells strongly correlates with the magnitude of the antibody response following vaccination. **d** | The second dose of the SARS-CoV-2 mRNA-based vaccine does not induce any further increase in antibody titre or neutralizing activity in individuals who have recovered from previous SARS-CoV-2 infection. T<sub>FH</sub> cell, T follicular helper cell.

mRNA-based vaccination also induces a significant increase in the numbers of SARS-CoV-2-specific antibodies and memory B cells in individuals who were previously infected with SARS-CoV-2<sup>63,78,84,85</sup> (FIG. 2b). The magnitude of this increase strongly correlates with the number of pre-existing SARS-CoV-2 memory B cells, indicating that memory B cells are critical in driving a recall response upon re-exposure to SARS-CoV-2 antigens<sup>78</sup>. Consistent with this model, vaccination results in an increase in the number of all pre-existing SARS-CoV-2-specific memory B cell clones<sup>63</sup>. No further increase in the SARS-CoV-2-specific antibody or memory B cell response is observed upon administration of a second dose to previously infected individuals, suggesting that only one dose of the mRNA-based vaccine is needed to reach peak humoral immunity in previously infected individuals<sup>78,83,86–88</sup>. However, this does not exclude a potential beneficial role for the second dose in promoting SARS-CoV-2-specific B cell survival or affinity maturation. Additionally, mRNA-based vaccination induces a robust SARS-CoV-2-specific T cell response, which could be further boosted upon administration of a second dose<sup>85,89–91</sup>. The importance of T cells in the establishment of protective immunity against SARS-CoV-2 infection is a subject of active investigation (BOX 2). While previously infected individuals have elevated numbers of SARS-CoV-2-specific memory B cells at 3 months after vaccination compared with vaccinated uninfected individuals, there is a similar number of memory B cells in both groups at 6 months<sup>92</sup>.

SARS-CoV-2 mRNA-based vaccines induce a robust GC and T<sub>FH</sub> cell response in mice<sup>93,94</sup>. However, the



role of the GC response in the human B cell response to vaccination was until recently unclear owing to an inability to directly sample draining lymph nodes following vaccination. We used ultrasound-guided fine needle aspiration to serially sample the draining lymph node following influenza vaccination and found that vaccination induced a robust GC response in which B cells undergo somatic hypermutation<sup>95,96</sup>. We then used this approach to assess the B cell response in the draining axillary draining lymph nodes of individuals who received the Pfizer–BioNTech SARS-CoV-2 vaccine<sup>97</sup>. We found that vaccination induced a robust SARS-CoV-2-specific GC B cell and T<sub>FH</sub> cell response, with administration of a second dose further increasing the percentage of GC B cells<sup>97,98</sup>. The GC response was composed of both pre-existing memory B cell clones specific for seasonal coronaviruses and newly recruited naive B cells that were specific for unique epitopes within the SARS-CoV-2 spike protein<sup>97</sup>. Remarkably, SARS-CoV-2-specific GC B cells were maintained in the lymph node at near peak frequency for at least 15 weeks following vaccination, indicating that these cells are likely undergoing affinity maturation<sup>97</sup>. Memory B cells that bind to SARS-CoV-2 variants display elevated levels of somatic hypermutation compared with cells that bind only wild-type SARS-CoV-2, suggesting a role for the GC in the acquisition of broadly protective immunity<sup>92</sup>.

We have now extended these findings to assess the GC response at 30 weeks following vaccination (FIG. 3). We recently reported that 10 of 15 individuals analysed displayed a persistent SARS-CoV-2-specific GC B cell response in the lymph node, with spike protein-binding GC B cells not detected in the other five individuals<sup>99</sup>. These findings indicate that there is heterogeneity in the duration of the SARS-CoV-2-specific GC response induced by vaccination. It will be important to determine whether GC persistence is associated with enhanced quality of the B cell response and if spike protein antigen is detectable in individuals with persistent GCs.

