

Immunological memory to SARS-CoV-2 infection and COVID-19 vaccines

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ABSTRACT

Immunological memory is the basis of protective immunity provided by vaccines and previous infections. Immunological memory can develop from multiple branches of the adaptive immune system, including CD4 T cells, CD8 T cells, B cells, and long-lasting antibody responses. Extraordinary progress has been made in understanding memory to SARS-CoV-2 infection and COVID-19 vaccines, addressing development; quantitative and qualitative features of different cellular and anatomical compartments; and durability of each cellular component and antibodies. Given the sophistication of the measurements; the size of the human studies; the use of longitudinal samples and cross-sectional studies; and head-to-head comparisons between infection and vaccines or between multiple vaccines, the understanding of immune memory for one year to SARS-CoV-2 infection and vaccines already supersedes that of any other acute infectious disease. This knowledge may help inform public policies regarding COVID-19 and COVID-19 vaccines, as well as the scientific development of future vaccines against SARS-CoV-2 and other diseases.

Running title: Immune memory to SARS-CoV-2

Introduction

Protective immunity provided by vaccines is predicated on the existence of immunological memory: the capacity of the adaptive immune system to not only recognize a novel pathogen but to also remember it. Only in the past few decades have the cellular and molecular sources of immunological memory been defined, and much remains to be determined. The three main branches of the adaptive immune system are B cells (the source of antibodies, “Abs”), CD4 T cells, and CD8 T cells. Immune memory is encoded in four main compartments of adaptive immunity: memory CD8 T cells, memory CD4 T cells, memory B cells (MBCs), and circulating Abs¹ (**Figure 1**). There is evidence of roles for B cells (including Abs), CD4 T cells, and CD8 T cells in protective immunity to SARS-CoV-2, and thus it is important to study immune memory to SARS-CoV-2 and COVID-19 vaccines to understand protective immunity against COVID-19. Because of the size and scope of immunological studies of SARS-CoV-2 in humans, the large number of first-time infections, the large number of first-time vaccinations, and the diversity of COVID-19 vaccines developed in a short period of time, there is now more data on human antigen-specific immune responses to SARS-CoV-2 than any other acute pathogen. As a result, immune memory to SARS-CoV-2 is now a benchmark in human immunology for understanding antigen-specific T cell and B cell memory.

Immune memory to SARS-CoV-2 can be generated by infection (classically referred to as “natural immunity”), vaccination, or hybrid immunity. Hybrid immunity is the combination of infection-induced immunity and vaccine-induced immunity². Each of these causes of immune memory is discussed in each section of this review. Overall, immune memory from prior infection, vaccination, or hybrid immunity each have distinctive characteristics. Previous infection can generate robust immune memory^{3,4}, including memory CD8 T cell, CD4 T cell, MBCs, durable Abs, and local immune memory (**Figure 2**). Epidemiological data on protective immunity in previously-infected individuals are consistent with the immune memory measurements. Multiple large studies observe that prior infection provides ~80-95% protection against symptomatic COVID-19 re-infections for 8+ months, for SARS-CoV-2 ancestral strain and the Alpha through Delta VOCs⁵⁻¹¹, and significant protection against disease with Omicron¹²⁻¹⁴.

COVID-19 vaccines, focusing for the moment on 2-dose mRNA vaccines (Moderna mRNA-1273, Pfizer/BioNTech BNT162b2), clearly provide high levels of protective immunity against SARS-CoV-2 ancestral strain and the Alpha through Delta VOCs^{9,15,16}. However, the high levels of vaccine immunity against detectable SARS-CoV-2 infections wanes over a period of months^{17,18}. Immunity provided by 2-dose ChAdOx1 (AstraZeneca/Oxford ChAdOx1-nCoV-19 AZD1222 “ChAdOx1”) is somewhat lower and wanes faster than the mRNA vaccines¹⁹. With hybrid immunity, neutralizing Ab (nAb) titers and breadth of recognition of SARS-CoV-2 variants are dramatically higher in previously-infected individuals receiving at least one dose of a COVID-19 RNA vaccine² (**Figure 2**). Hybrid immunity from vaccination plus subsequent infection (breakthrough infection) also results in similarly robust immune responses^{20,21}. Multiple epidemiological studies have now validated those immunological findings, by observing that hybrid immunity results in more robust protection against COVID-19 than either previous infection immunity or vaccine-induced immunity^{9,11}. These types of antigen exposure(s) — infection-induced memory, vaccine-induced memory, and hybrid immunity — each have distinct characteristics of immune memory (**Figure 2**), which are key to the observed protective immunity in each case. High circulating nAb titers can clearly provide protective immunity. However, such high nAb titers are not present in many cases, particularly after SARS-CoV-2 infection, and there is substantial evidence for roles of T cells, MBCs, and local tissue immunity in protection from COVID-19^{22,23} (see companion article by Goldblatt et al., this volume). For example, previous infection provides substantial immunity with significantly lower circulating nAb titers than after BNT162b2 or ChAdOx1 vaccination¹⁹. Local tissue immunity contributes to protective immunity after infection (**Figure 3**). Different adaptive immunity mechanisms may be involved in protective immunity to differing degrees with immune memory generated by previous infection, vaccination, or

hybrid immunity. Thus, each are discussed in this review for CD8 T cells, CD4 T cells, MBCs, and Abs.

CD8 T cell memory to SARS-CoV-2

In general, CD8 T cells are important in the control and clearance of viral infections²⁴. In particular, several lines of evidence suggest that CD8 T cells are a relevant and valuable component of the overall adaptive immune response to SARS-CoV-2. One line of evidence is derived from studies in acute SARS-CoV-2 infection, which observed that early CD8 T cell responses were significantly associated with milder disease²⁵. An inverse association between CD8 T cell response magnitude and disease severity was also reported in 4 of 5 additional independent studies^{4,26–29}. Additional evidence for a role of CD8 T cells comes from studies in non-human primates. McMahan and colleagues directly showed that depletion of CD8 T cells in COVID convalescent animals affected immunity against SARS-CoV-2 re-challenge³⁰. An important role for CD8 T cell responses was also reported in an antibody-independent COVID-19 vaccine study³¹. See companion article by Plotkin and colleagues for a review of T cells in protection [ref] and³².

Multiple techniques are commonly utilized to measure antigen-specific T cells responses, with antigen specificity ensured by the use of SARS-CoV-2 derived peptides or defined epitopes, utilized as pools or isolated epitopes. The techniques utilized included Activation Induced Marker (AIM), ICS (intracellular cytokine staining), ELISPOT, and tetramer staining assays and their strengths and weaknesses are reviewed elsewhere^{33,34}.

CD8 T cell memory to SARS-CoV-2 infection

SARS-CoV-2-specific CD8 T cells are detectable in ~70% of COVID-19 cases one-month after infection^{3,4}. The frequency of responders then declines to ~50% by 8 months post-infection^{3,4}. The Dan et al. study included SARS-CoV-2-specific CD8 T cell measurements from 169 COVID-19 case subjects and the Cohen et al study included 114 subjects, making them the two largest studies of CD8 T cell memory to an acute viral infection examining a 6+ month period. The estimated SARS-CoV-2-specific memory CD8 T cell kinetics from the Dan et al. study was $t_{1/2} = 125\text{-}190$ days, while the Cohen et al. $t_{1/2}$ was 196 days. That is strong concordance between the two studies, given that the studies utilized different CD8 T cell assays (AIM and ICS) and the calculations were based predominantly on cross-sectional sampling. By comparison, a rigorous study using in vivo deuterium labelling found yellow fever virus (YFV) vaccine CD8 T cell responses to have an initial $t_{1/2}$ of 123 days³⁵. Given that the YFV vaccine is highly effective, elicits robust CD8 T cells as a live attenuated viral vaccine, and deuterium labelling determined a subsequent $t_{1/2}$ of 460 days³⁵, the observation of similar initial $t_{1/2}$ for memory CD8 T cells after a SARS-CoV-2 infection indicates the generation of long-lasting memory SARS-CoV-2-specific CD8 T cells^{3,4} (Figure 2). Memory CD8 T cells to SARS-CoV were detected 17 years post-infection³⁶.

SARS-CoV-2-specific CD8 T cells generated in response to SARS-CoV-2 infection predominantly express IFN γ and granzyme B (GzB)^{4,37,38}, with some expression of TNF and IL-2⁴. Eight months post-infection, effector memory (T_{EM}) and CD45RA+ effector memory (T_{EMRA}) phenotype memory CD8 T cells predominate, with a smaller fraction of central memory (T_{CM}) phenotype cells^{3,4}. Other studies have corroborated these central findings, with fewer COVID-19 cases, shorter study periods, or inferred CD8 T cells from PBMC ELISPOT assays^{39,40}. Bystander CD8 T cell activation can occur during COVID-19⁴¹, and some AIM markers can represent bystander activation of CD8 T cells and must be used carefully, depending on the experiment context, to avoid miscalculation of antigen-specific CD8 T cells. SARS-CoV-2-specific memory CD8 T cells have also been identified with MHC I tetramers/multimers^{26,42–46}. There has been some confusion about the expression of PD-1 on CD8 T cells in COVID-19. PD-1 is expressed on virtually all activated CD8 T cells. PD-1 is also a marker of exhausted CD8 cells in some contexts. Expression of PD-1 by itself does not indicate an exhausted T cell. While CD8 T cells have been observed to express PD-1 after COVID-19, and increased activation/exhaustion markers were noted in mild as compared to

hospitalization-level or severe disease^{47,48}; subsequent studies using tetramers reported that at later time points the memory PD-1-expressing CD8 T cells are not exhausted, and appear to be highly functional⁴⁵.

