Lessons for COVID-19 immunity from other coronavirus infections

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Abstract

A key goal to controlling COVID-19 is developing an effective vaccine. Development of a vaccine requires knowledge of what constitutes a protective immune response and also features that might be pathogenic. Protective and pathogenic aspects of the response to SARS-CoV-2 are not well understood, partly because the virus has infected humans for only 6 months. However, insight into coronavirus immunity can be informed by previous studies of immune responses to non-human coronaviruses, to common cold coronaviruses, and to SARS-CoV and MERS-CoV. Here we review the literature describing these responses and discuss their relevance to the SARS-CoV-2 immune response.

Introduction

COVID-19, caused by a novel coronavirus (CoV), SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2), is the cause of a worldwide pandemic that has infected over 10,000,000 people with a mortality of about 5% to date (World Health Organization, 2020a). Two previously identified CoVs, SARS-CoV and MERS-CoV (Middle East respiratory syndrome-coronavirus), caused severe pneumonia, but unlike SARS-CoV-2 exhibited only limited person to person spread, resulting in dramatically lower numbers of confirmed cases (about 8100 and 2500, respectively). Because COVID-19 has been associated with huge mortality and economic loss, efforts are underway to rapidly develop a vaccine, which will result in a safer and more expedient path to herd immunity. After vaccination, the goal will not only be protection of the vaccinated individual, but also decreasing transmission by minimizing the number of susceptible individuals. Vaccine development is highly dependent on understanding the immune response to SARS-CoV-2, especially those components that are protective. However, the immune response to CoVs is not well understood and in specific, aspects that are protective versus pathogenic are not well defined. While some aspects of SARS-CoV-2 immunity appear to be novel, much of the immune response parallels that observed in humans, domestic and companion non-human animals naturally infected with CoVs, and experimentally infected laboratory animals. In this review, we will focus on studies that described innate and adaptive immune responses in the setting of these non-SARS-CoV-2 infections, focusing on those studies that potentially provide insight into COVID-19 immunity and vaccine development in humans.

Coronavirus biology

Coronaviridae is a family of large (31 kb) single-stranded positive-sense RNA viruses that consist of viruses from 4 genera (α, β, γ, δ -CoV). SARS-CoV, MERS-CoV and SARS-CoV-2 are all betacoronaviruses. Genomic CoV RNA is translated into a long polyprotein that contains proteins involved in RNA replication (Figure 1A). Structural proteins, which encompass the spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, and accessory proteins believed to be involved in immunoevasion, are translated from a nested set of subgenomic RNAs that have the same 5' and 3' ends (Figure 1B). A CoV protein, nonstructural protein 14 (nsp14), has proofreading capabilities and is critical for maintaining and is responsible for the increased replication fidelity of CoVs. This is especially important given the size of the CoV genome. CoVs have an estimated error rate of 10^{-6} to 10^{-7} errors per nucleotide, relative to most smaller RNA viruses (error rates of 10^{-3}-10^{-5}) (Smith et al., 2014).

Animal coronaviruses

CoVs are known to cause a wide variety of mild and severe diseases in domestic and companion animals, including livestock such as chickens, pigs, and cattle, as well as companion animals such as cats and dogs (Table 1). Because these CoVs have significant economic and psychological importance to humans, correlates of immunity have been investigated to guide development of protective vaccines against these pathogens.

Infectious bronchitis virus (IBV), a chicken coronavirus, causes bronchitis, kidney, and reproductive tract disease (Cavanagh, 2007). A number of vaccines, particularly live virus attenuated by passage in chicken eggs, generate neutralizing antibodies and have been successfully used for decades to protect flocks against IBV. Caveats are that protection provided by many of these vaccines is short-lived, with protective immunity waning after about 9 weeks (Cavanagh, 2007) and these vaccines afford poor protection from heterologous strains of IBV (Jackwood, 2012). The strength of cross-protection between variants is predicted by differences in the S1 subunit of the S protein, the site of most neutralizing antibody epitopes (Cavanagh et al., 1997). Of note for live attenuated vaccine strategies, high rates of recombination and frequent exposure of chickens to multiple vaccine and field IBV strains can contribute to the generation of novel virus strains and reversion to virulence (Jackwood and Lee, 2017; Jia et al., 1995; Zhang et al., 2010). S1 and the nucleocapsid (N) protein, contain CD8 T

cell epitopes, which are known to confer protection, though little is known about the longevity of the T cell response to IBV or their relevance in vaccine-mediated immunity (Collisson et al., 2000).

Transmissible gastroenteritis virus (TGEV) is an enteropathic and highly contagious CoV that causes mild disease in adult animals but is nearly always fatal in piglets under 2 weeks of age, causing significant economic burden (Saif et al., 2019). As such, a substantive portion of vaccine and immunity research has focused on the generation of IgA responses in sows, which confer passive lactogenic immunity to suckling pigs via colostrum or milk (Chattha et al., 2015; Saif et al., 1972). T cell responses are correlated with the generation of lactogenic immunity in immunized sows, highlighting the importance of a cellular response (Antón et al., 1995; Park et al., 1998). While various live attenuated vaccines have been used to immunize sows, these vaccines do not induce as strong an IgA response as infection with virulent TGEV and are thus less protective to newborn piglets (Saif et al., 2019). Interestingly, the decline of TGEV incidence worldwide has correlated with the emergence of the closely related porcine respiratory CoV (PRCV) in 1983 (Schwegmann-Wessels and Herrler, 2006). PRCV, which generally causes subclinical to mild respiratory infections, is an S protein deletion mutant of TGEV. This roughly 200 amino acid deletion in the N-terminal region of the S protein results in a shift of tropism from the enteric and respiratory tracts to only the respiratory tract (Sánchez et al., 1992). Because this virus provides protection against TGEV infection, including in newborn piglets, it represents a natural TGEV vaccine (Brim et al., 1995; Wesley and Woods, 1996). Interesting and perhaps relevant for COVID-19 immunity, IgA-mediated mucosal immunity following PRCV infection wanes over time, requiring reinfection or reimmunization prior to farrowing to produce protective lactogenic immunity (Callebaut et al., 1990; Wesley, 2002).

Similar features have also been observed in cattle infected with bovine coronavirus (BCoV), which causes respiratory and enteric disease. Reinfection is commonly observed in animals with measurable antibody titers, with concomitant virus shedding from the respiratory tract. Of note, disease was mitigated in duration in animals with high IgA titers prior to infection (Cho et al., 2001; Heckert et al., 1990). This recurrent theme of waning immunity and need for periodic boosts following initial infection or vaccination is relevant to our understanding of human respiratory CoVs and has implications for vaccine strategies against these viruses, especially SARS-CoV-2, in humans.

Feline infectious peritonitis virus (FIPV), a highly lethal feline CoV, is thought to arise from mutations in the S protein during persistent infection with otherwise mild enteric strains of FCoV, resulting in a shift in tropism from intestinal epithelial cells to macrophages that allows systemic spread of the virus (Rottier et al., 2005). FIP results in lymphopenia and severe serositis and is uniformly fatal. Antibody-dependent enhancement (ADE), a phenomenon in which virus-specific antibodies potentiate infection via Fc or complement receptor-mediated uptake of infectious virus into myeloid cells, has been observed after vaccination against FIPV. This development of ADE reflects the macrophage tropism of FIPV and complicates vaccine development (Vennema et al., 1990; Weiss and Scott, 1981). ADE in the context of FIPV vaccination raises concerns about the same phenomenon occurring after SARS-CoV-2 vaccination, but ADE has not been described in any other CoV infection *in vivo*.