#### Box 2 | Cellular immunity to SARS-CoV-2

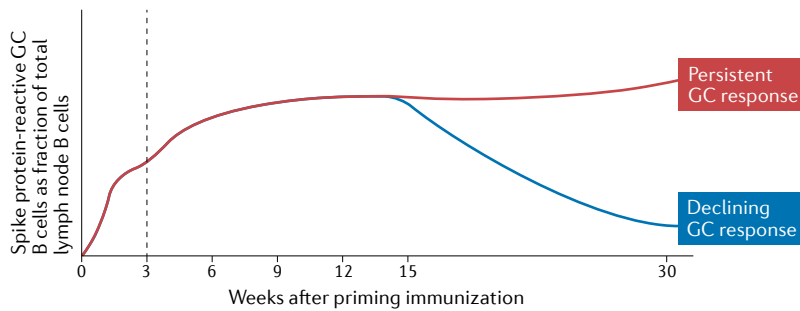
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces a T cell response in almost all individuals, with the magnitude of this response correlated with control of primary infection<sup>17,175–177</sup>. SARS-CoV-2-specific T cells persist for at least 6 months following infection and maintain polyfunctionality upon peptide stimulation<sup>178</sup>. SARS-CoV-2 vaccination also induces a robust T cell response with broad specificity to peptides present in the spike protein, with the magnitude of this response bolstered by the administration of a second vaccine dose<sup>82,91,179–181</sup>. Epitopes recognized by SARS-CoV-2-specific CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells were 93% and 97% conserved, respectively, in emerging viral variants<sup>89,182</sup>. Accordingly, the T cell response to peptide restimulation was minimally impacted by variant mutations<sup>182</sup>. T cells recognizing conserved epitopes are more abundant in individuals with mild disease and display enhanced expression of markers associated with long-lived memory<sup>183</sup>. While SARS-CoV-2-specific T cells alone are not expected to be able to prevent reinfection by variant viruses, they may have an important contribution in limiting disease severity<sup>184</sup>. For example, memory CD4<sup>+</sup> T cells can provide accelerated help to B cells upon antigen re-encounter, facilitating the induction of antibodies capable of mediating viral clearance<sup>185</sup>. Memory T cells that establish residence in mucosal tissues following SARS-CoV-2 infection may also contribute to protective immunity by limiting viral spread beyond the site of reinfection<sup>186</sup>. Finally, circulating SARS-CoV-2-specific T cells may promote long-term immunity through direct killing of infected cells.

A requirement for antigen in the persistence of the GC response would indicate that antigen availability is an important mechanism governing the development of broadly protective immunity.

#### B cell response to SARS-CoV-2 variants

Coronaviruses have a reduced mutation rate and frequency of escape from antibody neutralization compared with smaller RNA viruses owing to their expression of a proofreading 3′-5′ exoribonuclease<sup>100,101</sup>. Nevertheless, thousands of mutations have been identified in circulating SARS-CoV-2 particles, including a host of mutations in the spike protein that impact disease pathogenesis and susceptibility to antibody neutralization<sup>75,102</sup>. While convalescent serum is capable of neutralizing viruses expressing the wild-type spike protein, there is a marked decrease in neutralization sensitivity for several of the spike proteins expressing mutations that map to the ACE2-binding site and that are found in variant viruses<sup>75,103–108</sup>. High concentrations of convalescent serum are still capable of neutralizing viruses expressing escape mutations. However, the existence of confirmed cases of SARS-CoV-2 reinfection suggests that some previously infected individuals may not have sufficient antibody titres to protect against reinfection by SARS-CoV-2 variants<sup>75,109</sup>. It is important to note that there has been no evidence of antibody-dependent enhancement following infection of vaccinated individuals by escape variants.