Notably, SARS-CoV-2-specific memory CD8 T cell responses are undetectable in ~30% of COVID-19 cases^{3,4,37}, even when testing the full SARS-CoV-2 ORFeome of epitopes³. It is unknown whether those subjects have CD8 T cell responses to untested epitopes, CD8 T cell responses just below the technical limit of detection of the assays used, or whether those subjects truly did not develop CD8 T cell response to SARS-CoV-2 infection.

Lower SARS-CoV-2-specific CD8 T cell responses have been observed in hospitalized COVID-19 cases in multiple studies^{4,25,28}, including memory, consistent with a weak CD8 T cell response predisposing for more severe COVID-19, particularly in older adults possessing fewer naïve CD8 T cells²⁵. This contrasts with CD8 T cell responses to YFV vaccine, which positively correlate with viral load. This also contrasts with positive correlations in SARS-CoV-2 infections between spike Ab titers, MBC frequencies, and disease severity, indicating that the humoral immune response and memory development correlates with acute SARS-CoV-2 viral loads (see MBC and Antibody sections). One interpretation of these data is that acute T cell responses are important for the control and clearance of SARS-CoV-2 infection²².

Many SARS-CoV-2 antigens are recognized by human CD8 T cell responses in SARS-CoV-2 infected individuals³⁷, with an estimated median of 17 epitopes per individual⁴⁹. Recognized class I epitopes are distributed throughout the SARS-CoV-2 ORFeome, but structural proteins (spike, nucleocapsid, and M) are relatively immunodominant^{37,49}. CD8 T cell epitopes are in general well conserved between variants⁵⁰⁻⁵². SARS-CoV-2 CD8 T cell specificities have been recently reviewed elsewhere^{53,54}.

The frequencies of circulating memory CD8 T cells after SARS-CoV-2 infection are lower than the frequencies reported for influenza in humans⁵⁵, though influenza memory reflects the accumulation of many exposures throughout life. The frequencies of circulating SARS-CoV-2 memory CD8 T cells can be considered relatively low in comparison to frequencies generated to viruses in animal models associated with high levels of CD8 T cell mediated protective immunity. However, the frequency of memory CD8 T cell required for control of an infection is generally highly dependent on the speed of the clinical disease. Most animal models of CD8 T cell mediated protection require CD8 T cell immediate effector functions (e.g., cell killing at the site of infection within hours), or viral clearance within a few days. However, once activated CD8 T cells proliferate rapidly and migrate to infected tissues (sites of inflammation), with the cells potentially expanding in number 10-fold every 24 hours. Thus, within 72 hours of activation memory CD8 T cell can increase in number close to 1000-fold. Importantly, progression of hospitalization with COVID-19 is relatively slow, often occurring 10 days post-infection or later^{56,57}. Thus, a role for CD8 T cell in prevention of severe COVID-19 may require quite low levels of circulating memory CD8 T cells at the time of infection. In contrast, since CD8 T cells must exert their functions directly on infected cells, a role for CD8 T cells in prevention of SARS-CoV-2 transmission (half of which occurs within the first 5 days), before reported symptoms⁵⁸⁻⁶⁰ is a high bar and likely requires a large number of tissue resident memory (T_{RM}) CD8 T cells in the URT (**Figure 3**), which nevertheless can be achieved by immunization³¹.

T_{RM} are an important category of T cells for protective immunity. They are underreported in the human immunology literature because it is much more difficult to obtain human tissue samples and isolate T cells from diverse tissues in comparison to blood. It is also much more difficult to identify antigen-specific T cells from such samples, due to limited cell numbers recovered and different cellular phenotypic characteristics⁶¹. In the context of SARS-CoV-2, immune memory in tissues is particularly relevant in the nasal passages, oral cavity, throat, and lungs (**Figure 3**). SARS-CoV-2-specific CD8 T cell T_{RM} have been identified in humans^{62,63}. Lung tissue was examined from four subjects up to 6+ months after unremarkable (non-hospitalized) cases of COVID-19. Lymphoid tissues such as blood and lymph nodes (LNs) were examined for comparison. While SARS-CoV-2-specific CD8 T cells were identified in blood from only 2 out of 4 subjects (consistent with the detection rate in much larger studies^{3,4}), SARS-CoV-2-specific CD8 T cell

were identified in lung LNs from 4 out of 4 subjects, and SARS-CoV-2-specific CD8 T cell were identified in lung tissue from 3 or 4 out of 4 subjects⁶². Additionally, substantial fractions of the CD8 T cells in both lungs and lung LNs were T_{RM} cells. Notably, in two studies SARS-CoV-2-specific CD8 T cell frequencies in lung tissue or bronchoalveolar lavage (BAL) were substantially higher than blood^{62,63}. SARS-CoV-2 is also present in gut tissues. While intestinal tissue was not available, intestinal LNs were examined, and SARS-CoV-2-specific CD8 T cell and CD8 T cell T_{RM} were found in all three samples tested, suggesting that substantial CD8 T cell T_{RM} may be present in intestinal tissue of previously-infected individuals⁶⁴. Thus, blood samples may significantly underreport SARS-CoV-2-specific CD8 T cell memory in previously-infected individuals. SARS-CoV-2-specific T_{RM} from throat, nasal passages, or the oral cavity after COVID-19 are less well studied⁶⁵, representing a major knowledge gap for immune memory.

Development of pediatric T cell memory is of particular interest in the context of the well-known lower disease susceptibility of children to severe COVID-19, and in the context of the many differences in adult versus pediatric immune reactivity⁶⁶. Conflicting data have been reported regarding pediatric T cell responses to COVID-19. In one study, significantly stronger acute and memory T cell responses were reported⁶⁷. In another study, significantly lower acute and memory CD8 T cell responses were reported⁶⁸. Of potential interest is also the observation that T cell memory in children may have differences in immunodominance, perhaps as a result of different exposure to common cold coronaviruses^{67,68}. A small fraction of pediatric SARS-CoV-2 infections later develop a serious hyperinflammatory condition, multisystem inflammatory syndrome in children (MIS-C). Conflicting data have been reported regarding the relative strength of T cell memory in MIS-C versus non-MIS-C cases⁶⁹⁻⁷⁴.

Long COVID (aka post-acute sequelae of SARS-CoV-2 infection [PASC]) is an important collection of conditions, with unclear etiology⁷⁵. Given that SARS-CoV-2 viral RNA and protein have been detected 90+ days post-infection in gut biopsies from unremarkable COVID-19 cases (not hospitalized, and not long COVID), it is plausible that significant SARS-CoV-2 viral persistence occurs in some individuals in some tissues. This could be a source of inflammation and symptoms for at least some cases of long COVID. It is unclear why CD8 T cell would not clear SARS-CoV-2 infection from intestines within a few weeks [Plotkin, Crotty...]. Efficacy of CD8 T cell clearance of virus in humans remains an important knowledge gap. Notably, SARS-CoV-2-specific CD8 T cell responses are undetectable in ~30% of COVID-19 cases^{3,4,37}, even when testing the full SARS-CoV-2 ORFeome of epitopes³. It is unknown whether those subjects have CD8 T cell responses to untested epitopes, CD8 T cell responses just below the technical limit of detection of the assays used, or whether those subjects truly have no CD8 T cell response to SARS-CoV-2 infection. It is also possible that some subjects in which SARS-CoV-2-specific CD8 T cell responses are undetectable in the periphery, might nevertheless have T_{RM} antigen specific cells residing in the lung or upper respiratory tract tissues^{64,76}. Separately, CXCR6⁺ CD8 T cells in lungs have been associated with extended periods of COVID-19 inflammation and may have a role in long COVID⁶³.

CD8 T cell memory to vaccination

Spike-specific CD8 T cell responses are detected in ~70-90% of individuals weeks after receiving 2-dose mRNA COVID-19 vaccines⁷⁷⁻⁸⁰, and memory CD8 T cells are detectable in ~41-65% of individuals at 6 months after the 2nd dose (7 months from 1st dose)^{77-79,81}. A low dose (25 µg) of mRNA-1273 was found to generate memory CD8 T cells at similar frequencies as previous infection, comparing 6 months after the 2nd dose to 6 months after infection, indicating similar spike-specific CD8 T cell responses between mRNA vaccination and infection. A separate study also found similar spike-specific CD8 T cell responses at earlier times⁸². Among individuals with detectable CD8 T cell memory to mRNA vaccines months after immunization, the magnitude of the memory is generally observed to be low^{77,78,80,81,83}, both in comparison to spike-specific CD4 T cell memory, and memory to influenza⁵⁵.

There was initial confusion about whether both BNT162b2 and mRNA-1273 mRNA COVID-19

vaccines generated CD8 T cell responses^{42,84,85}. More recently, multiple groups have observed similar CD8 T cell responses to both vaccines⁷⁸, including in head-to-head comparisons^{78,80,83}. Methodological differences measuring antigen-specific T cells can result in different findings, as studies not detecting memory CD8 T cells usually utilized a less than optimal short stimulation ICS protocol, or less sensitive ELISPOT formats. The mRNA vaccine-elicited memory CD8 T cells detected predominantly have a T_{EM} surface phenotype, consistently express IFN γ , and have proliferative capacity^{43,80}.