In addition, the most extensively studied CoV is mouse hepatitis virus (MHV), the prototypical laboratory coronavirus, which causes a wide variety of respiratory, enteric, neurological, and hepatic disease in susceptible rodents (Barthold and Smith, 1984). Some strains, such as the neurotropic JHMV or the neurotropic and hepatotropic MHV-A59 cause immune-mediated demyelination as a consequence of viral clearance (Bergmann et al., 2006; Wang et al., 1990). The immune responses to these neurotropic coronaviruses are among the most studied aspects of CoV immunology, as these central nervous system (CNS) infections require an exquisite balance between immune activation to clear virus and suppression to prevent immunopathology. A crucial aspect of the immune response to these viruses is type I IFN, as mice lacking the type I IFN receptor (IFNAR) are rapidly succumb to strains and doses of MHV that would ordinarily be sub-lethal or even non-pathogenic (Ireland et al., 2008; Khanolkar et al., 2009; Roth-Cross et al., 2008). Type I IFN is produced both by macrophages or microglia and plasmacytoid dendritic cells (pDCs) in these infections, and signals through $LysM^+$ macrophages and $CD11c^+$ DCs for protection (Cervantes-Barragán et al., 2009; Roth-Cross et al., 2008).

Virus-specific $CD4^+$ and $CD8^+$ T cell responses are necessary to clear CNS infection with JHMV (Savarin et al., 2008; Williamson and Stohlman, 1990); however, these same virus-specific T cell responses are pathogenic and mediate myelin destruction (Anghelina et al., 2006; Castro and Perlman, 1995; Wu et al., 2000). The role of type II interferon (IFN) in T cells in protection and pathogenesis differs between $CD4^+$ and $CD8^+$ T cells, as IFNγ produced by $CD4^+$ T cells is protective against demyelination, whereas that produced by $CD8^+$ T cells, while critical for viral

clearance, contributes to demyelination (Bergmann et al., 2004; Pewe and Perlman, 2002; Pewe et al., 2002). Adding further to the complexity of the role of T cells in balancing viral clearance and immunopathogenesis, some subsets of these T cells, including T regulatory (Treg) cells and IL-10-producing $CD8^+$ T cells, are necessary for protection against excessive immune responses in the CNS (Anghelina et al., 2009; Cervantes-Barragán et al., 2012; Trandem et al., 2011). Interestingly, virus-specific Treg cells targeting the same immunodominant epitope as effector T cells are particularly critical for suppressing immunopathology (Zhao et al., 2011a, 2014a). Of particular relevance to SARS-CoV-2 and other highly pathogenic human CoVs, T cells are essential to prevent cytokine storm in MHV-A59 via tempering the innate immune response in both a Treg and non-Treg cell-dependent manner (Dong Kim et al., 2007).

In addition to T cells, a virus-specific antibody response is required to prevent recrudescence after initial virus clearance and passively transferred antibodies against MHV are protective against subsequent infection (Lin et al., 1999; Matthews et al., 2001; Ramakrishna et al., 2003). Neutralizing antibodies are also thought to play a key role in preventing $CD8^+$ T cell escape, a feature of some persistent MHV infections (Butler et al., 2007; Chua et al., 2004; Dandekar et al., 2003). An immunopathogenic role for infiltrating monocytes and macrophages, which are found at high numbers in demyelinating lesions, has also been implicated (Templeton et al., 2008). The role for these myeloid cells in demyelination is further supported by the finding that in *Rag1*$^{-/-}$ mice, expression of a macrophage chemoattractant (CCL2) encoded by recombinant virus is sufficient to mediate demyelination (Kim and Perlman, 2005).

Together, these studies of CoV infections of domestic and companion animals and of experimentally infected animals illustrate the waning nature of the immune response, the requirement for both T cell and antibody responses for protection, and the fine balance between protective and pathogenic immune responses, which may all be relevant for understanding SARS-CoV-2 immunity.

Human Common Cold Coronaviruses

The first human CoVs were isolated in the 1960s from nasopharyngeal samples of individuals experiencing common colds (McIntosh et al., 1967; Tyrrell and Bynoe, 1965). These viruses were found to be morphologically similar to IBV and ultimately classified as coronaviruses. Four

strains of these common cold CoVs are known to circulate globally, HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1, the latter two of which were discovered following heightened attention on human CoVs in the aftermath of the SARS epidemic (Fouchier et al., 2004; van der Hoek et al., 2004; Woo et al., 2005). Together, these CoVs are thought to cause about 15% of common colds, and it has been estimated that 90% or more of adults have serum antibodies against these 4 viruses (Gorse et al., 2010; Perlman and McIntosh, 2019). Because these CoVs are the closest to SARS-CoV-2 in transmissibility and ability to replicate in the nasopharyngeal tract, albeit without the same predilection for severe lower respiratory tract disease, studies of the immune responses to these viruses may be of particular relevance to the current pandemic (Figure 2A) (Dijkman et al., 2013; Sungnak et al., 2020).

The majority of our understanding of immunity against these viruses comes from experimental infections of volunteers with HCoV-229E or HCoV-OC43, as well as longitudinal serological surveys monitoring respiratory infections. These volunteer studies demonstrated that reinfection with a homologous virus can occur even when measurable titers of neutralizing antibodies are present in serum prior to infection, though there was an inverse correlation between antibody titer and likelihood of symptomatic infection (Bradburne et al., 1967). Similar to studies of animal CoVs, antibody titers in volunteers had waned substantially 1 year after initial infection and many could be reinfected and shed virus, though these secondary infections did not cause clinical symptoms (Figure 2B) (Callow et al., 1990). Large serological surveys of natural infections with HCoV-229E and HCoV-OC43 have revealed similar trends of reinfection and patterns of waning and rising antibody titers, with estimates of anywhere between 30% and 80% of infections with HCoV-229E or HCoV-OC43 representing reinfections based on pre-infection antibody titers (Hendley et al., 1972; Monto and Lim, 1974; Schmidt et al., 1986). It should be noted that in all of these studies, serum antibody titers are measured. In other experimental respiratory virus infections, levels of mucosal antibody appear to be more relevant for establishing the likelihood of reinfection (Habibi et al., 2015; Singleton et al., 2003). Measurements of mucosal antibodies in COVID-19 patients will be critical for fully determining the likelihood of developing clinical disease after primary infection or vaccination. Reinforcing this notion of frequent reinfections with community-acquired respiratory CoVs, a recent longitudinal survey of 196 individuals using qRT-PCR-based detection of viral genetic material found that, over an 18 month period, 12 of these individuals became reinfected with the same CoV at least once, with a mean of 37 weeks between positive tests (Shaman and Galanti, 2020). In terms of therapeutic interventions, intranasal administration of recombinant IFNα prior

to infection protected against experimental infection, resulting in reduced viral loads and diminished incidence and severity of symptoms (Higgins et al., 1983). Early IFNα treatment is thus likely to induce an anti-viral state independent of the presence of optimal anti-virus antibody and T cell responses.