Therefore, vaccination is critical to bolster the SARS-CoV-2-specific antibody response to a level sufficient to protect against infection by emerging SARS-CoV-2 variants. One dose of an mRNA-based vaccine was sufficient to significantly enhance the titre of neutralizing antibodies specific for the Alpha (B.1.1.7) and Beta (B.1.351) viral variants in previously infected individuals<sup>78</sup>. Conversely, two vaccine doses were required in SARS-CoV-2-naive individuals to reliably elicit neutralizing antibodies against the Alpha, Beta and Delta (B.1.617) variants<sup>78,85,110</sup>. The neutralizing antibody response to viruses expressing escape mutations is reduced relative to that to the wild-type virus in SARS-CoV-2-naive individuals, although it is still present at significant levels<sup>63,78,110–116</sup>. Viruses expressing mutations in E484 were particularly adept at escaping neutralization from vaccine-induced serum<sup>69,105,107,111</sup>. The E484 mutation is in the receptor-binding domain of the spike protein and is important for ACE2 binding<sup>102</sup>. Interestingly, antibodies from previously infected individuals who were vaccinated did not show a reduction in neutralizing titre against the Beta variant<sup>63,78</sup>. The neutralizing titre against both the wild-type virus and variant viruses is increased in previously infected individuals who were vaccinated relative to vaccinated SARS-CoV-2-naive individuals<sup>78,85,117</sup>. There is not a significant increase in the mutational load of memory B cells following vaccination in previously infected individuals<sup>63</sup>. These data suggest that previously infected individuals who were vaccinated may have enhanced immunity to escape variants compared with vaccinated SARS-CoV-2-naive individuals. This may be a result of ongoing clonal evolution



**Fig. 3 | The germinal centre B cell response at 30 weeks following vaccination.** Following vaccination with the Pfizer–BioNTech severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA-based vaccine, the fraction of B cells in the axillary lymph node that are spike protein-reactive germinal centre (GC) B cells increases rapidly. This population further increases upon administration of a second vaccine dose (indicated by the dotted line) and is stably maintained for at least 15 weeks. We have now found that 10 of 15 individuals tested maintain a persistent spike protein-reactive GC B cell response at 30 weeks after vaccination, with the remaining five individuals having no detectable response at this time point. This finding indicates that there is heterogeneity in the longevity of the GC response elicited by vaccination.

increasing the breadth of the B cell response following infection<sup>63,118</sup>. Broader and/or more persistent exposure to SARS-CoV-2 antigens, as well as differences in the specificity and phenotype of the memory T cell response, likely contribute to the enhanced protective immunity to viral variants in previously infected individuals<sup>40,119</sup>.

High neutralizing antibody levels are associated with lower infectivity and reduced likelihood of reinfection by SARS-CoV-2 (REFS<sup>73,120,121</sup>). However, individuals who do not have a sufficiently high neutralizing antibody titre to prevent reinfection may still exhibit significant protection from hospitalization and death owing to the memory B cell response. Memory B cells continue to undergo clonal evolution for at least 1 year following infection, with antibodies encoded by these cells capable of binding to the Alpha, Beta and Delta variants<sup>63,92</sup>. Antibodies derived from 10 of 15 memory B cell clones present at 12 months following infection were able to neutralize all variants tested (including E484-expressing variants) compared with only 1 of 15 clones present at 1.3 months<sup>63</sup>. The rapid differentiation of cross-reactive SARS-CoV-2-specific memory B cells into antibody-secreting cells may therefore represent a critical mechanism limiting disease pathogenesis upon reinfection with variant viruses.

The persistence of the GC response induced by vaccination suggests that vaccine-induced memory B cells may also increase their neutralizing breadth over time<sup>97</sup>. Indeed, memory B cells continue to undergo clonal evolution for at least 5 months following vaccination and contain levels of mutations in antibody genes similar to those of memory B cells present at 6 months following infection<sup>118</sup>. However, there was no significant increase in the neutralizing activity of antibodies encoded by memory B cells between 1.3 and 5 months after vaccination<sup>118</sup>. Additionally, antibodies encoded by vaccine-induced memory B cells displayed minimal increase in affinity and breadth, with only 4 of 19 antibody pairs conserved between 1.3 and 5 months showing increased potency against pseudotyped viruses

expressing the spike protein with mutations found in the Delta variant compared with 11 of 16 antibody pairs conserved between 1.3 and 6 months after infection<sup>118</sup>. It will be important to expand this analysis to consider additional antibodies encoded by memory B cells and to examine how the duration of the GC response induced by vaccination influences the clonal evolution of memory B cells. The administration of an additional booster vaccine encoding a protein expressed by variant viruses was effective in increasing neutralizing antibody titres against the variant virus in mice and may be necessary to increase the breadth of antibodies encoded by vaccine-induced memory B cells<sup>122</sup>.