The first 6 months are likely to be the period with the fastest decline in T cell memory³⁵. The observation of ~2-fold declines at 6 months in spike-specific CD8 T cell memory from peak cytokine-positive CD8 T cell frequencies is encouraging evidence that CD8 T cell memory to mRNA vaccines is long-lived and may last many years^{77,79,80} (**Figure 2**). Memory CD4 T cells exhibit similar kinetics, as discussed in the CD4 T cell section below.

The adenoviral vector vaccines ChAdOx1 and Ad26.COVS2.S elicit spike-specific CD8 T cell responses in 51-64% of individuals in immunogenicity clinical trials⁸⁶, though the response rate drops to 24-36% in individuals ≥ 65 years old⁸⁶. Stable CD8 T cell memory to Ad26.COVS2.S is observed to 8 months⁸⁷. Some comparisons between mRNA vaccines and adenoviral vector vaccines are available for CD8 T cell memory. Similar (within ~2-fold) spike-specific CD8 T cell responses to mRNA vaccines and adenoviral vector vaccines are observed ~1 month after immunization, including the 1-dose Ad26.COVS2.S^{78,80,83,88}, 2-dose Ad26.COVS2.S⁸⁸, or 2-dose ChAdOx1⁸⁹⁻⁹¹. Two studies that assessed CD8 T cell memory at 5+ months determined that mRNA-1273 elicited larger spike-specific CD8 T cell memory than Ad26.COVS2.S^{78,80}. Two other studies reported the opposite^{92,93}, with a clinical trial reporting 45/57 Ad26.COVS2.S subjects and only 20/116 BNT162b2 or mRNA-1273 subjects positive for CD8 T cell memory⁹³. In PBMC IFN γ ELISPOT assays, T cell memory 2-4 months after ChAdOx1 and BNT162b2 appears to be equivalent, though CD8 and CD4 T cells were not distinguished^{94,95} (bulk PBMC IFN γ ELISPOT assay signal comes from a mixture of CD8 T cells and CD4 T cells⁴²). A similar observation was made for Ad.COVS2.S⁹⁶. In sum, CD8 T cell memory to mRNA and adenoviral vector COVID-19 vaccines appears to be similar in magnitude and % responders (**Figure 2**), but conclusions vary depending on the study. Additional head-to-head studies or memory are warranted, including examination of CD8 T cell functionality.

Memory CD8 T cells elicited by mRNA vaccines recognize diverse spike epitopes^{49,50,78}. Memory CD8 T cells largely have conserved recognition of variants, including Omicron^{78,82,88,97-99}. Mix & match adenoviral vector + mRNA vaccine approaches may increase CD8 T cell responses^{89,90,96}, and thereby may alter CD8 T cell memory. Perplexingly, lower CD8 T cell responses were reported to vaccine extended dose intervals, with the caveat that minimal CD8 T cells were measurable in any group¹⁰⁰.

CD8 T cell memory in hybrid immunity

Modest differences have been observed between vaccination only and hybrid immunity for circulating spike-specific CD8 T cells in most studies¹⁰⁰, as well as no difference based on symptomatic or asymptomatic infection¹⁰¹ (**Figure 2**). In one study, no difference in memory IFN γ ⁺ spike-specific CD8 T cells was observed between vaccination only and hybrid immunity after 6 months⁸¹. Multiple studies observed increased T cell responses in hybrid immunity compared to infection or vaccination alone without distinguishing between CD4 and CD8 T cells^{82,100}.

CD4 T cell memory to SARS-CoV-2

Memory CD4 T cells are important in the control and clearance of viral infections, both directly and by the effects exerted in the support and amplification of antibody responses. Several different subsets of CD4 T cells can differentiate in antigen-specific responses to infections. This heterogeneity is manifested at the level of different memory subsets, each associated with distinctive patterns of cytokine secretion, transcription factors and differentiation profiles (T_H1, T_H2, T_H17, T_{FH} and others¹⁰²). This heterogeneity is

further amplified by a diverse array of functional roles. T_{FH} cells play a key role in orchestrating the development and maturation of antibody responses^{103,104}, while Th1 and cytotoxic CD4 T cells (CD4-CTL) can exert direct antiviral functions^{105–107}. Multiple lines of evidence suggest that CD4 T cells are a relevant and valuable component of the overall adaptive immune response to SARS-CoV-2^{22,32,108}. Protective effects of CD4 T cells against COVID-19 are fully reviewed in the companion article [Plotkin, Crotty and colleagues, this volume].

CD4 T cell memory to SARS-CoV-2 infection

Dan et al. found that antibody, CD4 T cell, CD8 T cell, and B cell memory responses were durable over 8 months after infection, with 95% of the subjects still retaining multiple measurable memory responses, including memory CD4 T cells³. Notably, memory CD4 T cells are detectable in 93% of COVID-19 cases one-month after infection³, and still 92% at ≥ 6 months post-infection³. Multiple studies have reported similar memory CD4 T cell findings^{4,38,39,109}, with a notable large longitudinal study⁴. The estimated $t_{1/2}$ of memory SARS-CoV-2-specific CD4 T cells is 94 to 207 days during the first 8 months^{3,4}, with the $t_{1/2}$ likely increasing substantially over time, based on a study determining a $t_{1/2}$ of 377 days for memory SARS-CoV-2-specific CD4 T cells at 6 to 15 months post-infection¹¹⁰ (Figure 2), as well as similar data on CD8 T cell memory against a different virus³⁵. These SARS-CoV-2 infection data are consistent with T cell memory to SARS-CoV being detected 17 years post-infection^{36,111–113}.

SARS-CoV-2-specific memory CD4 T cells after SARS-CoV-2 infection predominantly are T_H1 , T_{FH} , and CD4-CTL cells^{3,4,110}. Eight months post-infection, the memory CD4 T cells predominantly have central memory (T_{CM}) and effector memory (T_{EM}) surface phenotypes^{3,4}. Virus-specific T_H2 cells and T_H17 cells are generally not detectable^{4,25,37}. Regarding the T_H1 memory cells, they are a stably maintained population⁴, predominantly expressing CD40L and IFN γ ⁴, with significant expression of TNF and some expression of IL-2^{4,28,55,101,110,114}. The CD4-CTL cells express CD40L and granzyme B (GzB)^{4,80,115,116}. CD4-CTL cells are of interest because SARS-CoV-2-infected epithelial cells upregulate class II expression¹¹⁷, and CD8 T cell responses appear to be low in many individuals, leaving open the possibility that memory CD4-CTL may compensate^{117,118}. Memory T_{FH} cells are generated after SARS-CoV-2 infection and are stably maintained after a brief decline^{3,110,119} (Figure 2). The memory T_{FH} cells are highly functional, as they greatly enhance nAb responses to COVID-19 vaccines^{2,120,121}. Some memory T_{FH} cells express CCR6, which is associated with lung homing^{3,119}. Other memory T_{FH} cells express CXCR3, which is associated with rapid anamnestic antibody responses^{104,122}, while the CXCR3^{neg} memory T_{FH} population is associated with higher quality germinal center and antibody responses^{123,124}. Germinal centers are discussed in the B cell memory section.

In terms of anatomical location of memory T cells, memory CD4 T cells are detectable in the bone marrow, spleen, lung, and multiple lymph nodes (LNs) for 6+ months after infection⁶⁴. Memory T_{FH} cells are observed in LNs⁶⁴. CD4 T_{RM} cells were present at substantial frequencies in lungs⁶⁴ and BAL⁶³ (Figure 3). Less is known regarding SARS-CoV-2-specific CD4 T_{RM} in the URT and oral cavity.

Many SARS-CoV-2 antigens are recognized by human memory CD4 T cells in previously-infected individuals³⁷, with an estimated median of 19 epitopes per individual⁴⁹. Recognized class II epitopes are distributed throughout the SARS-CoV-2 ORFeome, but structural proteins (spike, nucleocapsid, and M) are relatively immunodominant^{4,37,49,125}. CD4 T cell epitopes are in general well conserved between variants^{50–52}. SARS-CoV-2 CD4 T cell specificities have been recently reviewed elsewhere^{53,54}.

Human antiviral immune memory may be influenced by variables such as viral factors related to the infection event such as viral dose and tissue distribution, and host factors such as age, sex and general health of the host¹²⁶. A distinctive feature of SARS-CoV-2 infection and COVID-19 disease is the wide range of clinical outcomes, ranging from fully asymptomatic infection to severe disease and death. The heterogeneity in clinical outcomes associated with SARS-CoV-2 infection and COVID-19 disease is paralleled by large variations in heterogeneity at the level of CD4 T cell responses^{3,25}. Specifically, SARS-

CoV-2 T cell responses are influenced by older age and the size of the pool of naïve T cells²⁵. No significant difference in CD4 T cell memory is observed between males and females^{3,4}. Pre-existing comorbidities in COVID patients have been reported to affect magnitude and helper T cell subset composition¹²⁷. T cell responses of a homogenous group of healthy young males were still widely heterogeneous¹²⁸, suggesting that heterogeneity of responses is driven by variables other than predisposing conditions, age and sex. As noted above, conflicting data have been reported regarding pediatric T cell responses to COVID-19. In one study, stronger acute and memory CD4 T cell responses were reported in one study⁶⁷, but significantly lower acute and memory CD4 T cell responses were reported in another study⁶⁸. Conflicting data have been reported regarding CD4 T cell memory in MISC versus non-MISC cases⁶⁹⁻⁷⁴.

