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Highlights
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macaques from SARS-CoV-2 reinfection, and even substerilizing titres can provide functional immunity and lessen disease severity [18,19].

Human epidemiological data also support the association between antibody and protection; a study of 12,000 healthcare workers reported that antibody responses provided protection from reinfection for the 6 months of study follow up [20]. Additionally, individuals with SARS-CoV-2-positive antibody tests only rarely suffered reinfection in large COVID-19 outbreaks with high attack rates [21]. Similarly, an investigation of a high attack rate outbreak on a fishing vessel demonstrated an association between protection and the presence of neutralizing antibodies [22]. Furthermore, in a recent study of high-titre convalescent plasma therapy, patients with early COVID-19 showed a 48% relative reduction in severe disease [23], indicating a protective role for antibody early in infection.
As with SARS-CoV-1, the transmembrane spike (S) glycoprotein and nucleocapsid (N) protein represent the dominant targets of induced antibodies [24]. Seroreactivity to S protein, specifically subunit 1 (S1) and its receptor-binding site (RBD), are highly correlated with neutralising activity [3,10,14], and antibodies against the RBD are reported to account for 90% of neutralising activity in convalescent sera [25]. By contrast, antibodies against the internal N protein do not neutralise [8,14]. Although cross-reactive antibodies, particularly against spike subunit 2 (S2), have been reported in prepandemic sera [26], they do not possess appreciable neutralising activity [27]. Notably, SARS-CoV-2 RBD has little sequence homology with those of the seasonal coronaviruses [28].

In addition to neutralising activity, diverse antibody Fc effector functions, including antibody-dependent cellular cytotoxicity and antibody-dependent complement deposition, have been induced by experimental vaccination against SARS-CoV-2 and could contribute to antibody-mediated protection [18,19], as documented for other respiratory viruses [29]. Taken together, measurement of antibodies against RBD or S1 by robust serological assays would be predicted to correlate with protection to most natural exposure to SARS-CoV-2. However, it should be recognised that immunity is not absolute and high-dose or prolonged exposure to a pathogen can overwhelm what normally constitutes robust protection [30].

Durability of Antibody Response to SARS-CoV-2
Initial reports concerning the persistence of the antibody response warned of extremely rapid waning, particularly following milder COVID-19 infections [7], indicating that protective immunity might be transient. Though decline of specific IgM within a few months of an acute infection is usual [9], return of a primary IgG response to a nonprotective baseline within this time frame is not typical. Many subsequent studies have since reported more stable antibody kinetics in both blood and saliva, reporting detectable neutralising activity against SARS-CoV-2 in the majority during the period of assessment (3–8 months) [8,9,13,14,31,32], including in asymptomatic healthcare workers at 4 months postdiagnosis [33]. These data are consistent with protective immunity lasting several years for most individuals.

Publications with contrasting estimates of anti-SARS-CoV-2 IgG durability present largely consistent primary data but differ in interpretation. Decay in antibody production after infection or vaccination is not linear and is especially difficult to extrapolate from early time points. Even for long-lived antibody responses, decay half-life within the first few months is often around 30 days and may not reach steady state until about 3 years [34]. Extrapolation of antibody persistence after the first few months is more reliable, and sustained production of SARS-CoV-2 specific antibody at around 3 months postinfection is predictive of antibody persistence at 5 months [35]. Although individuals that produce higher initial antibody levels also tend to have slower decay rates and longer-lived protection, significant heterogeneity exists [36].