### Approaches to induce a broadly reactive memory B cell response

The efficacy of mRNA-based vaccines in protecting against SARS-CoV-2 highlights the importance of continuing to develop new approaches to combat emerging viruses. Development of mRNA-based vaccines was initiated as early as 1990 and was intended to protect against pathogens such as Ebola virus, Zika virus, rabies virus and influenza virus before being adapted to target SARS-CoV-2 (REFS<sup>123,124</sup>). Given the likelihood that the rate at which novel diseases emerge from the environment will continue to increase, there is an urgent need to develop new approaches to proactively combat potential sources of future pandemics<sup>125</sup>. In particular, the development of new strategies to drive a broadly protective memory B cell response against rapidly mutating pathogens would be a valuable tool to combat the threat of future pandemics.

**Novel vaccination approaches.** One approach to drive a more broadly reactive memory B cell response is to alter the viral regions that are targeted by vaccination. Traditional vaccines induce antibodies specific for the immunodominant viral regions, which tend to undergo frequent mutation to allow the virus to escape antibody neutralization<sup>126</sup>. However, regions that are conserved between different viral strains, such as the influenza virus haemagglutinin (HA) stalk, undergo much slower mutation, with the mutations that do occur less likely to result in immune evasion<sup>127</sup>. Therefore, the development of a vaccine that induces antibodies targeting conserved viral regions would be an attractive option to elicit heterosubtypic immunity.

Multiple approaches have been designed to induce broadly reactive memory B cells. A chimeric HA-based influenza vaccine recently completed a phase I trial and was shown to safely elicit cross-reactive antibodies to the HA stalk region expressed by group 1 influenza viruses<sup>128</sup>. This approach relies on sequential administration of chimeric HA proteins expressing divergent head regions but the same stalk regions to selectively boost stalk-reactive memory B cells. Antibodies induced in humans using this vaccination approach were sufficient to protect mice against a lethal challenge with a divergent strain of influenza virus<sup>128</sup>. Alternative approaches under development include vaccination with HA proteins in which the head region is masked or removed to drive stalk-specific B cell responses, as well as vaccination

with divergent HA proteins<sup>129–133</sup>. However, significant work remains to optimize these approaches to reliably elicit antibodies capable of providing long-term immunity against group 1 influenza, group 2 influenza and influenza B viruses. Extending these approaches to other pathogens will require identification of surface protein regions that are broadly conserved between different variants and that lead to viral neutralization upon antibody binding. The lack of protective efficacy of antibodies that cross-react between seasonal coronaviruses and SARS-CoV-2 highlights the challenge of identifying the optimal surface region to target to induce heterosubtypic immunity<sup>68</sup>.

**Memory B cell subsets.** Another approach to elicit broadly reactive memory B cells following vaccination is to induce an immune response that gives rise to more memory B cells capable of undergoing affinity maturation upon re-exposure to viral antigens. Memory B cells develop through both GC-dependent and GC-independent pathways, with both populations contributing to protective immunity<sup>70,134</sup>. Atypical memory B cells, which are distinguished on the basis of their expression of T-bet and CD11c, are expanded following severe SARS-CoV-2 infection and may develop independently of the GC<sup>50,52,135–138</sup>. However, GC-independent memory B cells generally do not go through class switching or affinity maturation, and may not be able to undergo the clonal evolution necessary to neutralize emerging viral variants<sup>63,71,134</sup>. Therefore, the GC response is an attractive target for efforts to induce a memory B cell response capable of ongoing clonal evolution.

The memory B cell population is composed of multiple functionally and transcriptionally distinct subsets that emerge from the GC at different times<sup>9,11,139</sup> (FIG. 4a). While the markers used to identify these subsets differ between mice and humans, transcriptionally distinct memory B cell subsets have been identified in numerous immune contexts, including following SARS-CoV-2 infection<sup>136,138,140–142</sup>. Memory B cells expressing CD80 and PDL2 in mice tend to differentiate into plasma cells upon antigen re-encounter, while those lacking CD80 and PDL2 re-enter the GC and undergo further somatic hypermutation<sup>11,143</sup> (FIG. 4b). Bolstering the number of memory B cells capable of re-entering the GC may therefore enhance the capacity of the memory B cell pool to evolve to neutralize emerging viral variants (FIG. 4c,d). CD80<sup>−</sup>PDL2<sup>−</sup> memory B cells display differential expression of numerous cytokine receptors and downstream transcription factors<sup>11,143</sup>. A better understanding of how these pathways shape the composition of the memory B cell pool is needed to design vaccines that can modulate these pathways to favour the development of a particular memory B cell subset.