Asymptomatic SARS-CoV-2 infections may reflect shorter infections with lower overall viral loads in tissues, which could be expected to have lower T cell memory as a result of lower antigen exposure. Comparison between asymptomatic and mild symptomatic COVID-19 cases revealed slightly lower T cell memory among asymptomatic COVID-19 cases^{38,129}. The relation between COVID-19 severity and quality of memory CD4 T cells is still an open topic of debate and investigation^{115,125,130,131}. In the context of long COVID⁷⁵, alterations of T cell responses lasting several months post-infection have been reported⁶³, as have increased total T cell accumulation in BAL¹³².

Crossreactive memory T cells

Memory CD4 T cells able to recognize SARS-CoV-2 have been demonstrated in unexposed subjects, with the clearest evidence coming from blood samples obtained during pre-pandemic times^{36,37,115,133,134}. It was hypothesized that these cells may predominantly be memory T cells to previous common cold coronavirus (CCC) infections^{53,135}. Indeed, at least in some cases these memory T cells cross-recognize SARS-CoV-2 and CCCs^{27,45,125,136-139}. Detailed studies suggest that cross-recognition across distant viral species can occur, but rather infrequently^{140,141}, and is observed for SARS-CoV-2 sequences^{129,142}. In general, SARS-CoV-2 crossreactive memory T cells have been most often described in the case of CD4 T cells, and less often for CD8 T cells³⁷. In terms of antigen specificity, the sequences associated with crossreactive memory are often derived from non-structural antigens encoded in the Orf1ab, which correlates with the higher degree of conservation of across the genome of CCCs and other coronaviruses⁵³.

It has been debated to what extent this pre-existing crossreactive T cell memory is functional and biologically relevant^{135,143}. The T cells associated with this pre-existing immunity display classical memory markers¹³⁶, and were detected by a variety of assays. However, this crossreactive recognition can be of low affinity, particularly in the case of more distant unrelated viruses¹⁴². Additionally, SARS-CoV-2 infection is associated with development of T cell response that is largely focus on novel epitopes⁴⁹. Nevertheless, it has now been demonstrated that the crossreactive memory T cells are biologically functional. Pre-existing crossreactive memory T cells exert a positive influence on COVID-19 vaccination outcomes^{77,144,145}. This is consistent with two reports that persons with CCC infections within recent years preferentially had less severe COVID-19 outcomes^{146,147}, while a different study found no association¹⁴⁸. Healthcare workers were observed to have high levels of SARS-CoV-2 crossreactive memory T cells, and CCC-specific T cells¹⁴⁹. It was further shown that the presence of these crossreactive T cells was linked to favorable outcomes in a large healthcare worker cohort during the first wave of the pandemic, with crossreactive memory CD4 T cells possibly providing protection resulting in abortive SARS-CoV-2 infection¹⁵⁰. Evidence of protection was also observed in a household contacts study¹⁵¹. Overall, crossreactive memory CD4 T cells recognizing SARS-CoV-2 existed in ~50% of individuals pre-pandemic, those crossreactive CD4 T cells have functional properties *in vivo*, and they have been associated with some degree of protection from COVID-19.

CD4 T cell memory to vaccination

COVID-19 vaccines can elicit robust CD4 T cell memory. Spike-specific CD4 T cell responses are detected in close to 100% of individuals weeks after receiving 2-dose mRNA COVID-19 vaccines⁷⁷⁻⁸¹, and memory CD4 T cells are detectable in ~100% of individuals at 6 months after the 2nd dose (7 months from 1st dose)^{77-79,81}. mRNA-1273 generated spike-specific memory CD4 T cell frequencies higher than seen in previously infected individuals⁸⁰, while BNT162b2 generate spike-specific memory CD4 T cell frequencies similar to infection^{80,81}. A dose of mRNA-1273 similar to that of BNT162b2 generated spike-specific memory CD4 T cells at frequencies comparable to previous infection⁷⁷, indicating that differences between memory CD4 T cells after the two mRNA vaccines most likely predominantly relate to the different doses of the two vaccines. Reductions in memory CD4 T cell frequencies over 6 months were modest, and half-lives of memory CD4 T cells after mRNA COVID-19 vaccines appear to be at least as long as after infection^{77,80,81} (Figure 2). Memory CD4 T cells are generated after a single dose of mRNA vaccine or Ad26.COV2.S that maintained at least several months^{80,87,96,100}. In the context of vaccine interval extension protocols, IL-2⁺ memory CD4 T cells were increased in vaccinees who waited longer before the 2nd mRNA vaccine dose¹⁰⁰.

After vaccination, memory T_H1 cells are stably maintained^{78-81,98}, and express CD40L, IFN γ , TNF, and IL-2^{79,80}. Memory T_{FH} cells represent ~25% of CD4 T cell memory after mRNA immunization⁸⁰, and the abundance of the cT_{FH} cells is associated with the magnitude of the nAb response^{77,80,120,121,152}. Vaccine-elicited memory T_{FH} cells in blood are stably maintained with minimal decline over 6+ months⁸⁰, though the cT_{FH} may change phenotype during the first months^{81,110,153}. Active germinal center T_{FH} (GC-T_{FH}) cells are found in LNs for at least 6 months, and appear to be critical for maintaining germinal centers and development of nAbs after vaccination^{152,153}. Durable T_{FH} cell memory in blood was observed for mRNA vaccines, Ad26.COV2.S, and NVX-CoV2373⁸⁰. Memory CD4-CTL cells are also generated in response to several COVID-19 vaccines and are stably maintained for at least 6 months⁸⁰. Overall, each major subset of memory CD4 T cells are maintained for at least 6 months after vaccination with BNT162b2, mRNA-1273, Ad26.COV2.S, and NVX-CoV2373, with kinetics that indicate the memory CD4 T cells will be substantially maintained for years (Figure 2).

After ChAdOx1-nCoV-19 immunization, polyfunctional T_H1 memory CD4 T cells are induced^{154,155}. Similar (within ~2-fold) spike-specific CD4 T cell responses to mRNA vaccines and ChAdOx1-nCoV-19 are observed ~1 month after 2 doses⁸⁹. Immunization with 2 doses of the inactivated SARS-CoV-2 alum and imidazoquinolin adjuvanted vaccine BBV152 (Covaxin) generates memory CD4 T cell responses comparable to that seen in infected individuals, stably maintained for over 6 months¹⁵⁶. Limited T cell memory data are available for several other vaccines, including Coronavac, Sinopharm, and Sputnik.

Memory CD4 T cells elicited by mRNA vaccines recognize diverse spike epitopes^{49,50,78}. Recognition of variants by memory CD4 T cells is maintained in mRNA, Ad26.COV2.S, and NVX-CoV2373 vaccinees^{78,82,97,98}.

CD4 T cell memory in hybrid immunity

Modest differences have been observed between vaccination only and hybrid immunity for circulating spike-specific memory CD4 T cells in most studies^{100,114,120,157}, as well as no difference based on symptomatic or asymptomatic infection¹⁰¹. In one study, no difference in memory spike-specific CD4 T cells was observed between vaccination only and hybrid immunity after 6 months⁸¹ (Figure 2). Multiple studies observed increased T cell responses in hybrid immunity compared to infection or vaccination alone using IFN γ ELISPOTs that do not distinguish between CD4 and CD8 T cells^{82,100}, suggesting functional changes may occur. Indeed, a distinct population of spike-specific IFN γ ⁺ IL-10⁺ T_H1 memory cells is observed in hybrid immunity but not after vaccination alone, demonstrating a function of imprinting on the memory T_H1 cells by infection¹¹⁴. There is dramatic enhancement of antibody and B cell responses in persons with hybrid immunity, demonstrating a strong functional role for memory T_{FH} cells in hybrid

immunity, discussed elsewhere.

An additional important aspect of hybrid immunity is the location of the T cell memory. Intramuscular vaccination is expected to generate almost exclusively circulating T cell memory. In contrast, SARS-CoV-2 infection generates both circulating T cell memory and T_{RM} (Figure 3). Thus, hybrid immunity is expected to result in both circulating and T_{RM} , but it is unclear if the vaccines enhance T_{RM} already present from infection. Lastly, if the order is vax+infection, it is unknown whether the T_{RM} are qualitatively or quantitatively different than what occurs after infection alone.

B cell memory to SARS-CoV-2

Human MBCs can be exceptionally long-lived, with smallpox vaccine MBCs lasting > 50 years¹⁵⁸, and MBCs generated from infections during the 1918 pandemic lasting at least 90 years¹⁵⁹. MBCs are reactivated upon an infection and are the source of classic anamnestic antibody responses. MBCs serve two purposes. The first is a cellular source for the anamnestic antibody response. MBCs can plausibly reactivate and generate an anamnestic antibody response within 3-5 days¹⁶⁰. The second important value of MBCs is to serve as a library of predictions by the immune system of possible future viral variants^{2,161}. The COVID-19 pandemic has dramatically demonstrated the importance of MBC diversity in the recognition of a pathogen and variants, also highlighting the brilliance of the immune system at predicting viral mutations, embedding those predictions in the MBC repertoire. MBCs likely play a role in protective immunity against SARS-CoV-2 infection by both of the mechanisms above, and protection by MBCs is reviewed in the accompanying article [].