SARS-CoV

Beginning in Guangdong Province in China in November 2002, SARS-CoV, the causative agent of SARS, infected an estimated 8,098 people with a near 10% mortality rate until being declared contained by the WHO in 2003 (Peiris et al., 2004). This epidemic caused substantial global concern, and sparked interest in CoV research. Relative to the common cold CoVs and to SARS-CoV-2, SARS-CoV was significantly less transmissible, and, despite worldwide dissemination, predominantly spread within healthcare settings and among households, with no evidence of asymptomatic transmission (Peiris et al., 2003a).

SARS-CoV like SARS-CoV-2 caused severe pulmonary pathology, manifested by edema, hyaline membrane formation, infiltration of inflammatory cells including lymphocytes and macrophages in the alveoli and interstitium, and epithelial denudation (Lee et al., 2003; Nicholls et al., 2003). This pulmonary disease progressed to acute respiratory distress syndrome (ARDS), particularly in older individuals and those with underlying conditions (Lew et al., 2003). Vasculitis, lymphopenia, spleen and lymph node atrophy, and virus presence in several tissues, including the blood, brain, spleen, and other tissues were observed. Similar features are shared with COVID-19 (Ding et al., 2003; Gu and Korteweg, 2007; Puelles et al., 2020). While viral load began to decline around day 10 post-onset, clinical disease worsened in many patients around this time, suggesting potential immunopathology, rather than excessive viral replication, as the cause of clinical progression (Peiris et al., 2003b). SARS-CoV, like SARS-CoV-2, uses angiotensin-converting enzyme 2 (ACE2) as its receptor for entry into the cell, and primarily infects airway and alveolar epithelial cells (Figure 2A) (He et al., 2006; Zhou et al., 2020). Some studies suggested that the use of ACE2 as the viral receptor contributed directly to the virulence and pathology of SARS-CoV, as ACE2, a regulator of renin-angiotensin signaling, is downregulated upon entry and this inhibition can lead to enhanced lung pathology (Imai et al., 2005; Kuba et al., 2005). Downregulation of ACE2 has been observed in mice infected with influenza A virus (IAV), which results in

elevated serum angiotensin II compared to wild type mice (Yang et al., 2014; Zou et al., 2014). In IAV-infected mice and patients, elevated serum angiotensin II is correlated with disease severity. Further, *Ace2*$^{-/-}$ mice develop more severe IAV-mediated disease than do their wild type counterparts. These results support the notion that downregulation of ACE2 may contribute to SARS-CoV pathogenesis.

Studies of the immune response to SARS-CoV have consisted of both direct study of human SARS patients and animal models of SARS, including macaques, marmosets, and ferrets, as well as smaller animals, such as hamsters and particularly mice (Gretebeck and Subbarao, 2015). While mice are susceptible to infection with SARS-CoV, young mice develop no illness, and aged mice develop mild clinical disease (Roberts et al., 2005). In order to address this limitation, transgenic mice expressing the human ACE2 (hACE2) gene were developed; however, though they develop pulmonary disease, they also develop a lethal encephalitis (McCray et al., 2007; Tseng et al., 2007). A different approach instead adapted SARS-CoV to mice by serially passaging the virus in mouse lungs. MA15, the first of these mouse-adapted SARS-CoV strains, caused severe pulmonary disease in young mice (Roberts et al., 2007). This virus had six coding mutations relative to the original virus, four of which were in located in ORF1 non-structural proteins, one in the receptor binding domain of the S protein, and one in the M protein. Subsequent experiments determined that the substitution in the receptor binding domain of the S protein and, to a lesser extent, a second one in nsp9, contributed to the enhanced disease in mice relative to unadapted virus (Frieman et al., 2012).

Innate immune responses

The cytokine response to SARS-CoV was frequently characterized by high level production of pro-inflammatory chemokines and cytokines, such as CCL2, CCL3, CCL5, and CXCL10, and IL-6, TNF, and IL-8 production, all of which were further upregulated in patients with more severe disease (He et al., 2006; Jiang et al., 2005; Zhang et al., 2004). Similar findings were also observed in SARS animal models and *in vitro*, both in human airway epithelial cells and in human monocyte-derived macrophages and dendritic cells (DCs) after infection (Cheung et al., 2005; Law et al., 2005; Yen et al., 2006). Interestingly, while macrophages and DCs can be infected by SARS-CoV and produce cytokines following infection, replication is abortive in these cells. Of note, infected monocytes/macrophages and monocyte-derived DCs do not produce

type I IFN, suggesting that SARS-CoV immune evasion strategies are effective in these cells (Cheung et al., 2005; Law et al., 2005; Yilla et al., 2005).

As is the case of other viruses, such as measles virus, influenza virus, Dengue virus, and Ebola virus (García-Sastre, 2017), CoVs, including SARS-CoV, have developed numerous mechanisms to counter the type I IFN response, both via evasion and direct antagonism of interferon signaling. Evasion of sensors of viral dsRNA, including Mda5, RIG-I, and MAVS, is mediated by an array of mechanisms including 2'-O-methylation of the 5' viral mRNA cap by nsp16 (Menachery et al., 2014; Züst et al., 2011), as well as endoribonuclease degradation of viral RNAs and selective RNA packaging mediated by nsp15 (Athmer et al., 2018; Deng et al., 2017; Kindler et al., 2017). Other coronavirus proteins mediate inhibition of pattern recognition receptors or IFN production and signaling pathway molecules, reflecting an extensive array of mechanisms of immune evasion (Fehr et al., 2016; Frieman et al., 2009; Hu et al., 2017; Zhao et al., 2012b). Despite these immune evasion strategies, it has been shown that both primary human and mouse plasmacytoid DCs are capable of inducing a type I IFN response after SARS-CoV infection in a manner dependent on TLR7, which detects single stranded RNA (Cervantes-Barragan et al., 2007; Channappanavar et al., 2016).

The type I IFN response in SARS patients was observed to be dysregulated in patients that experienced adverse outcomes and severe disease, with one report finding that IFN responses persisted significantly longer than in those patients that went on to recover, and were accompanied by the lack of a protective anti-virus neutralizing antibody response (Cameron et al., 2007). Other reports did not describe this persistent IFN expression, and instead found a poor IFN response relative to other respiratory viruses, a pattern that seems to be reflected in patients infected with SARS-CoV-2 (Blanco-Melo et al., 2020; Reghunathan et al., 2005). A pathogenic role for dysregulated IFN signaling is reflected in mouse studies of SARS-CoV. While pre-infection or early treatment with recombinant IFNβ or with poly(I:C) to induce a type I IFN response resulted in complete protection from lethal disease, administration of IFNβ to mice at the peak of SARS-CoV replication led to delayed viral clearance and enhanced lethality, rather than protection (Channappanavar et al., 2016, 2019; Zhao et al., 2012a). This delayed IFN-enhanced disease was characterized by T cell apoptosis and elevated inflammatory monocyte and macrophage accumulation in the lungs, with production of inflammatory cytokines such as IL-6, CCL2, and TNF. Antibody-mediated depletion of these inflammatory monocytes and macrophages was fully protective against lethality, suggesting that these cells were

responsible for significant immunopathology. Together, these data suggest a role for dysregulated IFN signaling in the immunopathogenesis of SARS-CoV and other CoVs.