**Mucosal memory B cell response.** Many viruses that are potential sources of future pandemics, including SARS-CoV-2 and influenza virus, primarily infect mucosal surfaces and induce a local immune response<sup>144,145</sup> (FIG. 5). While antibodies present in the serum are capable of mediating viral clearance in

mucosal sites, the establishment of a mucosal memory B cell response would enable a rapid increase in local antibody titre that could mediate rapid viral clearance following reinfection<sup>146</sup>. Additionally, the induction of a robust mucosal antibody response is critical in preventing viral spread. A subset of SARS-CoV-2-vaccinated individuals who were infected by the Delta variant were recently found to have a similar level of viral transcripts in their upper respiratory tract as infected unvaccinated individuals<sup>147</sup>. While vaccinated individuals who are reinfected still display reduced duration of viral shedding and infectivity compared with unvaccinated individuals, the development of vaccination approaches that induce sterilizing immunity at mucosal sites is critical to limit the spread of variants that have increased transmission risk<sup>148,149</sup>.

Memory B cells have been identified in multiple mucosal tissues, including in the lungs of mice following influenza virus infection<sup>150–152</sup>. Lung-resident memory B cells were associated with enhanced protective immunity upon challenge infection and displayed increased cross-reactivity relative to cells present in the draining lymph node<sup>150,153</sup>. B cells are found in many mucosal tissues in humans<sup>154</sup>. SARS-CoV-2 infection induces virus-specific memory B cells in the bone marrow, spleen, lungs and lymph nodes<sup>66</sup>. Residual antigen depots are also present in mucosal tissues, including in the gut, following SARS-CoV-2 infection, and may fuel the continued clonal evolution of B cells in these sites<sup>40,63,155</sup>. It is currently unclear whether tissue-resident memory B cells arise from GC responses occurring in the tertiary lymphoid structures of mucosal tissues or whether they migrate to the mucosal tissue after developing in the draining lymph node<sup>156–158</sup>. Tertiary lymphoid structures are induced by inflammation and are key sites in which memory B cells become reactivated and give rise to antibodies capable of mediating rapid viral clearance<sup>159,160</sup>.