B cell memory to SARS-CoV-2 infection

Detectable MBCs develop within two weeks of symptom onset after SARS-CoV-2 infection^{3,4}. Strikingly, MBC frequencies continuously increase over the course of 3 to 6 months post-infection^{3,4,162}. Spike-, RBD-, and nucleocapsid-specific MBCs all exhibit this increase, in a cohort of 160 individuals³. SARS-CoV-2-specific MBC frequencies stabilize ~4 months post-infection³ and are maintained for at least 15 months^{162,163} (Figure 2). These Spike- and RBD-binding MBCs frequency increases are associated with substantial somatic hypermutation (SHM) for 6-months^{162,164,165}, continuing for at least 12 months¹⁶². The MBC antibody mutations accumulated over 6 to 12 months demonstrated increased affinity maturation and increased neutralization potency, particularly against variants^{162,165}. These patterns are all indicative of long-lasting germinal centers after SARS-CoV-2 infection; an exception however is fatal COVID-19, in which profound disruption of germinal centers can be observed in autopsies^{166,167}. The high quality of the MBCs after SARS-CoV-2 infection is also evidenced by the anamnestic nAb responses to variants after a subsequent vaccination or infection, as discussed in the "Antibody durability" sections below.

While IgM⁺ MBCs initially comprise ~1/3rd of SARS-CoV-2-specific MBCs, IgM⁺ cells decline rapidly and are mostly undetectable after 5 months^{3,4}. IgA⁺ MBCs are uncommon, comprising only ~5% of Spike or RBD-specific MBCs on average^{3,4,165}, but the IgA⁺ MBCs are stably maintained over 8 months post-infection, in contrast to the IgM⁺ MBCs³. MBCs can have diverse phenotypes. After SARS-CoV-2 infection, activated SARS-CoV-2-specific MBC frequencies are initially high, but decline over the course of 7 months, with a reciprocal increase in resting MBCs¹⁶⁴.

COVID-19 severity does impact the magnitude of the MBC response. Patients with hospitalization-level COVID-19 develop higher RBD-specific MBC frequencies compared to individuals with mild COVID-19^{3,164}, similar to what is observed for antibody titers¹⁶⁸. Asymptomatic cases develop similar Spike-specific MBC frequencies compared to symptomatic but non-hospitalized COVID-19 cases [Crotty manuscript in prep].

The detailed study of SARS-CoV-2-specific MBCs in response to infection, over periods of 6 to 12 months, in multiple large independent cohorts, with a range of disease severities, and intensive BCR

sequencing, amounts to the most detailed understanding of the development of B cell memory to any acute infection. In a small data set from two YFV vaccine (a live viral vaccine) recipients, increases in MBC frequencies were observed for 6 months, increases in affinity maturation were observed for over 6 months, and declining frequencies of IgM⁺ or activated MBCs were observed over 6+ months¹⁶⁹. All of those features are commonalities shared with MBC responses to SARS-CoV-2 infection. Ebola infection MBC responses also have some commonalities, though the severity of Ebola disease and longevity of high viral loads may alter that response¹⁷⁰. Overall, the MBC response to SARS-CoV-2 infection is quite impressive, with substantial RBD- and Spike-specific MBC generation; and with only exposure to a single viral strain, the MBC compartment develops over several months to contain MBCs with high neutralization potency and MBCs capable of recognizing and neutralizing a range of variants.

Tissue resident MBCs (B_{RM}) can exist in some cases. Pathogen-specific tissue B_{RM} have been observed in lungs of mouse models¹⁷¹, and B_{RM} phenotype MBCs are found in multiple human tissues¹⁷². B_{RM} have now been demonstrated in humans after SARS-CoV-2 infection⁶⁴ (**Figure 3**). By studying organ donors with a previous history of unremarkable COVID-19 (non-hospitalized), it was shown that Spike/RBD-specific B_{RM} were observed in the lungs of all subjects⁶⁴. Notably, the frequencies of Spike/RBD-specific MBCs in lungs were significantly higher than in spleen, indicating enrichment of local memory in lungs after SARS-CoV-2-infection. Spike/RBD-specific MBCs were also found in bone marrow, lung LNs, and gut LNs⁶⁴. RBD-specific B_{RM} have also been observed in BAL⁶³. Local reactivation of B_{RM} in lungs could result in faster anamnestic antibody responses than from circulating MBCs, based on data from a mouse influenza model¹⁷¹. URT tissues were not available for MBC analysis, and this remains a knowledge gap, given that the URT is the primary site of SARS-CoV-2 replication and transmission.

Regarding long COVID, there is no SARS-CoV-2-specific MBC study reported for long COVID. As noted in the memory T cell sections, it is plausible that at least some long COVID cases are due to persistent infection in some tissue sites. As such, some of the extended SHM of MBCs may be due to new SARS-CoV-2 antigen generation after the acute phase of the disease was resolved. These are significant remaining knowledge gaps.

B cell memory to vaccination

MBC are generated in response to COVID-19 vaccines. Similar frequencies of RBD-binding IgG⁺ MBCs are generated after 2-dose RNA vaccines or SARS-CoV-2 infection⁸¹ (**Figure 2**). SHM levels are also substantial, and comparable between 2-dose RNA vaccines and SARS-CoV-2 infection at 5 months^{81,173}. A substantial fraction of RBD-binding IgG⁺ MBCs from 2-dose RNA vaccinated individuals also bind to VOC RBDs^{78,81}. Thus, 2-dose RNA vaccines generate substantial affinity matured MBCs. Nevertheless, the affinity maturation after a standard 2-dose RNA vaccine regimen is qualitatively poorer than that after SARS-CoV-2 infection. Substantial improvements in nAb breadth were observed months after infection but not after RNA vaccination (e.g., 69% of nAbs from previously-infected subjects had improved potency, but on 19% of nAbs did from 2-dose RNA vaccinees)¹⁷³. These qualitative differences may be related to the narrow time between dose 1 and dose 2 of the RNA vaccines. The priming period can be important for the quality of a B cell response. Extending the priming period can result in better nAb responses to HIV¹⁷⁴⁻¹⁷⁸. Extending the dose interval between RNA vaccine immunizations from 3 to 10 weeks significantly improves nAb titers and nAb breadth¹⁰⁰, most likely by impacting affinity maturation.

Spike and RBD IgG⁺ MBC frequencies increase between 3 to 6 months after immunization with mRNA vaccines^{80,81,173}, an adenoviral vector vaccine⁸⁰, or a recombinant protein vaccine⁸⁰. 1-dose Ad26.COVS vaccine elicits significantly lower Spike and RBD IgG⁺ MBC frequencies than the mRNA vaccines⁸⁰ (**Figure 2**). NVX-CoV2373 also elicits lower Spike and RBD IgG⁺ MBC frequencies than the mRNA COVID-19 vaccines⁸⁰ (**Figure 2**). Additionally, MBC frequencies are somewhat higher after mRNA-1273 compared to BNT162b2 vaccination⁸⁰. Less is known regarding MBCs after ChAdOx1 immunizations.

Germinal centers appear to be central to the immune responses to COVID-19 vaccines. Most nAb responses, class-switched MBCs, and durable antibody responses to viral infections and vaccines are dependent on germinal centers¹⁰⁴. For COVID-19 vaccines, nAb responses are substantially reduced in many immunocompromised individuals, such as kidney transplant recipients. Direct examination of germinal centers in healthy subjects compared to kidney transplant recipients revealed dramatically weaker germinal center responses in kidney transplant recipients after mRNA vaccination¹⁵². The smaller germinal center responses may be due to weaker GC-T_{FH} cell responses, as GC-T_{FH} cell frequencies were severely reduced and associated with poor nAb titers¹⁵². Germinal centers are observed to continue in draining LNs of healthy vaccinated individuals for at least 6 months after BNT162b2 immunization^{153,179,180}. This is associated with presence of vaccine mRNA in germinal centers for at least a month, as well as detectable spike protein in the germinal centers¹⁶⁷. Since the vast majority of the MBC response to COVID-19 vaccines is class-switched and contains SHMs, the data indicate that the vast majority of the MBC response, and nAb response, to COVID-19 vaccines is T_{FH}-dependent and germinal center-dependent.

B cell memory in hybrid immunity

Circulating spike and RBD IgG⁺ MBC frequencies increase substantially in hybrid immunity^{81,162,181}, but become similar to 2-dose mRNA vaccination after 6 months⁸¹ (Figure 2). In hybrid immunity the RBD-binding MBCs have substantially more SHM and affinity maturation than after vaccination alone^{81,162,181}. Functionally this is observed most clearly with the significantly higher potency and variant breadth of nAbs from MBCs in people with hybrid immunity compared to vaccination alone or infection alone^{162,181}. The robustness and quality of these responses is likely driven by memory T_{FH} cells and MBCs, and can occur after infection + vax or vax + infection (“breakthrough”), discussed in the “Antibody durability” section below.

Antibody durability to SARS-CoV-2 infection or COVID-19 vaccines

Abs are key components of protective immunity against SARS-CoV-2. Thus, durability of Abs is a major topic of interest for protective immunity against SARS-CoV-2 for previously-infected, vaccinated, or person with hybrid immunity. Acute Ab responses are primarily generated by B cells differentiating into short-lived plasma cells (short-lived B_{PC}). These short-lived B_{PC} only live for a few days. IgG protein has a long half-life of 21-28 days in the blood, and thus a large short-lived B_{PC} response can result in detectable antibody titers in blood for months. Long-lived B_{PC} can survive for many years producing large quantities of Abs daily. Long-lived B_{PC} are typically the product of germinal center B (B_{GC}) cells.