The immune response to vaccines is influenced by many factors [37]. For natural infections, individual variation is further obfuscated by antigen load, which is dependent on infection severity (itself influenced by many factors) and impacts initial antibody titres [12,25]. Antibody durability is also affected by infection severity and is more variable following mild Middle East respiratory syndrome-related coronavirus (MERS-CoV) infection compared to severe disease [38]. Among mild COVID-19 patients, faster recovery from disease is associated with better sustained antibody [35], highlighting the potential for pathogen- or disease-mediated influence. Following infection, the inflammatory milieu, cellular infiltrate, and pathogen-associated molecular patterns can all influence levels and kinetics of antibody production [39]. Some respiratory viruses, such as RSV (and possibly coronaviruses), appear to directly interfere with development and duration of immunological memory, though protective antibody is still produced [4,40].
SARS-CoV-2-specific IgA in serum and saliva has been reported to show much more rapid decay than IgG [13], though some individuals maintain stable low levels of specific IgA in sera [31]. Mucosal IgA contributes to protection against respiratory viruses [4,41], and these dimeric forms of IgA possess enhanced neutralisation activity against SARS-CoV-2 [42]. Antibody prevalence to common coronaviruses was found to be lower in nasal secretions than in serum, suggesting that systemic IgG responses are also more durable than mucosal IgA for coronaviruses [43]. By contrast, decay rates of IgA from nasal washes have been reported to be similar to the kinetics of serum IgG assessed a year after experimental challenge infections with an endemic coronavirus [44]. IgA and IgG are believed to play complementary roles in protection against viruses, with the former dominant in the upper respiratory tract and latter dominant in the lower respiratory tract [45]. Though, even in the absence of IgA, serum IgG can access mucosal surfaces through the processes of transudation, exudation, and transcytosis (via FcRn) to mediate protection against viruses [46].

Predictions of SARS-CoV-2 protective antibody lifespan somewhat mirror assessment of SARS-CoV-1 antibody titres, which were initially thought to be relatively short-lived [47]. However, despite lack of re-exposure to this virus, around 90% of individuals had neutralising antibody at 3 years post SARS-CoV-1 infection, and specific IgG has since been measured in some up to 13 years postinfection [48]. As is common for antibody responses to other viruses, Guo et al. reported that, after a rapid decline of antibodies in the 2 years following infection, reduction over subsequent years was much slower [48]. Vaccinology has demonstrated that lifelong protective antibody responses result after inoculation of a repetitive protein antigen, with sufficient quantity and kinetics to reach an antigenic threshold, in combination with an appropriate immunostimulatory response [49]. Natural infection with influenza appears to fulfill these conditions, and neutralising antibodies conferring homologous immunity are maintained for life (Figure 2B); survivors of the 1918 H1N1 influenza pandemic had significantly higher seropositivity and serum-neutralizing activity against an antigenically identical virus than controls born in subsequent years [50].

Evasion of Humoral Immunity by Respiratory Viruses: Antigenic Variation
Antibody responses to the endemic human coronaviruses (HCoV-HKU1, HCoV-OC43, HCoV-229E, and HCoV-NL63) are often considered transient and short-lived (Figure 2A). Typically these viruses cause mild respiratory disease and have long circulated between humans [51]. First infection by all four endemic coronaviruses takes place early in childhood and seropositivity plateaus by age 6, remaining near universal in adults [43,52].

However, human experimental infection studies, performed with coronaviruses by Callow et al., showed that adult volunteers have high baseline antibody levels which are boosted and remain significantly elevated a year after infection [44]. These levels correlate with partial or total immunity upon homologous rechallenge. Another human experimental infection study, by Reed reported complete protection upon homologous viral rechallenge under similar conditions [2]. In the former study, specific antibodies peaked by day 12 postinfection, quicker than would be expected for a primary response but typical of an anamnestic response. Therefore, challenge studies in adults measure recall responses rather than primary responses, and it is feasible that the baseline levels of antibodies in study volunteers may protect from natural exposure but be overwhelmed by the high inoculum used for challenge. There is evidence that susceptibility to reinfection is elevated in challenge studies: although influenza reinfections of young healthy adults with homologous virus do not commonly occur naturally, they can be achieved after sequential experimental challenge [53].

Several studies of natural infections have shown widespread seasonal coronavirus infections in adults, including reinfections [54,55]. Importantly, data presented by Galanti and Shaman demonstrate that reinfections with the same coronavirus were usually milder in severity or asymptomatic,
particularly in adults, indicating that a degree of functional immunity remained between infections [54]. Additionally, these studies did not assess the contribution of strain variation to reinfection. Incomplete cross-protection to related strains of endemic coronaviruses has been previously established experimentally and is hypothesised as a significant factor in the epidemiology of infections [2] (Box 1).