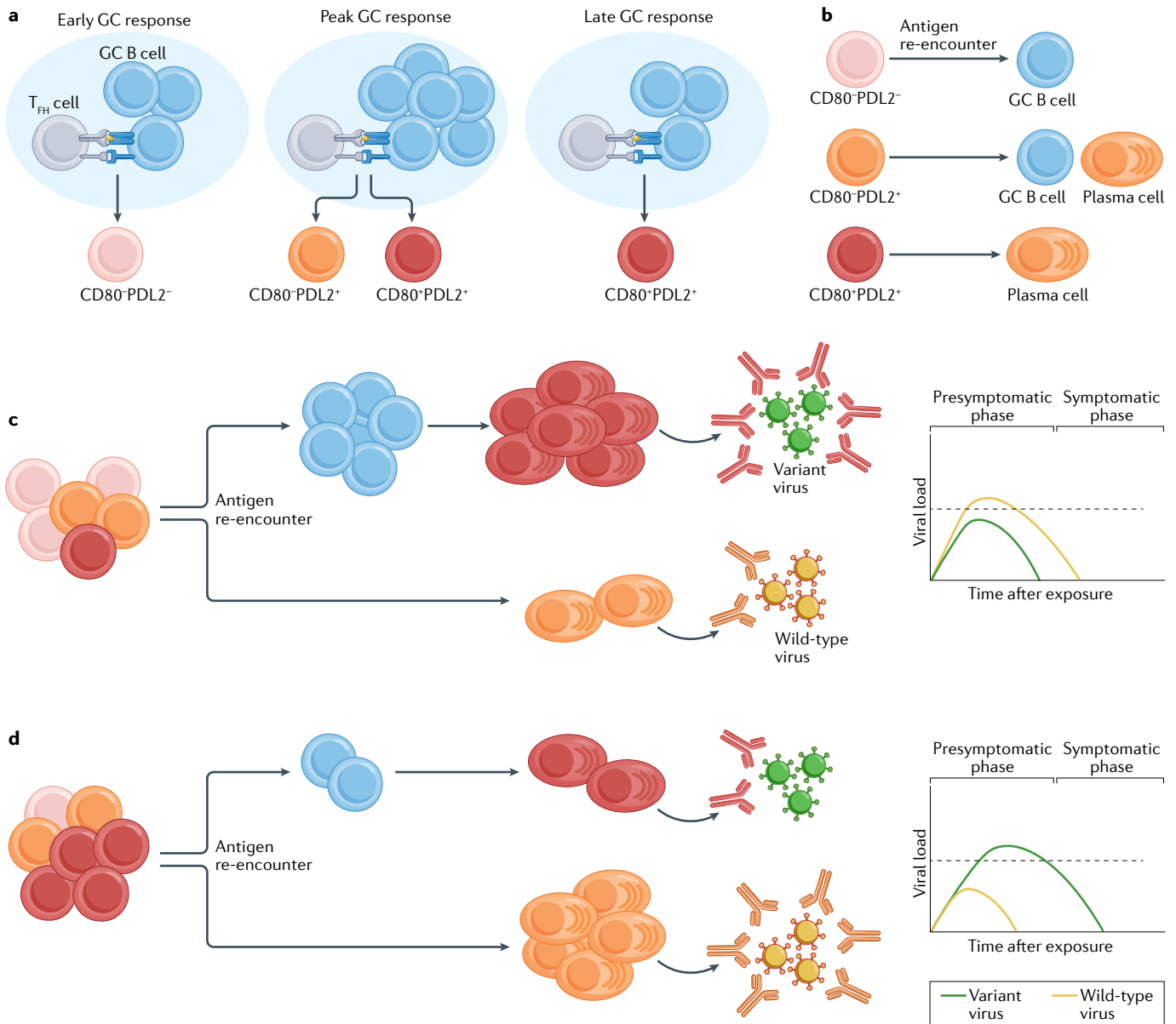
The development of vaccination approaches that induce a mucosal GC and memory B cell response may therefore significantly enhance the development of protective immunity against newly emerging viruses. For example, an intranasal adenovirus-based vaccine against SARS-CoV-2 that induced mucosal B cells had an enhanced ability to prevent upper and lower airway infection in mice and hamsters compared with the same vaccine administered intramuscularly<sup>161,162</sup>. An intranasal adenovirus vaccine also induced a cellular and humoral immune response in rhesus macaques and was protective against SARS-CoV-2 infection<sup>163</sup>. Intranasal delivery of SARS-CoV-2-specific IgM was also effective in protecting against infection in mice<sup>164</sup>. Together, these studies indicate that vaccines that induce immune responses at mucosal surfaces (that is, vaccines delivered orally or intranasally) may represent an effective strategy to induce protective immunity<sup>165</sup>.

### Concluding remarks and perspective

Remarkable progress had been made in elucidating the B cell response following SARS-CoV-2 infection. However, there remain many key knowledge gaps that will shape the public health response in the years ahead.

One central question is whether additional ‘booster’ vaccines expressing mRNA from variant strains will be necessary to induce a B cell response with sufficient breadth and affinity to neutralize future SARS-CoV-2 variants. While the administration of a third vaccine dose of the same formulation will likely result in an increase in antibody titres, it is unlikely to profoundly alter the specificity of the memory B cell response<sup>92</sup>. Variant-based booster vaccines may be necessary to