Antibody durability to infection

The vast majority of SARS-CoV-2-infected individuals seroconvert and develop nAbs (91-99%)¹⁸²⁻¹⁸⁴. While nAb titers decline during the first few months post-infection, nAb titers stabilize between 4-6 months post-infection, with little evidence of decline thereafter. After the initial decay phase (dominated by short-lived B_{PC}), the estimate SARS-CoV-2 nAb t_{1/2} is 254 days⁴. This may further stabilize over time (Figure 2). NAb titers are detectable in ~80-90% of SARS-CoV-2-infected individuals at 6 months and 12 months post-infection^{3,4}. Nevertheless, SARS-CoV-2 nAb titers in previously-infected individuals are relatively low, resulting in enhanced interest in understanding all of the other compartments of immune memory nAb titers in previously infected individuals are relatively low. This led to concern that low circulating nAb titers would be insufficient for protection, and increased interest in defining other branches of potential immunity to SARS-CoV-2, such as T cells. Nevertheless, immune memory overall in previously-infected individuals was robust,³ leading to a conclusion that natural immunity was likely sufficient to prevent reinfections of significant clinical concern in the majority of people for years^{3,185}.

SARS-CoV-2 Spike- and RBD-binding IgG titers exhibit similar kinetics to that of nAbs^{3,4,186-189}, though

not identical, depending on the study, likely due to affinity differences between the assays. A multi-phasic decay kinetic is observed, with a $t_{1/2}$ of > 700 days by six to nine months post-infection^{187,188}. Long-lived B_{PC} are found in bone marrow 7-8 months after infection¹⁸⁹. SARS-CoV-2-specific IgM responses are not durable, consistent with IgM responses being short-lived for most antigen exposures. SARS-CoV-2-specific serum IgA responses are relatively low but are durable at low levels in most individuals^{3,4,190}, with SARS-CoV-2-specific IgA long-live B_{PC} detected in ~50% of individuals¹⁸⁹.

Long-term antibody titers are lower in asymptomatic cases at 6 to 16 months post-infection^{191,192}, with some individuals being seronegative, though some amount of this difference is due to false-positive PCR tests with high Ct values¹⁹².

Antibody titers against other HCoVs are also relatively stable over time⁴. This is consistent with human immunology findings for multiple acute viral infections and the live attenuated YFV, measles, and smallpox vaccines^{158,193,194}.

Nucleocapsid antibody assays have been found to not be trustworthy indicators of previous infection at timepoints >6 months post-infection. This may be due to a faster decay kinetics of nucleocapsid Abs¹⁹⁵, or a high background signal from crossreactive nucleocapsid Abs against other HCoVs^{187,196} which may be more problematic in certain assays formats, making it more challenging to definitively distinguish SARS-CoV-2 nucleocapsid IgG. Thus, RBD IgG is more widely used as a serodiagnostic marker, though it cannot distinguish infection from vaccination.

Local immunity is important, and Abs are a key factor of local immunity, as they are the only component of adaptive immunity capable of providing sterilizing immunity (Figure 3). Circulating IgG is transudated into most mucosal tissues, and circulating IgG can provide protective immunity at mucosal surfaces. The most dramatic example of this is the human papillomavirus (HPV) vaccine, which provides 99% protective immunity in the vaginal tract, even though the vaccine is a conventional intramuscular immunization and elicits circulating IgG. For SARS-CoV-2 previously-infected individuals, the titers of circulating IgG correlate with saliva IgG^{55,190,197}, and the correlation was sustained over a period of 9 months⁵⁵. Correlation between circulating IgA and saliva IgA in previously-infected individuals was also substantial over a 9-month period⁵⁵. A more rapid decay of IgG and IgA titers was observed in saliva compared to blood, possibly indicating local production of Abs in salivary tissue for a limited number of months post-infection⁵⁵. Few studies have examined nasal passage Abs, but spike IgG is detectable 6 months after infection in the majority of individuals¹⁰¹. Overall, the evidence suggests that nAbs at nasal, oral, and lung tissues are important for protective immunity against SARS-CoV-2 and are likely present proportionally to serum IgG titers after infection.

Antibody durability to vaccination

Two doses of an COVID-19 mRNA vaccine are incredibly successful at eliciting high titers of nAbs. However, the biggest shortcoming of the mRNA COVID-19 vaccines has been that the nAb titers decline continuously over a period of months. Vaccination with the mRNA-1273 mRNA vaccine generates peak RBD IgG and SARS-CoV-2 nAb titers 2-fold higher than the BNT162b2 mRNA vaccine, on average^{93,198}; as a result, Ab durability analyses are confounded in studies that mix vaccinees receiving the two vaccines. In one large study of 2,600 recipients of the 2-dose BNT162b2 vaccine in Israel, RBD IgG continuously declined over 7-months from peak after the 2nd dose, with a 16-fold reduction in RBD IgG from peak¹⁹⁹ (Figure 2). In that study, a vaccinated cohort and a previous-infected cohort were directly compared; the RBD IgG titers declined extensively in the vaccinated individuals but were largely stable in the previously infected individuals¹⁹⁹. NAb titers and RBD IgG similarly declined 5-fold and 10-fold to the mRNA-1273 vaccine from peak over 6-months after the 2nd dose, ending with low but detectable levels of nAbs in 100% of subjects²⁰⁰⁻²⁰². 9- to 10-fold nAb declines were also observed for a low dose (25 µg) of the mRNA-1273 mRNA COVID vaccine (instead of 100 µg)⁷⁷, comparable to the BNT162b2 dose (30 µg), indicating that

the durability of the Ab responses to 2-dose mRNA vaccines is consistent, and the kinetics are not determined by the vaccine dose, though the absolute magnitude of the Ab response is higher with a higher vaccine dose.

Long-lived plasma cells specific for SARS-CoV-2 spike are detectable in a majority of individuals 6 months after 2-dose mRNA vaccination¹⁷⁹; however, given that nAb and RBD IgG titers continue to decline for at least 8 months after 2-dose RNA vaccination, these long-lived BPCs apparently represent low frequencies, or do not have the durability observed for B_{PC}S generated to other antigen exposures.

Due to the precipitous drop in nAb titers over 6-8 months after two doses, and the emergence of VOCs Delta and Omicron, 3-dose mRNA vaccine regimens have been implemented as the norm in many countries (i.e., 2-dose regimen plus a 'booster' at ~6 months) (Figure 3). A critical question about 3-dose mRNA regimens is whether they induce more durable Ab responses than 2-dose regimens. Given that the 2-dose mRNA vaccines were immunogenic and elicited substantial memory CD8 T cells, memory CD4 T cells, MBCs, and at least a few long-lived PCs, it was reasonable to predict that 3-dose mRNA vaccine regimens would induce substantially more durable Abs than the 2-dose regimen. Results from previously-infected individuals cleared demonstrated that the human immune system is capable of making durable Ab responses to SARS-CoV-2, and hybrid immunity also demonstrated that the human immune system is clearly capable of making high nAb titers to SARS-CoV-2. Additionally, many vaccines are three dose regimens, with durable Abs only being developed after the third dose. Teleologically, one can consider that this is because the immune system performs a cost-benefit analysis of durable memory to each antigen exposure. Durable Ab responses for 10 years or more have a high caloric resource cost commitment, whereas durable MBCs or T cells have significantly lower caloric costs. As such, it frequently takes multiple antigen exposures to trigger significant durable Ab responses. Nevertheless, it was unclear if mRNA vaccines were capable of triggering durable Ab responses.

Acute Ab responses to a 3rd dose of mRNA vaccine were strong, with peak nAb titers above that of 2-dose immunization^{203,204}. Two studies found much more durable nAb titers at 4-months or 6-months after a 3rd dose of mRNA vaccine compared to 2-doses^{202,205}. NAb titers against Ac SARS-CoV-2 only declined 1.6-fold for the BNT162b2 vaccine at 4-months and 2.3-fold for the mRNA-1273 vaccine at 6-months after a 3rd dose^{202,205}. Those findings indicate robust long-lived Ab production after 3 doses (Figure 2). However, not all results agree. In the study of mRNA-1273 vaccinees, there was a substantial discordance between the durability of nAbs against Ac SARS-CoV-2 or Omicron, with nAbs against Ac SARS-CoV-2 only declining 2.3-fold after 6 months, but nAbs against Omicron declining 6.3-fold²⁰². In a third study, of an Israeli population receiving the BNT162b2 vaccine, Ac SARS-CoV-2 nAbs declined 5.5-fold over ~4-months after 3 doses²⁰⁶. Thus, conclusions about durability of Abs after 3-dose mRNA vaccination remain uncertain.

Adenoviral vector COVID-19 vaccines ChAdOx1 (2-dose) and Ad26.COVS.2 (1-dose) initially elicit substantially lower Ab responses than mRNA vaccines. Spike or RBD IgG titers after 1-dose Ad26.COVS.2 are ~70-fold to 355-fold lower than 2-dose mRNA vaccines^{80,83,207}. NAb titers are ~10- to 70-fold lower 30 to 60 days after Ad26.COVS.2 compared to mRNA vaccines^{80,83,93}. NAb titers increase some over time after Ad26.COVS.2 in some individuals, but this is variable^{80,83,87,208} (Figure 2). NAb titers are at least stably maintained in most individuals who receive Ad26.COVS.2 vaccination, such that 6-8 months after Ad26.COVS.2 vaccination nAb titers are detectable in almost all individuals, albeit at low levels^{80,87}, though not all studies agree, with some cohorts reporting many negative individuals (Table 40 ref. ²⁰⁸) and one study reporting higher levels⁹². ChAdOx1 vaccine (2-dose) generates early nAb titers that are also substantially lower than mRNA vaccine generated nAb titers. nAb titers are 8.3-fold lower after ChAdOx1 compared to BNT162b2 one month after immunization⁹⁴. Spike IgG titers after 2-dose ChAdOx1 decline with a $t_{1/2}$ comparable to that of 2-dose BNT162b2¹⁹, with no evidence of greater durability. However, in one study the difference between ChAdOx1 and BNT162b2 nAb titers was only ~2-fold at 3-months after

the 2nd dose⁹⁵. There are limited data for 2-dose ChAdOx1 at longer time points with head-to-head comparisons, but when comparing ChAdOx1/ChAdOx1 to ChAdOx1/ BNT162b2, spike Ab titers at 6-months were 6-fold lower in the ChAdOx1/ChAdOx1 group.