Evasion of Immunity by Respiratory Viruses: Immunomodulation

RSV is another respiratory virus commonly associated with reinfection. Its genetic variability is relatively low, particularly in the highly conserved Fusion (F) protein. Neutralising antibodies raised
against F protein following infection are associated with protection [4]; thus, antigenic variation is not usually considered to make a significant contribution to reinfection. Instead, virally mediated immunomodulation is postulated to underlie the short duration of immunity [4,40]. Although protective antibodies are induced by infection, disturbance of type I and III interferon signalling, antigen presentation, and chemokine-induced inflammation are implicated in suppression of long-lived protection against RSV [56], and similar factors may influence development of long-term immunity to SARS-CoV-2 [57].

RSV is increasingly recognised as a major pathogen of those with respiratory comorbidities and elderly adults. Though waning immunity, along with immunosenescence, is believed to contribute to the increased burden of disease in the elderly, protection resulting from RSV infection is perhaps more robust than widely appreciated. While adults can be reinfected with RSV, disease is typically mild and confined to the upper respiratory tract, with much lower viral loads recovered. Reinfections in young children are also associated with milder disease [58]. Moreover, natural infection with RSV increases neutralising serum antibody responses to protective levels [3]; however, such increases in antibody titre may be short-lived [4].

One study demonstrated that neutralising antibody titres remained above a threshold associated with protection in 19 of 20 volunteers followed for 2 years postinfection, with only one reinfection observed in this time [59]. In an experimental rechallenge study using homologous RSV, only six of 15 adult volunteers could be reinfected with the same strain within the 2-year study period, and just three of 15 individuals were reinfected with the same strain twice [60]. Additionally, higher levels of neutralising antibodies correlated with protection, over half of reinfections were asymptomatic, and the duration of viral shedding for homologous reinfections was reduced to 1.7 days from 4.6 days during the initial challenge [60].

While antigenic variation does not appear to be a firm requirement for reinfection, it could be that underappreciated antigenic variation, particularly in the more variable attachment glycoprotein (G protein), enhances the ability of RSV to cause repeated infections through life [61]. Importantly, innate immunity has been demonstrated to make a significant contribution to the ability of RSV to

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**Box 1. Antigenic Variability of Coronaviruses and SARS-CoV-2 Variants**

While coronaviruses possess proofreading capacity which corrects many errors that arise during replication, different cocirculating genetic clusters of HCoV-NL63, HCoV-OC43, and HCoV-HKU1 exist, and HCoV-OC43 and HCoV-229E display continuous genetic drift [51]. Hence, rather than inherently transient immunity, strain heterogeneity and insufficient cross-protection may be key determinants of susceptibility to reinfection, as observed with serotypes of rhinovirus [107]. Coronaviruses have nonsegmented genomes, so are not capable of recombination through reassortment, which leads to large antigenic shifts in viruses such as influenza A virus [108]. However, recombination does play an important role in the evolution of coronaviruses, including SARS-CoV-2. At the present time, SARS-CoV-2 still shows much lower genetic diversity than the endemic coronaviruses, which have accumulated genomic variation over a long period of time, up to 1000 years in the case of HCoV-NL63 [51,109].

In the ongoing COVID-19 pandemic, reinfection with divergent or antigenically drifted variants, commonly seen in influenza [108], is at present rare [109] but may become more frequent as immunity builds in the population and becomes a driving force favouring variant emergence. New variants are now emerging worldwide that may have a greater propensity for reinfection. At the time of writing (March 2021), three variants of concern have received particular attention, namely B.1.1.7, B1.451, and P1; colloquially known as ‘Kent’/‘UK’, ‘South Africa’, and ‘Brazil’ variants, respectively. These variants possess significant mutations, including in key S protein and RBD sites, and consequential impacts on transmissibility, mortality, and immune escape have been reported [110,111]. The polyclonal nature of adaptive immunity raises neutralising antibodies to numerous epitopes on S protein. Although this makes immune evasion extremely difficult for a virus, it is not unachievable, particularly during prolonged selective pressure. Irrespective of immune evasion, increased infectivity of viral variants, as reported for B.1.1.7, could increase the titre of neutralising antibodies required for protection and shorten the duration of effective immunity.
reinfect: the presence of neutrophilic inflammation at the time of exposure has been demonstrated to be a major determinant to susceptibility to RSV challenge [62] and could contribute to reinfections observed with other respiratory viruses.