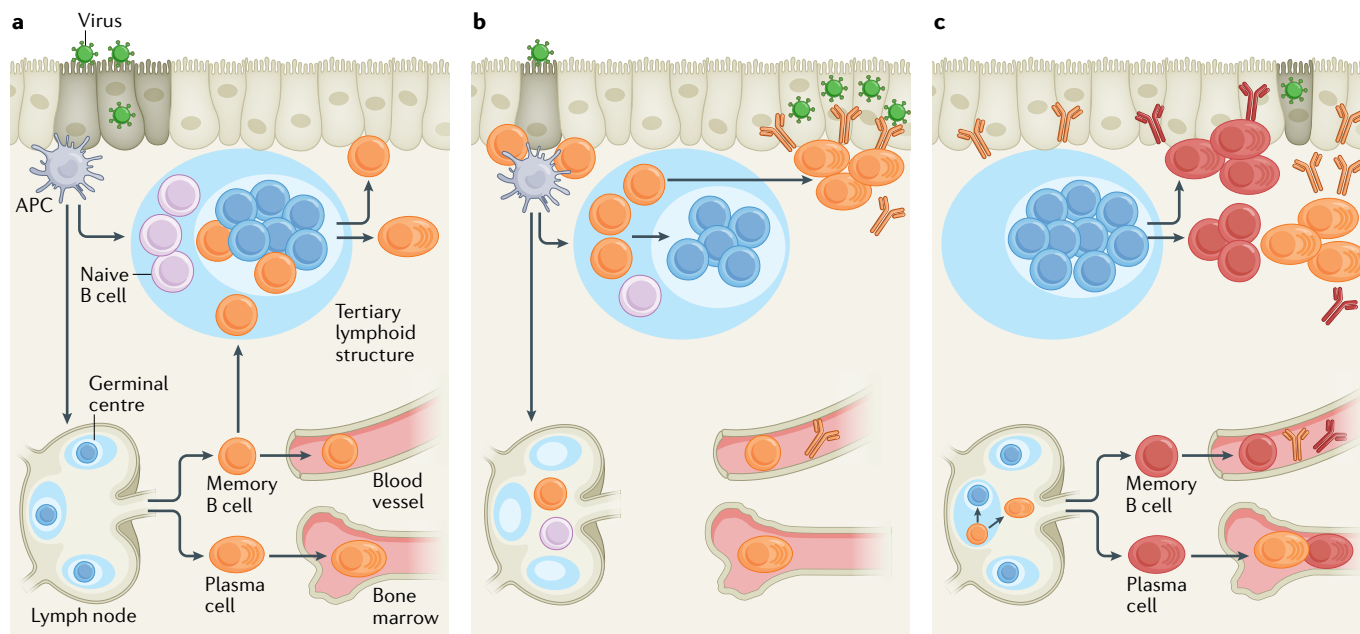
engage naive B cells that recognize variant-specific epitopes and reshape the composition of the memory B cell response. The memory B cell response continues to undergo clonal evolution even 12 months after SARS-CoV-2 infection, with these mutations critical in increasing the potency and breadth of antibodies derived from these cells<sup>63</sup>. While vaccine-induced B cells also undergo clonal evolution, likely owing to the persistence of the GC response, it is unclear whether



**Fig. 4 | Memory B cell subset development and function. a** | During an immune response, memory B cells emerging from the early germinal centre (GC) response are predominantly CD80<sup>-</sup>PDL2<sup>-</sup>. As the GC response matures, memory B cells begin to express PDL2 and CD80, with the memory B cells emerging from the late GC response predominantly being CD80<sup>+</sup>PDL2<sup>+</sup>. **b** | Upon antigen re-encounter, CD80<sup>-</sup>PDL2<sup>-</sup> memory B cells predominantly differentiate into GC B cells, CD80<sup>+</sup>PDL2<sup>+</sup> memory B cells differentiate into either GC B cells or plasma cells and CD80<sup>+</sup>PDL2<sup>+</sup> memory B cells differentiate into plasma cells. **c** | A memory B cell population that is skewed towards CD80<sup>-</sup>PDL2<sup>-</sup> memory B cells would be predisposed

to differentiate into GC B cells upon antigen re-encounter. This response would promote the development of neutralizing antibodies to variant viruses but would generate a delayed response to wild-type viruses. **d** | A memory B cell population that is skewed towards CD80<sup>+</sup>PDL2<sup>+</sup> memory B cells would be predisposed to differentiate into plasma cells upon antigen re-encounter. This response would promote the rapid clearance of wild-type viruses but would result in a delay in the induction of antibodies capable of neutralizing variant viruses. The dotted line in the plots on the right in parts **c** and **d** indicates the viral load necessary to enable spread of the virus to uninfected individuals. T<sub>FH</sub> cell, follicular helper T cell.