Adaptive immune responses

The antibody response to SARS-CoV is characterized by seroconversion as early as 4 days and generally around 10-16 days post-onset, with titers peaking around 15-20 days post-infection (Hsueh et al., 2004; Lee et al., 2006; Wu et al., 2007). Several neutralizing antibody epitopes, predominantly against the S1 and S2 subunits of the S protein, and particularly the RBD in the S1 subunit, have been identified (Buchholz et al., 2004; Zhong et al., 2005). While antibodies against other structural proteins have been observed, these are largely non-neutralizing (Åkerström et al., 2006; Qiu et al., 2005). A positive correlation between N- and S protein-specific serum antibody titers and recovery from SARS-CoV was observed, and passive transfer of neutralizing antibodies was found to prevent replication in mouse models of SARS (Bisht et al., 2004; Subbarao et al., 2004; Zhang et al., 2006). However, these antibody responses have been found to lack longevity. While serum antibody titers remain high for the first 2 years after infection, by 3 years post-infection only 55% of patients tested had detectable IgG responses to SARS-CoV proteins, and by 6 years post-infection, no detectable memory B cell responses remained in the periphery (Tang et al., 2011; Wu et al., 2007). These data suggest that antibody responses to SARS-CoV, like those to common cold CoVs, wane significantly with time (Figure 2B). However, a recent study suggests that as late as 13 years post-infection, low levels of IgG against whole SARS-CoV could be detected some survivors, suggesting variability in the longevity of the antibody response (Guo et al., 2020). Further, a meta-analysis convalescent plasma therapy during the SARS epidemic demonstrated some efficacy, highlighting the importance of the humoral response to SARS-CoV (Mair-Jenkins et al., 2015).

In contrast to the poor longevity of the antibody response to SARS-CoV, the memory T cell response has been reported to have significant longevity in patients (Figure 2B), with CD4 and CD8 T cell responses in the blood identified by ELISpot at 4 and 6 years after infection in from 70-100% of patients, including those with no identifiable memory B cell responses in the blood (Fan et al., 2009; Oh et al., 2011; Tang et al., 2011). These T cells were frequently polyfunctional, expressing IFNγ, TNF, and other cytokines. Others have identified positive CD8 T cell responses as late as 11 years post-infection (Ng et al., 2016b).The duration of this memory T cell response was positively correlated, at least in part, with disease severity (Tang et

al., 2011). A number of T cell epitopes have been identified, with most found in the S, N, and membrane (M) proteins (Liu et al., 2017). While the longevity and specificity of the T cell response in human studies have been well studied, the kinetics of the T cell response during acute infection and the correlates of protection are less well understood. Lymphopenia was a commonly observed phenotype in SARS patients during acute disease and T cell activation was also found to be suppressed, particularly in patients with severe disease (Cameron et al., 2008; He et al., 2005; Yu et al., 2003). Additionally, increased Th2 cytokine expression correlate with poor outcomes in patients, a finding also supported in mouse studies of SARS-CoV (Li et al., 2008; Page et al., 2012).

Because of the general lack of human data regarding T cell kinetics and function during acute CoV infections, much of our understanding of their role comes from studies of mice. Zhao et al. found that sub-optimal T cell responses result from an impairment of respiratory dendritic cell migration from the lungs to the lymph nodes (Zhao et al., 2009). This inhibition of DC migration was mediated, at least in part, by inhibitory alveolar macrophages, as depletion of these cells prior to infection resulted in enhanced T cell responses, viral clearance, and survival in mice. Aging is thought to play a significant role in this process, as expression of prostaglandin D2 (PGD_2) and an upstream phospholipase (PLA_2G2D) increase with age and are strongly correlated with this migration defect and sub-optimal T cell response. Inhibition or depletion of these factors reverse these age-related impairments (Vijay et al., 2015; Zhao et al., 2011b). PGD_2 signaling through its receptor on DCs may contribute to the exacerbated disease and enhanced mortality observed with age in the SARS epidemic. Infected human airway epithelial cells have also been observed to produce cytokines, particularly IL-6 and IL-8, that inhibit priming of naïve T cells by DCs (Yoshikawa et al., 2009).

Further, T cells alone are sufficient to partly control SARS-CoV in mice, as adoptive transfer of activated T cells into *Rag1*$^{-/-}$ mice lacking T cell responses ameliorated disease and conferred significant protection and viral clearance. Depletion of CD4 T cells during SARS-CoV infection resulted in impaired viral clearance and reduced neutralizing antibody titers (Chen et al., 2010; Zhao et al., 2010). Immunization with vaccinia encoding CD4 or CD8 T cell epitopes, or DCs coated with these peptides prior to infection with SARS-CoV resulted in significant protection from SARS-CoV lethality (Channappanavar et al., 2014; Zhao et al., 2010). Intranasal immunization of mice with Venezuelan equine encephalitis replicon particles (VRP) encoding an N protein-specific CD4 T cell epitope resulted in the generation of an airway memory T cell

response that conferred complete protection from lethality and reduced pulmonary edema upon SARS-CoV infection, and resulted in enhanced DC and CD8 T cell responses in an IFNγ-dependent manner, highlighting the role of type II IFN in the lungs (Zhao et al., 2016). However, others have observed enhanced immunopathology and eosinophilic infiltrates in the lungs in mice immunized peripherally with VRP-N and challenged with SARS-CoV, demonstrating the importance of the route of immunization in protection (Deming et al., 2006). Together, these data highlight the important roles that both the humoral and cellular response to SARS-CoV have in controlling disease and guide vaccine studies.

MERS-CoV

MERS-CoV was first identified in 2012 and to date has resulted in roughly 2500 confirmed infections with a mortality rate of around 35% (World Health Organization, 2020b; Zaki et al., 2012). Like SARS-CoV, this virus is significantly less transmissible than the common cold CoVs or SARS-CoV-2, with all cases occurring on the Arabian Peninsula or travelers from this region with local transmission. The most notable outbreak occurred in South Korea, in which the index case had recently returned from the Arabian peninsula (Cho et al., 2016). Primary infections are believed to occur via camel-to-human transmission, as the virus circulates widely in dromedary camels throughout Asia and Africa (Chu et al., 2018; Kiambi et al., 2018; Zheng et al., 2019). Secondary infections largely occur in healthcare and household settings (Drosten et al., 2014; Memish et al., 2020). In severe cases, MERS manifests clinically as pneumonia than can rapidly progress to ARDS and multiorgan failure (Arabi et al., 2017). While only two autopsies have been performed, diffuse alveolar damage with hyaline membrane formation in the lungs and alveolar edema were observed (Alsaad et al., 2018; Ng et al., 2016a). MERS-CoV predominantly infects cells of the respiratory tract, using dipeptidyl peptidase 4 (DPP4) as its receptor for cell entry, which is highly expressed on airway epithelial cells and some hematopoietic cells (Figure 2A) (Raj et al., 2013).