Immunology of Antibody Durability
Following antigenic stimulation during acute viral infection, extralymphocytic clonal expansion of naïve B cells produces a wave of short-lived proliferating plasmablasts and plasma cells that secrete mainly lower-affinity antibodies. Some activated B cells enter lymphoid follicles and initiate germinal centre reactions to generate higher affinity antibody-secreting long-lived plasma cells and memory B cells [63,64]. Short-lived plasma cells are responsible for the initial high titres of antibody, particularly IgM, but levels wane as this cell population contracts. The average half-life of IgG is around 3 weeks and the rate of antibody decay slows dramatically as free immunoglobins are removed from circulation and antibody decay kinetics become determined by the remaining longer-lived plasma cell populations.

Once antigen is cleared, protective levels of specific antibody are maintained by nonproliferating long-lived plasma cells that primarily reside in the bone marrow, where they continually secrete high-affinity antibodies into the circulation [65]. A single plasma cell can produce up to $10^9$ molecules of Ig in a day (~15 ng), and so a relatively small number of long-lived plasma cells could confer protection [66]. For many antibody responses, the rate of decay does not reach a steady state until 2–3 years after antigen exposure, suggestive of lengthy retention of antigen following viral clearance and long-lived plasma cells with a range of intermediate lifespans [67].

Infections with respiratory viruses, including influenza viruses, generate robust plasma cell responses [4,68]. Comparable circulating plasma cells, which correlate with specific antibody levels, have been observed following SARS-CoV-2 infection [31,42,69]. Importantly, SARS-CoV-2-specific plasma cells were found to be present in bone marrow in a majority of donors at 8 months postinfection [70]. Additionally, as these cells were present in numbers similar to those of plasma cells specific for contemporary influenza viruses [70], it seems that there is no SARS-CoV-2-mediated deficiency in plasma cell formation or survival. Plasma cells are also abundant in mucosal tissues, and IgA-expressing plasmablasts with mucosal-homing profiles are prevalent in the early circulating plasma-cell responses to SARS-CoV-2 and RSV infections [4,42].

However, what determines the longevity of a given antigen-specific plasma cell is still not well understood (Box 2). The magnitudes of B cell activation and T cell help are central concepts in the ‘imprinted lifespan’ model which hypothesises that an adequate number of plasma cells must initially enter the long-lived pool in order to sustain antibody production above a protective threshold long-term [49]. Analysis of vaccine responses suggests that antigen type (protein and multivalent/repetitive epitopes) and antigen load are the most important parameters for sustained antibody responses. Most respiratory viruses feature repetitive protein antigen on their surface, including the S protein of SARS-CoV-2, and so antigen load is likely to be an important variable in natural infection.

As well as bone marrow, long-lived plasma cells can also survive for decades in mucosa-associated lymphoid tissue, including IgA forms [67]. Yet, the more rapid decay of mucosal IgA compared to serum IgG following primary SARS-CoV-2 infection suggests that long-lived mucosal plasma cells may be lesser in number than those in the bone marrow. For now, definitive data on the survival of mucosal long-lived plasma cells and their contribution to long-term immunity are lacking.
Contribution of Memory B Cells and Recall Responses

While plasma cells are the source of circulating antibodies, memory B cells direct antibody recall responses against viruses. Memory B cells are mainly generated with T cell help in germinal-centre reactions, and robust numbers appear in the circulation in the weeks following respiratory infections [71]. These specific memory B cells are long-lived and reside in the spleen, lymph nodes, or sites of infection, including the lungs [72–74], where they can readily sample antigen.

