

A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease

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Abstract

The duration and nature of immunity generated in response to SARS-CoV-2 infection is unknown. Many public health responses and modeled scenarios for COVID-19 outbreaks caused by SARS-CoV-2 assume that infection results in an immune response that protects individuals from future infections or illness for some amount of time. The timescale of protection is a critical determinant of the future impact of the pathogen. The presence or absence of protective immunity due to infection or vaccination (when available) will affect future transmission and illness severity. The dynamics of immunity and nature of protection are relevant to discussions surrounding therapeutic use of convalescent sera as well as efforts to identify individuals with protective immunity. Here, we review the scientific literature on antibody immunity to coronaviruses, including SARS-CoV-2 as well as the related SARS-CoV-1, MERS-CoV and human endemic coronaviruses (HCoVs). We reviewed 1281 abstracts and identified 322 manuscripts relevant to 5 areas of focus: 1) antibody kinetics, 2) correlates of protection, 3) immunopathogenesis, 4) antigenic diversity and cross-reactivity, and 5) population seroprevalence. While studies of SARS-CoV-2 are necessary to determine immune responses to it, evidence from other coronaviruses can provide clues and guide future research.

Key Questions

Key Questions for SARS-CoV-2

- What are the kinetics of immune responses to infection?
- Do people who have more severe disease mount stronger antibody responses after infection?
- How do antibody responses vary between different types of antibodies or as measured by different assays?
- How does the presence of antibodies impact the clinical course and severity of the disease?
- Is there cross-reactivity with different coronaviruses?
- Does cross-reactivity lead to cross-protection?
- Will infection protect you from future infection?
- How long will immunity last?
- What are correlates of protection?

Introduction

A pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently underway resulting in worldwide severe morbidity and mortality. Limited pre-existing immunity to this virus is thought to be responsible for the explosive increase in cases across the world. Nearly all transmission models of SARS-CoV-2 assume that infection produces immunity to reinfection for durations of at least one year¹⁻³. This assumption is relevant to public health officials implementing and managing various non-pharmaceutical interventions, the utility of sera from infected individuals as a therapeutic⁴, and the ability for serological tests to identify those who are immune⁵. The dynamics of immunity will also affect the performance of serological testing to quantify the extent of infection in populations. However, knowledge of the dynamics and nature of immune response to SARS-CoV-2 infection is limited, and the scientific basis for durable immunity, upon which these key public health and clinical strategies are dependent, is not well developed.

Several authors have noted human experimental infection studies (called human challenge studies) suggesting that protection after coronavirus infections may last only 1 or 2 years⁶⁻⁹. HCoV have been used in human challenge experiments since shortly after their discovery in 1965^{10,11}. These experiments, where individuals were intentionally infected with HCoV, provide some of the clearest characterization of human responses to coronaviruses and the potential for immune responses to limit infection and disease. Multiple human challenge studies measured antibody immunity before a coronavirus challenge and identified antibody responses that were associated with protection from infection, serological response or symptom¹². The low severity of HCoV allowed for safe use of these viruses in human challenge experiments. The greater likelihood of severe illness in SARS-CoV-2 limits the applicability of such experiments, although some have argued for their use in subsets of the population¹³.

The duration of immunity of SARS-CoV-2 will dictate the overall course of the pandemic and the post-pandemic dynamics⁷, and so an understanding of the temporal dynamics of protective immunity is critical. As with other introductions of novel pathogens¹⁴, explosive outbreaks of SARS-CoV-2 across the globe may threaten its persistence by reducing the number of available hosts susceptible to infection. Immune interactions with endemic coronaviruses could theoretically affect the short- and long-term dynamics of SARS-CoV-2, and vice versa^{15,16} through cross-protection or antibody-dependent enhancement¹⁷, but these interactions and effects are not yet understood. If SARS-CoV-2 does become endemic, age-stratified seroprevalence studies of endemic coronaviruses may provide estimates for incidence rates in the presence of higher levels of population immunity.