Protein-based COVID-19 vaccines are in two categories, recombinant spike vaccines, such as NVX-CoV2373, and inactivated virus vaccines such as BBV152 and Sinovac. Minimal data on Ab durability are available for inactivated vaccines. NVX-CoV2373 generates significant nAb titers after two doses^{209,210}. NAb titers 6 months after the 2nd dose are approximately equivalent between individuals receiving NVX-CoV2373, mRNA-1273, or BNT162b2 vaccines (Figure 2), suggesting that high nAb titers may wane after 2-dose NVX-CoV2373⁸⁰.

Mix & match vaccine strategies could potentially elicit more durable Ab responses. Limited data are available on immune memory after mix & match vaccination^{93–95}. Given that peak nAb titers are higher with 2-dose mRNA or recombinant protein vaccination compared to adenoviral vaccines, but that adenoviral vaccines might elicit more stable Ab responses at 6 months, it is plausible that mix & match approaches may combine the best of both and result in higher level durable nAb titers. This may also be relevant for boosters⁹⁵.

Regarding local Abs in the respiratory tract and oral mucosa, the mRNA vaccines do elicit some circulating IgA^{101,173}. IgA and IgG are detectable in saliva and nasal swabs in a fraction of vaccinated individuals, but both the IgA and IgG decline substantially over the course of 6 months after 2-dose mRNA vaccination, mirroring the declines in circulating IgG and IgA^{101,211,212}. In immunized non-human primates, RBD IgG and IgA in bronchoalveolar lavage and nasal swabs directly correlated with circulating IgG and IgA levels²¹³.

Antibody durability in hybrid immunity

The most prominent characteristic of hybrid immunity is the impressive improvement in nAb titers and the breadth of neutralization of SARS-CoV-2 variants. In some individuals, SARS-CoV-2 nAb titers increase 100-fold after a single mRNA vaccination. Equally impressive, the nAbs are not only able to neutralize every known SARS-CoV-2 variant, including Omicron, they are also able to neutralize a different viral species, SARS-CoV. MBCs and memory CD4 T cells are at the root of these impressive outcomes. While circulating nAb titers are frequently low in previously-infected individuals, without much evidence of breadth, some MBCs from those same individuals encode Abs with impressive potency and breadth^{162,165,214,215}. Those MBCs are then recalled after vaccination to generate an anamnestic Ab response, now composed of Abs capable of neutralizing breadth against VOCs such as Omicron, and even neutralization of SARS-CoV^{20,81,157,162,216,217}, irrespective of original COVID-19 severity²¹⁸.

Hybrid immunity can also occur in the reverse order—vaccination and then infection—with similarly high titer and broad nAb responses, irrespective of whether the infection was Alpha, Delta, or Omicron, and irrespective of disease severity^{20,21,212,219–221}. These responses are again derived from MBCs, in this case MBCs generated in response to vaccination^{173,222}.

Ab durability at 6 months is robust in a majority of individuals with hybrid immunity, as measured by nAb titers (Figure 2). NAb titers were stable in a majority of hybrid immunity individuals, declined less than 2-fold over 6 months^{20,81}. Of note, RBD binding titers exhibited larger declines, for unclear reasons^{81,101}. After 6 months, people with hybrid immunity maintained 5- to 17-fold higher nAb titers against ancestral SARS-CoV-2, Beta, or Delta compared to individuals who were 2-dose mRNA vaccinated^{20,81}; compared to individuals who were previously infected alone, people with hybrid immunity maintained 10- to 51-fold higher nAb titers against ancestral SARS-CoV-2, Beta, Delta, or Omicron²⁰.

Higher nasal RBD IgG and IgA are found in individuals with hybrid immunity (either inf+vax or vax+inf) when sampled up to 10 months after vaccination^{101,212}.

Interrelationships between immune memory compartments

Studies of SARS-CoV-2 memory are the first time that large datasets have been collected of multiple antigen-specific memory cell compartments over a period of 6+ months after an acute infection. This provides key opportunities to understand relationships between different aspects of immune memory. It was observed that each compartment of immune memory after infection exhibit distinct kinetics over time, and different quantitative relationships to the other compartments of immune memory³. Some of the relationships changed dramatically over time³. Perhaps most importantly from a practical perspective, serum RBD IgG titers were not quantitatively predictive of the other components of immune memory, notably memory T cells³. Nevertheless, other relationships were observed³. T_{FH} cells, MBCs, and circulating Ab titers are functionally associated¹⁰⁴. However, cT_{FH} cell frequencies after infection were not quantitatively predictive of germinal centers¹⁵³, or nAb titers¹¹⁰, suggesting more complex relationships between circulating T cell memory, germinal centers, and nAbs.

For mRNA vaccines, relationships between nAbs and memory CD4 T cells are clear, and early T_{FH} cell responses do correlate with subsequent nAb titers⁸⁰. However, at any given memory timepoint, no clear association is observed between serum Ab titers and memory CD4 T cell and memory CD8 T cell frequencies⁸⁰. CD4 T cells provide help for CD8 T cell differentiation and memory CD8 T cells in multiple contexts²²³. Nevertheless, memory CD4 T cell frequencies and memory CD8 T cell frequencies do not show a strong relationship in mRNA vaccinated individuals⁸⁰. Overall, interrelationships between immune memory compartments exist, but much remains to be learned.

Immune memory in special populations

Immune memory in the immunocompromised or suppressed

Immune responses to COVID-19 vaccines in immunocompromised or immunosuppressed individuals varies depending on the specific immunocompromised or immunosuppressed condition. B cell depleted individuals (i.e., anti-CD20 mAb treatment) have defective Ab, MBC, and T_{FH} cell responses to mRNA COVID-19 vaccines, but their T_{H1} and CD8 T cell responses are normal or elevated²²⁴. Thus, it is expected that immune memory will be substantially defect in those individuals for durable Abs, MBCs, and memory T_{FH} cells; however, memory T_{H1} cells and CD8 T cells may or may not be compromised. Solid organ transplant patients frequently have reduced responses to COVID-19 vaccines because of their immunosuppressive drug therapies. Immune memory in such individuals is not well understood, but based on the severity of the germinal center, T_{FH} cell, T_{H1} cell, and CD8 T cell response defects in kidney transplant individuals responding to COVID-19 mRNA vaccines¹⁵², it is likely that there are severe immune memory defects in those patients. Certain categories of cancer patients on similar immunosuppressive drug regimens are likely to also have immune memory defects. Fingolimod, the S1P receptor antagonist, appears to cause an almost complete block of Ab and T cell responses to COVID-19 vaccines²²⁵, and would be expected to result in severe immune memory defects to COVID-19 vaccines. More information is needed about immune memory to COVID-19 vaccines in a diverse range of immunocompromised or immunosuppressed individuals, given that the efficacy of the vaccines is predicated on immune memory.

Boosters in persons with hybrid immunity

Many papers show substantial immunological and epidemiological evidence that hybrid immunity is the most robust immunity against COVID-19^{2,9}. This includes vax+vax+inf^{20,212,226}, inf+vax, and inf+vax+vax. These individuals have the best neutralizing Ab breadth—able to recognize every single known variant, include Omicron, and even able to recognize another species of virus (SARS)^{20,157,227} — and they also have substantially better local immunity in the nose and mouth^{62,212}, which is not generated by intramuscular vaccination. They also have more durable Ab responses, based on the available data^{3,4,101,186,200,228,229}. However, many governments have booster vaccination requirements within 90 days

of an infection. For people who had breakthrough infections with Delta or Omicron after being double vaccinated, this is most likely to be far sooner than needed, and may be counterproductive. It is plausible that such individuals may have such good immune memory that they do not need a booster for years. The quality of the Ab response needs time to develop. The immune system has done an amazing job making Ab responses and memory B cells against SARS-CoV-2 that are educated guesses about potential future variants^{2,20,162,165,214,228,230,231}. That is important for immunity against this virus, but takes time in germinal centers²³², and it is likely disrupted by a new immunization. Hence immunizations too close together are shortsighted and result in poorer quality immunity. We also know that memory B cell frequencies increase for almost 6 months after infection^{3,214,228}, or after vaccination^{162,228}. We know that germinal centers can persist for more than 6 months after SARS-CoV-2 infection⁶². We know that germinal centers can persist and be productive for more than 6 months after two doses of COVID-19 mRNA vaccines^{180,233,234}. And we know that the quality of neutralizing Abs can improve over 3 to 6 months^{87,162,173,214,235}, reflective of outcomes of these long processes of developing higher quality immune memory. Boosters too close together may disrupt those processes of generating broader protection against future variants.