Upon re-exposure to cognate antigen, mouse models suggest that memory B cells can quickly differentiate into plasma cells without requiring additional T cell help [75]. Alternatively, memory B cells can re-enter germinal centres to boost humoral immunity and replenish the memory B cell pool. These combined responses result in rapid production of specific antibodies that encompass higher affinities and wider breadth than a primary response. Memory B cell recall responses can top up waning levels of antibody and replenish long-lived plasma cells upon exposure to virus during subclinical infections of children [64,76]. Additionally, as memory B cells possess a broader range of specificities than the plasma cell pool, they can provide protection against antigenically variant viruses that can escape neutralisation by pre-existing antibodies in mice [77].

Pre-existing memory B cells in humans can also drive evolution of improved antibody responses by undergoing additional rounds of somatic hypermutation and selection with antigen persistence (Box 3), or upon re-exposure to homologous or antigenically similar viruses [78,79].

Anamnestic responses have been observed with SARS-CoV-2 following rechallenge of rhesus macaques 35 days after initial infection, resulting in further elevated neutralising antibody titres within 7 days [19]. In humans, S-specific memory B cells are very rare in unexposed individuals but appear in appreciable numbers as early as 2 weeks after SARS-CoV-2 infection [80]. Numbers of SARS-
CoV-2-specific memory B cells steadily increase over the following months and are still present more than 6 months after initial infection, indicating that this B cell memory to SARS-CoV-2 is likely long-lasting [31,32]. S- and RBD-specific memory B cells are increased in hospitalised cases compared with nonhospitalised cases [31], highlighting the importance of antigen load in the strength of humoral responses. While one group found that SARS-CoV-1 patients lacked peripheral memory B cell responses at 6-year follow up [81], another found memory B cells capable of producing neutralising antibodies in an individual 10 years after a SARS-CoV-1 infection [82]. Memory B cells, or their progeny, can be sustained for life: specific memory B cells, capable of producing potent neutralising antibodies, have been observed in individuals 90 years on from influenza infection [50]. Such long-term persistence may require periodic restimulation through encounter with antigenically similar viruses, or antigen-independent means [83].

Thus far, only circulating memory B cell responses to SARS-CoV-2 have been well studied. The outcome of RSV infection in human challenge is not influenced by circulating memory B cell frequencies [4]. Instead, it is likely that faster responding respiratory tract-resident memory B cells are more relevant to protection against RSV and SARS-CoV-2, as reported for influenza [73].

Box 3. Evolution of Humoral Responses during and Following Infection

While initial antibodies produced by an individual infected with SARS-CoV-2 show minimal somatic mutation [32,115], specific memory B cells display clonal turnover over the course of 6 months postinfection [32]. As a result, these latter memory B cells are capable of expressing antibodies that possess greater potency and antigenic breadth [32]. Such evolved antibody responses could be important for long-term protection by conferring neutralising activities at lower titres, as well as further limiting the potential of mutation-mediated immune escape by SARS-CoV-2 [119]. Though these processes are predominantly antigen-dependent, antigen is present during viral infection and can persist for months after recovery [32].

Shedding of SARS-CoV-2 RNA is commonly detectable from the upper and lower respiratory tracts and stool for several weeks, and even months, postinfection [119], likely representing clearance of inactive viral material rather than active virions. SARS-CoV-2 components have been observed in widely disseminated tissues [120], including the gut of asymptomatic individuals 3 months after infection [32]. Even following clearance of virus, antigen can persist for extended periods on follicular dendritic cells in antibody complexes.

Other respiratory viruses, including RSV, also exhibit prolonged viral shedding. Persistent RSV antigen is found associated with lymphocytes in the airway a month after challenge inoculation [100], and ongoing production of plasma cells persists for up to a month after [68]. Therefore, continued memory B cell-mediated evolution of antibody responses would be expected during the first weeks and months following viral infection.