As in SARS, study of the human immune response is limited. This has led to the use of MERS-CoV-susceptible animal models, such as macaques and marmosets, and the development of mouse models that express humanized DPP4, as well as mouse-adapted MERS-CoV, to facilitate study of the immune response to the virus (Cockrell et al., 2016; Falzarano et al., 2014; Li et al., 2017; de Wit et al., 2013; Zhao et al., 2014b).

Innate immune responses

The innate immune response in severe MERS is characterized by elevated levels of pro-inflammatory cytokines in the blood, particularly IL-6 and CXCL10, along with IL-8, CCL5, and IFNα (Kim et al., 2016; Min et al., 2016). These elevated cytokines correlated with elevated numbers of neutrophils and macrophages and lymphopenia in PBMC samples, suggesting that they contribute to immunopathology. Unlike SARS-CoV, which only abortively infected macrophages and DCs, MERS-CoV replicates in human monocyte-derived macrophages and DCs, causing elevated production of these cytokines relative to SARS-CoV in these cells (Chu et al., 2014; Tynell et al., 2016; Zhou et al., 2014). Infection of human airway epithelial (HAE) cells also resulted in production of pro-inflammatory cytokines, as well as downregulation of MHC class I and II molecules, in part via epigenetic modulation of MHC class I components (Josset et al., 2013; Menachery et al., 2018).

MERS infection of myeloid cells or HAEs did not result in type I IFN production, again reflecting the ability of CoVs to evade viral RNA sensing and antagonize the IFN response. Similar to SARS-CoV, however, infection of human pDCs resulted in abortive infection with expression of both type I and type III IFNs in a TLR7-mediated manner (Scheuplein et al., 2015). In experimentally infected macaques, early treatment with IFNα (beginning 8 hours post-infection) and ribavirin resulted in reduced pathology and viral load (Falzarano et al., 2013). Similar to experiments with SARS-CoV, treatment of mice with recombinant IFNβ was protective when provided prior to the peak of viral replication (1 day post-infection), whereas delaying treatment until the peak of viral replication (2-4 days post-infection) resulted in elevated viral load, an increase in neutrophils and inflammatory monocytes and macrophages in the lungs, and enhanced lethality (Channappanavar et al., 2019). Clinical trials of recombinant IFNs in combination with ribavirin, a nucleoside inhibitor and antiviral, have demonstrated no changes in 28 and 90-day survival rates or kinetics of viral clearance (Arabi et al., 2020a; Omrani et al., 2014), though clinical trials of IFN in combination with antiviral protease inhibitors, lopinavir and ritonavir, are ongoing (Arabi et al., 2020b). Taken together, these data reflect a role for dysregulation of the innate immune response in the pathogenesis of MERS-CoV similar to that observed with SARS-CoV.

Adaptive immune responses

While most patients showed seroconversion around 2-3 weeks post onset of disease, absent or delayed antibody responses were strongly associated with severe or fatal disease (Corman et al., 2016; Park et al., 2015). Neutralizing antibodies identified in human patients, as well as convalescent patient sera, showed both prophylactic and therapeutic protection in mice (Corti et al., 2015; Zhao et al., 2017). However, while these antibodies had a protective effect in mice, MERS-CoV clearance was demonstrated in mice lacking B cells, showing that antibodies are not necessary to clear acute infection (Zhao et al., 2014b). Because MERS-CoV frequently crosses from camels to infect humans, antibodies that allow neutralization of diverse camel strains of MERS-CoV, as well as antibodies or combinations of antibodies that prevent antibody escape, have been identified (Tai et al., 2017; Tang et al., 2014; Wang et al., 2018). While MERS-CoV-specific antibody responses persist for at least 2 years in patients who recovered from severe disease, responses are not detected or transient in patients with subclinical or mild disease, waning to low or undetectable levels by 2 years post-infection (Figure 2B) (Drosten et al., 2014; Zhao et al., 2017).

The T cell response to MERS-CoV has been partially characterized. Despite lymphopenia in many patients, MERS-specific CD8 T cell response were observed in patients with severe disease, whereas CD4 T cell responses did not develop until convalescence (Shin et al., 2019). It has been shown that activated T cells can be directly infected *ex vivo* with MERS-CoV, resulting in activation of apoptosis pathways, which could, along with the downregulation of MHC molecules in airway epithelial cells and dysregulated cytokine response, contribute to the lymphopenia observed in many patients (Chu et al., 2016). Memory T cell responses in MERS survivors were polyfunctional, expressing both IFNγ and TNF, consistent with greater protective ability. These responses could be detected in all patients as late as 2 years post-infection, including in patients with no detectable antibody response, suggesting that at least some immune memory remains intact despite transient antibody responses (Zhao et al., 2017). Further, T cell responses have been demonstrated to play critical protective roles in MERS-CoV infections of mice, as animals lacking T cells were incapable of clearing virus, resulting in persistent infection (Zhao et al., 2014b). Intriguingly, immunization with a VRP encoding a SARS-CoV N protein CD4 T cell epitope resulted in some degree of cross-protection against MERS-CoV, resulting in reduced viral load (Zhao et al., 2016). This epitope is fairly well conserved between these two and related bat CoVs. It was observed that mice immunized with the MERS-CoV-specific epitope mediated some protection upon SARS-CoV infection and the homologous epitope in a MERS-like bat CoV (HKU4) mediated protection against MERS-CoV

challenge. Despite these protective roles for T cells in MERS-CoV infection, others have found that depletion of CD8 T cells in a sublethal mouse model of MERS-CoV results in diminished lung pathology and clinical disease without impacting the viral titers, suggesting that these cells may also play a role in immunopathogenesis (Coleman et al., 2017).

While there are no currently licensed vaccines for MERS-CoV, three vaccine candidates, an adenovirus-vectored vaccine, a modified vaccinia Ankara-vectored vaccine, and a DNA vaccine, each of which encodes the full length S protein of MERS-CoV, have recently concluded phase I clinical trials and were demonstrated safe and capable of inducing neutralizing antibodies and virus-specific T cells responses in participants (Folegatti et al., 2020; Koch et al., 2020; Modjarrad et al., 2019). However, consistent with the results from the natural infection, immune responses, especially neutralizing antibody titers, had waned by one year after vaccination.

The Next Steps Forward

One can draw several conclusions relevant to our understanding of COVID-19 immunity from prior CoV studies. First, while less important for vaccine strategies, it is apparent from studies with MHV, as well as SARS-CoV and MERS-CoV, that an early type I interferon response is critical for protection from severe disease and preventing an exacerbated or aberrant pro-inflammatory cytokine response. However, CoVs engage in various immune evasion strategies that successfully prevent detection by pattern recognition receptors or inhibit IFN signaling pathways, resulting in either absent or delayed and dysregulated IFN responses that contribute to pathogenesis, rather than protection. Reflecting this, studies of SARS-CoV-2 have shown that the virus is sensitive to IFN-pre-treatment *in vitro*, but patients have impaired IFN responses with low levels of IFN production or signaling (Blanco-Melo et al., 2020; Hadjadj et al., 2020; Lokugamage et al., 2020). The cytokine and chemokine response in patients has also been found to be dysregulated in patients with impaired IFN responses and particularly those with severe disease, with many of the elevated pro-inflammatory cytokines and chemokines matching those seen in SARS and MERS, including CXCL10, CCL2, CCL3, IL-6, and TNF (Chen et al., 2020; Huang et al., 2020; Yang et al., 2020).