Concluding remarks

A remarkable amount has been learned about immune memory after SARS-CoV-2 infection. A remarkable amount has also been learned about a multitude of COVID-19 vaccines, and hybrid immunity. Increasing our understanding of the deterministic relationships between early immune responses and immune memory outcomes remain a major knowledge gap for further research. There is much to be learned about local immune memory in mucosal tissues such as nasal passages, oral cavity, the URT broadly, the intestinal tract, and lungs. Investigation of the relationships between local immune memory and systemic immune memory is of particular significance. Longer term durability of each compartment of immune memory after SARS-CoV-2 infection or COVID-19 vaccination of course remains to be empirically determined. However, the wealth of scientific literature already accumulated regarding immune memory provides strong predictions regarding the durability of T cell memory, B cell memory, and long-lasting antibody responses that can be extrapolated for several years, if not decades, and may provide determining factors of sustained protection against disease. Lastly, clearly this knowledge and experience can also be leveraged towards vaccines against other diseases that affect humanity now, and prevent future plagues.

ACKNOWLEDGEMENTS

Thanks to Zeli Zhang and Parham Ramezani-Rad for helpful input. Thanks to graphical assistance by Christina Corbaci. This work was funded by the NIH NIAID under award AI142742 (Cooperative Centers for Human Immunology, CCHI) and CHAVD UM1 AI144462, and was additionally supported in part by La Jolla Institute for Immunology Institutional Funds and an anonymous donor. SC has consulted for GSK, JP Morgan, Citi, Morgan Stanley, Avalia NZ, Nutcracker Therapeutics, University of California, California State Universities, United Airlines, and Roche. A.S. is a consultant for Gritstone Bio, Flow Pharma, ImmunoScape, Moderna, AstraZeneca, Avalia, Fortress, Repertoire, Gilead, Gerson Lehrman Group, RiverVest, MedaCorp, and Guggenheim.

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FIGURES

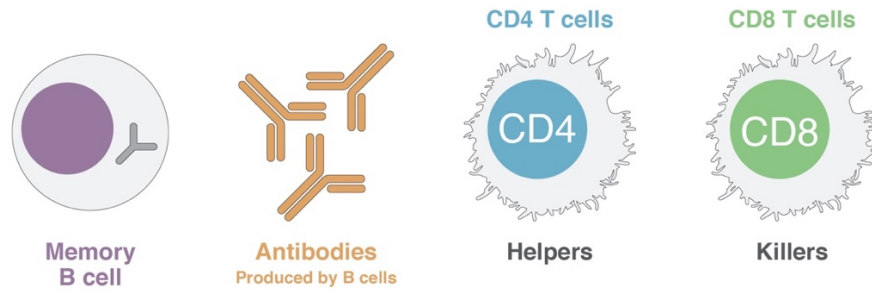


Figure 1. Components of immune memory. Virus-specific CD4 T cells, CD8 T cells, Abs, and MBCs constitute the four major components of immune memory to a viral infection.

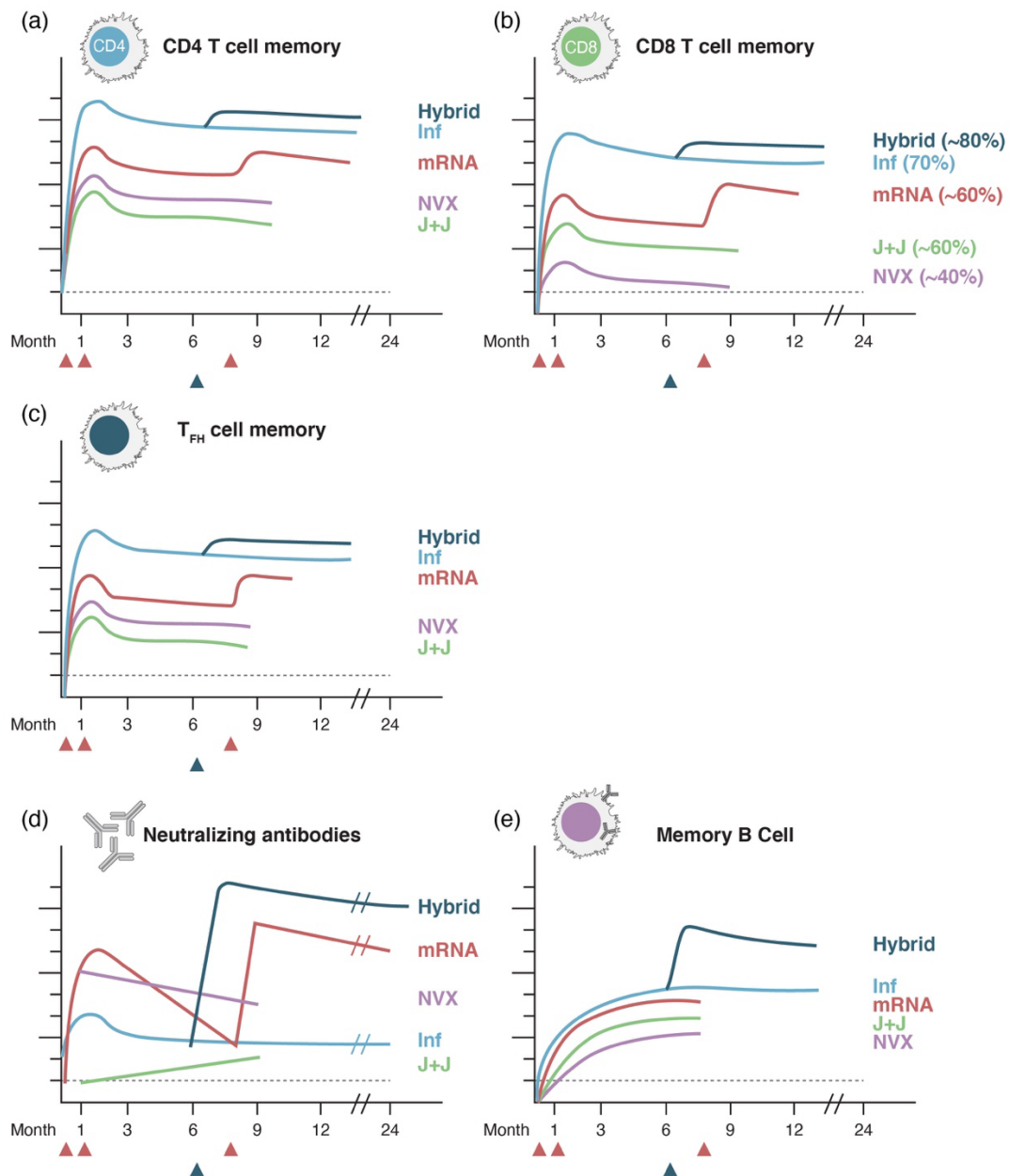


Figure 2. Kinetics of immune memory to SARS-CoV-2 infection and COVID-19 vaccines.

Schematics of immune memory components against SARS-CoV-2. **(a)** Memory CD8 T cells, **(b)** memory CD4 T cells, **(c)** memory T_{FH} cells, **(d)** neutralizing antibodies, and **(e)** MBCs. For T cell memory, with vaccines memory is to spike, and with infection memory is to the entire virus. For B cell memory, spike-specific is shown in all cases. "Inf" = SARS-CoV-2 infected. "Hybrid" = Hybrid immunity, infected and then vaccinated. "mRNA" = Moderna mRNA-1273 or Pfizer/BioNTech BNT162b2, a 3 dose regimen. "NVX" = Novavax NVX-CoV2373, given as the 2-dose regimen in the main clinical trials. "J&J" = Janssen Ad26.COVS.2.S, given as the 1-dose approved by EUAs. Lines are color coded by vaccine. CD8 T cell % indicates the % of individuals with detectable CD8 T cell memory at 3 to 6 months. Scales are non-quantitative, but the antibody scale approximates log10 and the cellular scales approximate log2. For hybrid immunity, in this schematic, the vaccination occurs at ~6 months, indicated by the blue triangle. For mRNA vaccines, in this schematic, the 1st two dose are given at d1 and d21-28, with the 3rd dose ("booster") given at ~8 months, indicated by the red arrows.

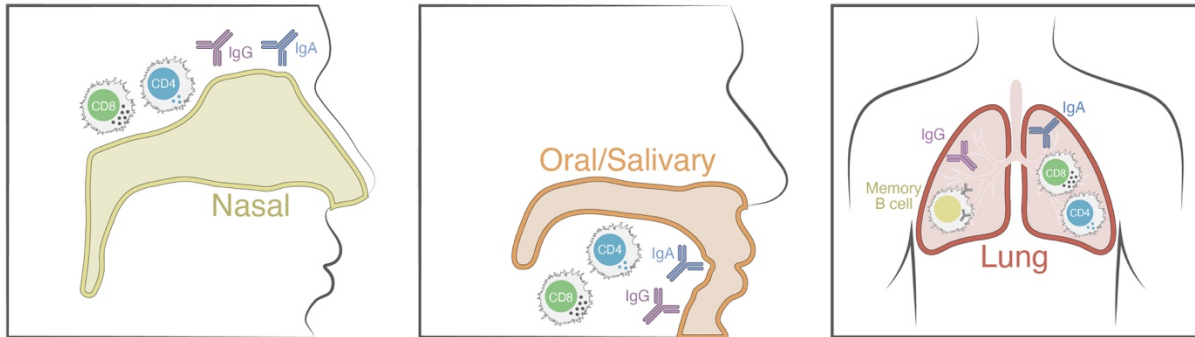


Figure 3. Components of local tissue immunity. Human immune responses are most often measured in blood, but immune responses at local sites of infection and/or portals of entry are important and may not be directly reflected by blood measurements.