Memory B cells themselves may provide a correlate of protection, even in the absence of pre-existing antibodies, particularly against infections that have a slow course of disease. Circulating memory B cells capable of producing potent SARS-CoV-2 neutralising antibodies are found in individuals who lack robust serum antibody titres [11]. As COVID-19 infection follows a relatively slow path for an acute disease, with hospital admission around 2 weeks post onset, and death after 3 weeks, evolved memory-cell responses might meaningfully contribute to protection.

CoV-2-specific memory B cells steadily increase over the following months and are still present more than 6 months after initial infection, indicating that this B cell memory to SARS-CoV-2 is likely long-lasting [31,32]. S- and RBD-specific memory B cells are increased in hospitalised cases compared with nonhospitalised cases [31], highlighting the importance of antigen load in the strength of humoral responses. While one group found that SARS-CoV-1 patients lacked peripheral memory B cell responses at 6-year follow up [81], another found memory B cells capable of producing neutralising antibodies in an individual 10 years after a SARS-CoV-1 infection [82]. Memory B cells, or their progeny, can be sustained for life: specific memory B cells, capable of producing potent neutralising antibodies, have been observed in individuals 90 years on from influenza infection [50]. Such long-term persistence may require periodic restimulation through encounter with antigenically similar viruses, or antigen-independent means [83].

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Contribution and Durability of T Cell Immunity

Antigen-specific effector T cells are vital components of the immune response to respiratory viral infections, and early T cell responses during COVID-19 are correlated with rapid viral clearance and reduced disease severity [84,85]. Subsets of CD4+ T cells coordinate innate and adaptive immunity; among numerous roles, these cells support the generation of high-affinity antibodies and long-lived plasma cells and memory B cells. Cytolytic CD8+ cells directly kill virally infected cells and play a critical role in mediating viral clearance following infection. After initiation of human infection, antigen-specific T cells undergo clonal expansion, peaking around 10 days later [86]. Upon successful clearance of a pathogen, these effector T cell populations contract, but both CD4+ and CD8+ long-lived memory T cells (T>M) are maintained in lymphoid organs, the peripheral circulation, and within tissue. The T>M classification covers a broad continuum of cell subsets with diverse immediate effector functions, turnover, and location [87].
Robust SARS-CoV-2 circulating CD4+ and CD8+ T_M responses are present in the majority of convalescent individuals, irrespective of severity [88–90], and these T_M populations are maintained for over 6–8 months postinfection [31,91]. Most CD4+ T_M cells possess the classical antiviral T_H phenotype or a T_FH phenotype [92]. T_FH recall responses can further enhance available T cell help to specific B cells in germinal centres and promote the generation of potent and lasting antibody responses.

Expanded pools of specific T_M cells undergo recall responses that are more rapid, stronger, and better tailored. While infections with respiratory viruses are usually confined to the respiratory tract, data from mice show that T_M cells can be recruited from the circulation or lymphoid tissues to a site of infection by inflammation [93]. Prior to trafficking, T_M cells typically undergo proliferation for several days. This intrinsic delay in the T_M recall response, in contrast to the instantaneous activity of antibodies that can achieve 'sterilising' immunity, means that circulating T cell-mediated immunity has historically been side-lined in consideration of correlates of protection.

Nonetheless, pre-existing numbers of specific circulating CD4+ and CD8+ memory T cells correlate with reduced disease severity for influenza infections in humans [94,95]. Furthermore, T cell responses are directed at different and more varied targets than those of neutralising antibodies. Notably, studies assessing T cell contribution to protection have measured cross-reactive T cell immunity to viral strains for which the donor lacked specific antibody. T cell responses might also have critical importance where antibody responses are insufficient for protection; consistent with this, deletion of CD8+ cells prior to SARS-CoV-2 rechallenge partially abrogates protective immunity in rhesus macaques that possessed subprotective antibody titres [18]. Prior studies in mice have also suggested important roles for specific CD8+ T cells in protection from SARS-CoV-1 [96]. As CD4+ and CD8+ T_M cell populations specific to membrane, nonstructural, and N proteins, as well as S protein, are generated following SARS-CoV-2 infection [31], T cells could also be important to exert protection against escape mutants that may be generated by the selective pressure of neutralising S protein-specific antibodies.