Second, studies of animal and human CoVs indicate that both the humoral and cellular adaptive immune responses are important mediators of protection, and a vaccine should robustly induce both. Neutralizing antibody responses are protective in CoV infections and are thus a primary

target for vaccine strategies. However, as described above, antibody responses to CoVs can wane rapidly following infection or immunization, allowing for potential reinfection, particularly in mild or subclinical disease such as those caused by the common cold CoVs or mild MERS. Because SARS-CoV-2 infection often presents with asymptomatic or mild disease similar to the common cold viruses (Arashiro et al., 2020; Black et al., 2020), this is of particular concern, as it is possible that those cases will develop rapidly waning immunity relative to severe cases, potentially allowing for reinfection similar to the common cold CoVs. While seroconversion is observed in all COVID-19 patients 2-3 weeks post-symptom onset, early observations have suggested that antibody titers can wane significantly as early as 30-50 days post-symptom onset (Adams et al., 2020; Long et al., 2020; Robbiani et al., 2020). To date, while SARS-CoV-2 RNA has been detected after periods of negative testing, there is no available culture-based evidence confirming reinfection (Kirkcaldy et al., 2020). Together these data suggest that vaccine strategies against SARS-CoV-2 could require boosting to maintain sufficient neutralizing antibody titers if the immune response is similar to that observed in mild disease. In contrast, based on our experience with MERS and SARS, it is probable that a more stable immune response will develop in patients with severe pneumonia.

Third, T cell responses are also sufficient for at least partial protection in many CoV infections and play a role in mitigating the exuberant innate immune responses involved in cytokine release syndromes. However, as in the case of SARS and MERS patients, COVID-19 patients develop lymphopenia, particularly those with severe disease, delaying the T cell response to the virus, though a virus-specific CD4 and CD8 T cell response are eventually mounted in most patients (Grifoni et al., 2020; Huang et al., 2020; Tan et al., 2020). T cell responses to SARS-CoV and MERS-CoV have also been observed to have enhanced durability relative to neutralizing antibody responses, and thus are crucial for longevity of immunity induced by vaccination. However, T cells have also been observed to play immunopathogenic roles in some CoV infections, including Th2-skewed responses to SARS-CoV. Defining and generating a protective T cell response, rather than a pathogenic Th2-driven response, will also be important for vaccine efficacy.

Another consideration for vaccination strategies is the generation of mucosal immunity, as studies of both animal CoVs and SARS-CoV and MERS-CoV have highlighted the importance of IgA-driven immune responses and localization of T cells to the respiratory tract and lungs. Reflecting this, preclinical animal studies of SARS-CoV and MERS-CoV vaccine candidates

555 have found enhanced protection correlated with intranasal immunization relative to parenteral
556 routes (Jia et al., 2019; Kim et al., 2019; Zhao et al., 2016).
557
558 Finally, on a cautionary note for vaccination, the potential for enhanced disease, in the forms of
559 ADE or vaccine-associated enhancement of respiratory disease (VAERD), must be considered.
560 As mentioned above, ADE has not been observed in any human CoV, or for the most part, in
561 non-human CoVs. Viruses associated with ADE shows a preferential tropism for macrophages,
562 unlike human respiratory CoVs. As SARS-CoV-2 primarily infects the respiratory tract and
563 lungs, a markedly different tropism than the macrophage-tropic FIPV, ADE is unlikely in our
564 estimation. ADE has also never been observed in SARS or MERS, and sera from rats
565 immunized with the receptor binding domain of the SARS-CoV-2 S protein does not enhance
566 viral entry into FcγR-expressing cells, further suggesting that this is unlikely for SARS-CoV-2
567 (Quinlan et al., 2020). VAERD, on the other hand, has some precedent in vaccination studies of
568 animal models of SARS, including in non-human primates (Liu et al., 2019) and in mice
569 immunized against a human SARS-CoV isolate and challenged with a heterologous strain of the
570 virus (Deming et al., 2006). These mouse studies also indicated that VAERD was most
571 prominent in aged mice. While vaccines need to be carefully evaluated for evidence of VAERD,
572 there is good reason to believe that proper vaccine and adjuvant formulation will minimize the
573 risks of this problem, yet will still induce a protective immune response (Iwata-Yoshikawa et al.,
574 2014). Critical will be to identify a vaccine strategy that elicits long lasting immune responses.
575
576 Reaching these goals will require progress on several fronts. Much of our understanding of
577 immune responses in the context of MERS and SARS resulted from studies of experimentally
578 infected animals. Thus, the establishment of useful animal models of COVID-19 will be
579 instrumental in understanding COVID-19 immunity. Taking cues from prior knowledge of SARS-
580 CoV and MERS-CoV animal models, several of these models are currently being explored,
581 including non-human primates, ferrets, hamsters, and mice. Each of these models presents
582 unique advantages and disadvantages.
583
584 Infection of non-human primates, macaques in specific, results in mild clinical disease, virus
585 replication in the respiratory tract and pathological features such as pulmonary edema and
586 hyaline membrane formation, features shared with COVID-19 (Munster et al., 2020; Rockx et
587 al., 2020). As non-human primates are our closest evolutionary relatives, these animals may
588 provide the most relevant data for human pathogenesis, immunity, and preclinical therapy and

589 vaccine safety and efficacy (Chandrashekar et al., 2020; Gao et al., 2020; Williamson et al.,
590 2020). However, the limited availability and expense associated with non-human primate
591 studies limits their potential for widespread use. The use of smaller, more abundant, and readily
592 available animal models is thus of importance as well.
593
594 While ferrets are often used in studies of respiratory disease and infection (Enkirch and von
595 Messling, 2015), infection with SARS-CoV-2 results in relatively low viral titers and a lack of
596 symptoms other than elevated body temperature (Kim et al., 2020; Shi et al., 2020). Ferrets will
597 be useful for transmission studies, because infection of ferrets results in transmission of SARS-
598 CoV-2 to co-housed naïve ferrets. Similarly, infection of hamsters results in transmission to
599 naïve animals, both with direct and indirect contact. Despite elevated viral genomic material
600 relative to ferrets, clinical symptoms are limited to relatively mild weight loss and moderate-to-
601 severe lung pathology (Chan et al., 2020; Imai et al., 2020; Sia et al., 2020). These models will
602 be best suited for study of SARS-CoV-2 transmission, particularly modeling asymptomatic or
603 mild COVID-19 patient spread, as well as evaluation of vaccines and antiviral drugs.
604
605 Laboratory mice, due to their widespread availability, diverse array of reagents and tools for
606 study, and past use as models for SARS-CoV and MERS-CoV, are of particular interest for
607 studies of the immune response to SARS-CoV-2. While mice do not naturally support SARS-
608 CoV-2 replication due to receptor incompatibility between the receptor binding domain of the
609 virus and mouse ACE2 (Zhou et al., 2020), several approaches are being used to render mice
610 susceptible to SARS-CoV-2 infection, informed by similar mouse models of MERS and SARS.
611 One such approach is the generation of transgenic mice expressing hACE2 under control of
612 promoters that allow for expression in airway epithelial cells (Bao et al., 2020; Jiang et al.,
613 2020). This approach allows for infection of the respiratory tract and the development of mild
614 lung pathology following infection; however, hACE2 may also be expressed in additional
615 tissues, including the brain. Infection of the brain results in a lethal encephalitis, similar to results
616 observed when hACE2-transgenic mice were infected with SARS-CoV (McCray et al., 2007).
617 While SARS-CoV-2 RNA has also been identified in the brains of COVID-19 patient autopsies
618 (Puelles et al., 2020), the paucity of lung findings compared to the severe brain disease makes
619 these mice not useful as models of the severe COVID-19 respiratory disease. ‘Knock-in’ (KI)
620 mice, in which hACE2 replaces the mouse ACE2 gene rather than being randomly inserted into
621 the genome, are also being developed. One such knock-in resulted in the expression of hACE2
622 in airways and in the development of pneumonia following infection; however, clinical disease