**Fig. 5 | The B cell response following mucosal infection. a** | Viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infect respiratory epithelial cells, leading to uptake of antigens by antigen-presenting cells (APCs). Activated APCs migrate to the draining lymph node, where they and lymph node-resident APCs present antigens to cognate T cells and B cells, leading to the induction of a germinal centre (GC) response. Tertiary lymphoid structures may also form in response to mucosal inflammation and serve as sites for local GCs. The GC response in the draining lymph node typically precedes the response occurring in the mucosal tissue, with memory B cells that develop in the lymph node capable of migrating to mucosal tissues. Plasma cells derived from the GC

response migrate to the bone marrow, where they reside long term. **b** | Upon antigen re-encounter, memory B cells residing in the mucosal tissues differentiate into plasma cells or re-enter the local GC. Antibodies derived from mucosal plasma cells cooperate with circulating antibodies to mediate early viral control. APCs that take up antigens will migrate to the draining lymph node, where they and lymph node-resident APCs will present antigens to cognate T cells and B cells. **c** | At later time points, antibodies derived from memory B cells that become reactivated in the draining lymph node contribute to viral clearance. Memory B cells and plasma cells that have undergone further affinity maturation in the mucosal and lymph node GCs will also help mediate viral clearance at later time points.

mutations that accumulate over time lead to enhanced neutralizing activity<sup>118</sup>. It is important to note that vaccination is still essential to bolster the infection-induced B cell response to levels sufficient to protect against reinfection. Determining whether the persistence of the GC following vaccination is associated with enhanced protective immunity as well as understanding the mechanisms underlying the persistence of the GC will be important in evaluating the necessity of additional booster vaccines.

Another key unanswered question is whether SARS-CoV-2 vaccination induces a B cell response in mucosal tissues. While SARS-CoV-2-specific antibodies are detectable in mucosal compartments such as the saliva and breast milk following vaccination, it is unclear whether these antibodies are a product of a local B cell response or how long they persist<sup>166–168</sup>. SARS-CoV-2 vaccines are administered intramuscularly and therefore are unlikely to induce sufficient levels of antigen expression or inflammation in mucosal tissues to support a local GC response. In the absence of a mucosal B cell response, protection from reinfection will be reliant on maintaining a high enough titre of circulating antibodies to neutralize viruses that infect the airways. The reduced capacity of serum antibodies induced solely by vaccination to neutralize variant viruses relative to antibodies induced by vaccination of previously infected individuals is therefore a significant concern

for the long-term prospect of maintaining a sufficient neutralizing antibody titre at mucosal sites to prevent SARS-CoV-2 reinfection, especially against variants such as the Delta variant that induce a significantly higher viral load<sup>63,78,148</sup>.

Relatedly, understanding how the SARS-CoV-2-specific IgA response differs between vaccinated and infected individuals will be important going forwards. The serum IgA response rapidly declines following both SARS-CoV-2 vaccination and SARS-CoV-2 infection and is less potent at neutralizing SARS-CoV-2 than IgG<sup>169,170</sup>. However, SARS-CoV-2 infection also elicits a virus-specific IgG, IgA and IgE antibody response in the saliva and bronchoalveolar fluid. Dimeric SARS-CoV-2-specific IgA, the primary form of IgA present in the nasopharynx, has an enhanced ability to neutralize the virus compared with IgG and may have an important role in preventing reinfection<sup>171,172</sup>. While it is not known whether SARS-CoV-2 vaccination induces a mucosal IgA response in humans, intramuscular vaccination of mice drove a minimal mucosal IgA response and was not as good at mediating viral clearance at mucosal sites as intranasal vaccination<sup>161</sup>. Therefore, developing vaccination approaches that induce dimeric IgA at mucosal surfaces may be an important tool to limit reinfection.

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**Author contributions**

The authors contributed equally to all aspects of the article.

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