Protection mediated by circulating specific T_M cells can be very long-lasting; T_M populations are well established to persist for over 50 years in response to smallpox vaccination of volunteers with vaccinia virus [97]. Although data for other viruses is sparse, it is likely that T_M responses to respiratory viruses are also likely to be long-lived. Circulating T_M cells specific for respiratory viruses are found in the elderly, albeit in low numbers for RSV [98]. Boosting of these specific T_M populations through reinfection or vaccination likely plays a role in lifelong maintenance. However, even in the absence of antigenic-boosting, CD4+ and CD8+ T_M responses targeting the SARS-CoV-1 coronavirus were present in individuals at 11 and 17 years postinfection [90,99] and so far the kinetics of T_M cell responses to SARS-CoV-2 appear similar [31].

**Role of Tissue-resident T Cell Immunity**

For some respiratory infections, such as RSV, T_M cells are not close correlates of protection [100]. Instead, noncirculating tissue-resident T memory (T_RM) cells are more important. T_RM cells possess distinct surface markers and transcriptional profiles and represent the frontline of T cell immunity due to their ability to mount quick immune responses in situ. While there is not sufficient evidence to suggest that T_RM can confer sterilizing immunity, both CD4+ and CD8+ T_RM cells are associated with optimal protection of humans from rechallenge with many respiratory viruses, including RSV and influenza [100,101]. Additionally, CD4+ airway T_RM cells mediate protection against SARS-CoV-1 and MERS-CoV [102]. T_RM cells also appear to contribute to protection against SARS-CoV-2; rhesus macaques depleted of CD8+ T cells showed differences in viral load in the upper respiratory tract after just 1 day postinfection, indicative of CD8+ T_RM-mediated activity [18].
T<sub>RM</sub> populations in the lung have been observed to survive for over a year in humans [103], but whether these cells can exhibit near lifelong persistence, like T<sub>M</sub> populations, or play a role in lifelong immunity is yet to be demonstrated. Experiments in mice have shown that CD8<sup>+</sup> T<sub>RM</sub> subsets persist in the lung after influenza infection, but survival of CD8<sup>+</sup> T<sub>RM</sub> cells is dependent on inflammation and so is relatively short-lived [104,105]. Tellingly, T<sub>RM</sub> cell-mediated cross-reactive immunity to influenza is lost at around 5 months post murine infection [106]. However, as specific T<sub>RM</sub> populations are amplified following recall responses, these cells may persist for longer periods following repeated exposures to antigen [106]. Therefore, CD8<sup>+</sup> T<sub>RM</sub> cells may be particularly important in reducing disease severity during frequent recurrent respiratory infections which show weaker associations with antibody-mediated protection [100].

**Concluding Remarks and Future Perspectives**

Much remains to be learned to understand the durability of protective immune responses following respiratory infections (Box 4). Certain viral infections, including influenza, result in neutralising antibodies, and circulating specific memory B and T cell populations can persist for many decades. For other viruses, such as RSV, repeated infections do not seem to be explained by antigenic variation, suggestive of significant waning immunity. Nevertheless, until old age, repeated infections by homologous viruses are nearly always milder in nature, indicating that functional immunity is formed. It is possible that, over time, most children will be infected with SARS-CoV-2 in early life and that primary infections in adulthood will not commonly occur. As it is these primary adult infections (and especially, infections in older adults) that result in serious disease, COVID-19 will likely become a generally mild disease similar to that seen with endemic human coronaviruses.

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**Box 4. Current Immunological Issues in the COVID-19 Pandemic**

Host responses evidently contribute to pathology and disease in COVID-19. Identifying (and inhibiting) the factors driving COVID-19 while maintaining long-term immune memory remains a priority. Similarly, understanding the contribution of immune responses to the diverse prolonged sequelae of COVID-19 (‘long COVID’) is an urgent priority.

The duration of immunity is uncertain following either vaccination or natural infection. However, it seems that levels of antibody and B cell responses reach a relatively stable protective level for many months following an expected initial early contraction. The role and duration of T cell-mediated immunity is less certain but also appears to be robust for at least 8 months. Factors such as age and COVID-19 severity seem to influence protective duration.