623 was mild and restricted to aged mice (Sun et al., 2020b). Based on previous studies of hDPP4-
624 KI mice, it is likely that passage through mouse lungs will be required for the generation of
625 virulent SARS-CoV-2 that will provide a model for severe pneumonia (Cockrell et al., 2016; Li et
626 al., 2017). An alternative method to generate hACE2 mice uses transduction of with an
627 adenoviral vector encoding for hACE2, a method also used for the generation of a mouse model
628 of MERS (Zhao et al., 2014b). Because vector is instilled intranasally, this results in expression
629 of hACE2 exclusively in the respiratory tract of mice (Hassan et al., 2020; Sun et al., 2020a).
630 Finally, another approach is to use reverse genetics to mutate residues in the receptor binding
631 domain, allowing for binding of the virus to mouse ACE2 and thereby facilitating viral entry into
632 mouse cells. One such mouse-adapted virus, generated via targeted mutation without serial
633 passage, is able to replicate in mice, though clinical disease was mild and observed primarily in
634 aged mice (Dinnon et al., 2020). As in the case of hDPP4-KI mice, further passage of this virus
635 through mouse lungs will likely result in more virulent virus. Thus, it is probable that some
636 combination of mouse-adapted virus and wild type or hACE2-expressing mice will produce the
637 most robust mouse models for severe COVID-19, and these models will complement other
638 models of mild disease.
639
640 **Critical questions for COVID-19 immunity**
641
642 Several outstanding questions are crucial to address to understand whether prior infection
643 confers protection upon subsequent reinfection and for informed development of vaccines. First,
644 determining whether a neutralizing antibody and/or SARS-CoV-2-specific T cell response is
645 sufficient to prevent clinical disease and transmission is critical. If so, it will also be important to
646 determine the magnitude of the responses required to provide protection in order to inform both
647 social measures and vaccine strategies that can limit spread. Second, it will be essential to
648 perform longitudinal studies to establish the longevity of these protective adaptive immune
649 responses, following natural infection or vaccination. Proper and detailed longitudinal studies
650 will require substantial investment of resources by governments, industry sources, non-
651 governmental agencies, and others. Third, identifying factors that contribute to the dysregulated
652 immune response and immunopathology in patients with severe disease could inform early
653 therapeutic options to limit disease severity. A critical part of these endeavors will require
654 identification of biomarkers that identify patients predisposed to severe disease, so that they can
655 be managed aggressively to prevent poor outcomes. Finally, it will be essential, as vaccines are
656 introduced into widespread use, to not only assess efficacy against severe disease and ability to

minimize transmission, but also to identify vaccine-enhanced disease, so that vaccination is safe and widely accepted by the public.

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Figure legends

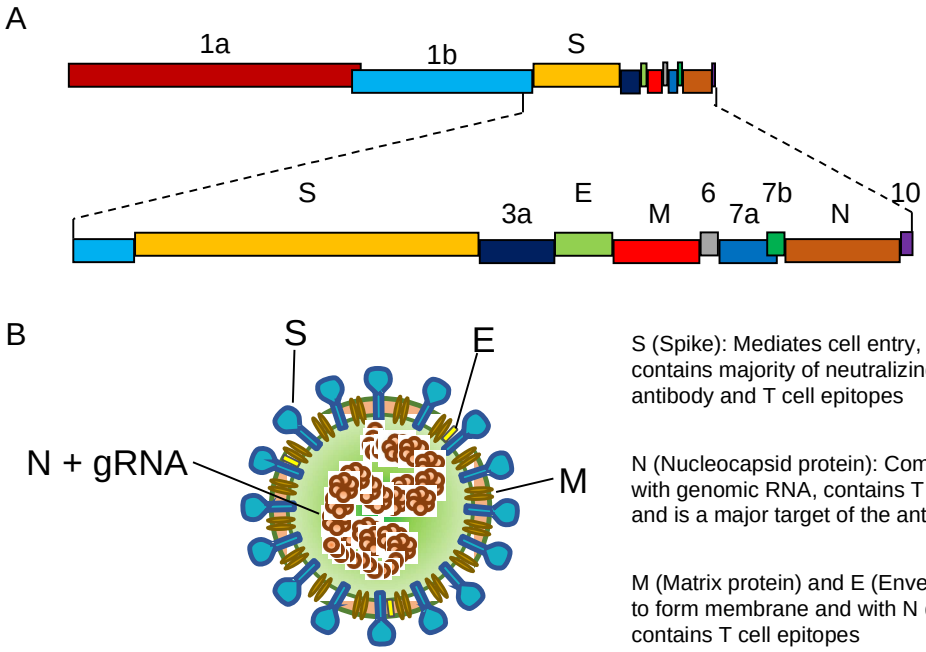
Figure 1: Genomic organization and virion structure. (A) Schematic of the 30kb SARS-CoV-2 genome. The first two-thirds of CoV genomes encode a polyprotein that is cleaved into constituent non-structural proteins involved in replication and immune evasion, while the remaining third encode the 4 main structural proteins, S, E, M, and N, along with accessory proteins. (B) Schematic representation of a CoV virion. gRNA, genomic RNA.

Figure 2: Human CoV tropism and longevity of immune responses. (A) Schematic depicting sites of replication of human CoVs and (B) schematic of longevity of immune responses to common cold CoVs, SARS-CoV, and MERS-CoV, not drawn to scale. Data not available for antibody longevity in patients following mild disease caused by SARS-CoV.

Virus	Genus	Host	Tropism	Available vaccine?
IBV	*Gammacoronavirus*	Chicken	Respiratory, kidney, reproductive tract	LAVs against several heterologous strains (Cavanagh, 2003)
TGEV	*Alphacoronavirus*	Pig	Enteric	LAV, PRCV as natural vaccine (Saif et al., 2019)
PRCV	*Alphacoronavirus*	Pig	Respiratory	No
BCoV	*Betacoronavirus*	Cattle	Respiratory, enteric	Enteric disease only - Inactivated virus, LAV (Saif, 2010)
FCoV/FIPV	*Alphacoronavirus*	Cat	Enteric (FCoV) Systemic (FIP)	Temperature-sensitive LAV (Fehr et al., 1997; Gerber et al., 1990)
MHV	*Betacoronavirus*	Mouse	Strain dependent (enteric, hepatic, respiratory, CNS)	No
HCoV-229E	*Alphacoronavirus*	Human	Respiratory	No
HCoV-NL63	*Alphacoronavirus*	Human	Respiratory	No
HCoV-OC43	*Betacoronavirus*	Human	Respiratory	No
HCoV-HKU1	*Betacoronavirus*	Human	Respiratory	No
SARS-CoV	*Betacoronavirus*	Human	Respiratory	No, multiple phase I trials (Lin et al., 2007; Martin et al., 2008)
MERS-CoV	*Betacoronavirus*	Human	Respiratory	No, three recently concluded phase I trials (Folegatti et al., 2020; Koch et al., 2020; Modjarrad et al., 2019)
SARS-CoV-2	*Betacoronavirus*	Human	Respiratory	No, several ongoing trials (World Health Organization, 2020c)

Table 1: Summary of discussed coronaviruses

IBV infectious bronchitis virus, *TGEV* transmissible gastroenteritis virus, *PRCV* porcine respiratory coronavirus, *BCoV* bovine coronavirus, *FCoV* feline coronavirus, *FIPV* feline infectious peritonitis virus, *MHV* mouse hepatitis virus, *HCoV* human coronavirus, *SARS-CoV* severe acute respiratory syndrome coronavirus, *MERS-CoV* Middle East respiratory syndrome coronavirus, *CNS* central nervous system, *LAV* live attenuated vaccine.



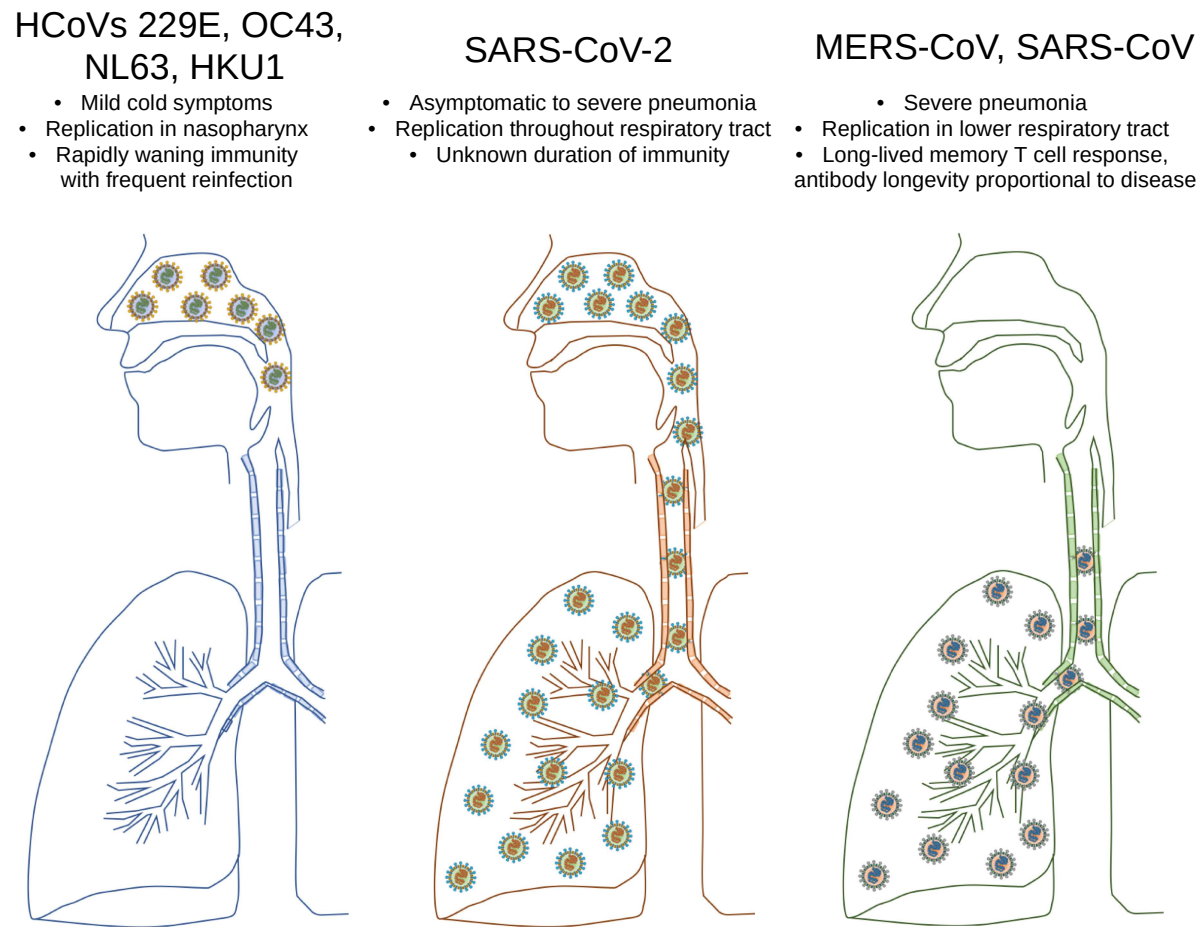
S (Spike): Mediates cell entry, contains majority of neutralizing antibody and T cell epitopes

N (Nucleocapsid protein): Complexes with genomic RNA, contains T cell epitopes and is a major target of the antibody response

M (Matrix protein) and E (Envelope protein): Interact to form membrane and with N during assembly, M contains T cell epitopes

Figure 1

A



B

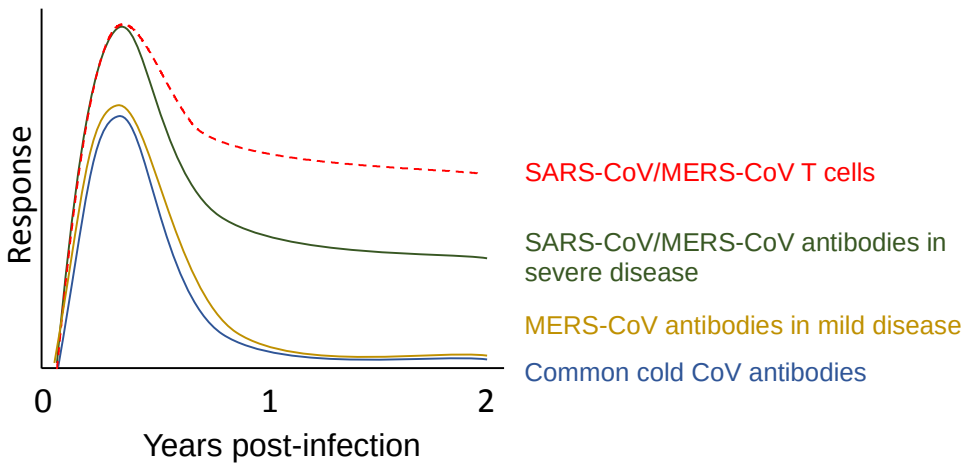


Figure 2

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eTOC/"In Brief"

While the immune response to SARS-CoV-2 is not yet well understood, insights may be gained from studies of other coronavirus infections. Here, Sariol and Perlman review the literature on animal and human coronavirus infections and discuss the critical outstanding questions for understanding SARS-CoV-2 vaccination and protective immunity.