Reinfections with a homologous variant appear to be rare, though they can occur. The reasons for reinfection need investigation but, as immunity wanes, more frequent reinfections are to be expected. Immunity induced by vaccination or natural infection appears to reduce disease severity, but effects on viral transmission may not be so great. Preliminary evidence indicates that there is both a reduced frequency of asymptomatic infection and a decrease in viral load in those with existing immunity; it is expected that this will decrease community transmission. Asymptomatic infections with other respiratory viruses, such as RSV and influenza virus, occur at high frequency but are considered to be less likely to contribute to spread. Overall, there are few data that conclusively demonstrate the importance of asymptomatic infection in viral transmission.

Booster vaccination, especially targeted to ‘at-risk’ groups, appears beneficial and is expected to boost the level, range, and duration of protection.

Defining strong correlates of protection (CoP) is essential in the development of vaccines, for public policy, and in tackling variants. Neutralising antibody in the blood (and antibody binding to the receptor-binding domain of S) are currently the most predictive CoPs; however, other aspects of immunity (e.g., mucosal antibody responses and T cells) need further study.

Variants of SARS-CoV-2 continue to emerge, increasingly under immune pressure (Box 1). Close monitoring of immune evasion by viral variants is essential and may necessitate modification of vaccines. Future vaccines should also be designed to stimulate mucosal immunity: induction of local immune responses in the respiratory mucosa is expected to have a greater effect on local viral replication and on onward transmission of SARS-CoV-2.
The relative inefficiency of the ability of IgG to protect in the upper respiratory tract, and the delay of systemic T cell responses, may underlie the apparent difficulty in preventing mild upper respiratory infections after one exposure to some respiratory viruses. Virus-mediated suppression of long-lived protection against is implicated in RSV infections and suggested for coronaviruses. However, specific plasma cells within bone marrow, as well as circulating memory B and T cells, and antibody are all present in the majority around 8 months after SARS-CoV-2 infection, demonstrating of a robust immune response.

While certain factors of what determines the magnitude and longevity of immune responses, such as antigen load, are known, the full picture remains elusive. This is exemplified by the significant heterogeneity between individuals in all immune responses to SARS-CoV-2. Following infection, facets of immunity can be discordant in their responses and durability. A sizeable proportion of individuals lack CD8+ T cells responses but possess specific antibody around 6 months after mild SARS-CoV-2, while in a minority, CD8+ T cells are maintained but antibody is undetectable. Certainly, the often-offered hypothesis that antibody to SARS-CoV-2 rapidly wanes, while circulating T cell responses are maintained, does not fit the data obtained during the COVID-19 pandemic.

SARS-CoV-2 reinfections with original variants are currently rare (Box 1), consistent with measurements of sustained systemic immunity so far [20]. The longevity of protective responses in the mucosal compartment remains a major gap in understanding of immunity. Mucosal antibody and resident cells have been shown to mediate protection for respiratory viruses, but the limited data available suggest that these responses may be less long-lived than systemic equivalents, especially in the absence of antigen.

Continued investigation of SARS-CoV-2 responses provides an extraordinary opportunity to further understand the durability of adaptive and mucosal immunity, and their relative contributions to long-term protection from respiratory infection (see Outstanding Questions). It is to be hoped that the lessons learnt from the intensive global research effort into COVID-19 will lead to new vaccines and treatments that will finally lessen the global toll of respiratory viral infections.

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Declaration of Interests
There are no interests to declare.

Resources
www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201

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Correction

Durability of Immunity to SARS-CoV-2 and Other Respiratory Viruses

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The publisher regrets the word ‘needed’ was not removed from the following sentence: ‘Through comparison with other respiratory viruses, we can now identify the key questions that need to be needed addressed to further our understanding of immunity to SARS-CoV-2 in order to manage the COVID-19 pandemic and mitigate future pandemic threats.’

This has now been corrected in the original article. The publisher would like to apologise for any inconvenience caused.