Here, we describe the results of a systematic review of the literature on antibody measures of immunity to coronaviruses, including endemic human coronaviruses (principally HCoV-229E, HCoV-HKU1, HCoV-OC43, HCoV-NL63), SARS-CoV-1, MERS-CoV (Middle East respiratory syndrome CoV) and early work on SARS-CoV-2. We conceptualize the stages of exposure and infection at which immunity may play a role in the dynamics of SARS-CoV-2, and how literature describing work on this and other coronaviruses can provide insights into these stages, as follows

(see Figure 1, a visual abstract of our review). First, an exposure to a pathogen generates an immune response that changes over time and between individuals (**antibody kinetics**). Upon exposure, infection history might play a role in providing protection against new infection, and the literature can provide evidence for such **correlates of protection** through challenge studies and longitudinal cohort studies. Upon infection, an individual's immune state, possibly impacted by pre-existing antibodies to other coronaviruses (among other mechanisms), may cause harm through **immunopathogenesis**, and the literature on this topic primarily consists of *in vitro* experiments. Correlates of immunity (or risk through immunopathogenesis) are complicated by the existence of multiple genera of coronaviruses that are **antigenically diverse** and may provide cross-protection, and may also cause false positive assay results due to **cross-reactivity**. Finally, the preceding phenomena at the individual level interact to determine **population seroprevalence**. Studies that measure these quantities across different age groups can provide evidence, albeit ecological evidence, for or against proposed mechanisms of immunity at the individual level.

Methods

Search strategy and selection criteria

We conducted searches of the PubMed database on March 20, 2020 using the search term “coronavirus” and each of the following terms or phrases: “serolog*”, “serop*”, “cross reactivity”, and “complement fixation”. We also searched for each of these terms with the search terms “SARS” and “MERS”. Articles were included in the search regardless of publication date. Articles included electronic, ahead-of-print publications available in the PubMed database. We did not attempt to contact authors to obtain unpublished data. Each abstract was reviewed by two reviewers. Articles that were not considered applicable were excluded (see below). Additionally, we identified articles that may be relevant from the reference list of other articles identified by our PubMed searches.

Assessment

Abstracts were classified as: 1) study of antibody immune responses to human coronavirus; 2) study of human coronavirus but not about antibody immunity; 3) study in non-humans or basic biological study of virus-antibody interactions not characterizing actual humans; 4) study in humans not about coronavirus; 5) in another language; 6) duplicate of another record; or 7) dead link/bad return/noise. Disagreement between two reviewers on classification was resolved by a third reviewer. Manuscripts classified in the first category (study of antibody immune responses to human coronavirus) were reviewed in their entirety and classified by one reviewer as relevant to one or more of the following: 1) antibody kinetics; 2) correlates of protection; 3) antigenic diversity and cross reactivity; 4) immunopathogenesis; and/or 5) population seroprevalence or incidence. Manuscripts that were not considered relevant to any of the preceding categories were excluded.

Data Abstraction

Data were digitized from papers according to pre-defined criteria for each area of focus, related to accessibility, utility in answering the key questions and suitability for the pooled analyses (see Supplementary Appendix for details). Data are available at <https://doi.org/10.5281/zenodo.3751566>.

Pooled Analyses

We conducted pooled analyses in two areas where data were available and sufficiently comparable to include in a single analysis.

Antibody kinetics and association of antibody responses with clinical severity

We summarized approximate time to detection across studies for two sets of studies. The first set includes studies with cumulative number of positive cases over time. Each additional positive case added to the cumulative curve was assumed to be a new detected case at that time point. This is approximate only, because cumulative curves sometimes decline (Figure S1), indicating some participants were lost to follow-up. Second, we identified data that described either seropositivity as a function of time, or measures of antibodies with a reported cutoff. Data was included if (i) the first seropositive time point was within three weeks of illness onset or (ii) the first estimate(s) were negative, but a subsequent measurement within three weeks of the first was positive.

Population seroprevalence

We estimated the annual force of infection from age-stratified seroprevalence data, assuming that individuals acquire infection with a single, strain-specific force of infection that is constant in time using standard methods¹⁸, and that once an individual becomes seropositive they remain seropositive for the remainder of their lifetime (regardless of their protective status). We estimated the total force of infection (FOI) from the four major endemic strains by drawing 100,000 bootstrap samples of four strain-specific FOIs and calculating the sum across strains. Age at first infection is given by the inverse of total FOI.

Results

Manuscript identification

Our searches identified 1281 abstracts of potential relevance (Figure 2). Two reviewers read each abstract and identified 322 manuscripts for full review. Manuscripts were classified into our areas of focus. Below, we present the findings of our review for each area of focus.

General background for multiple areas of focus: Serological assays

Multiple serological assays have been used to characterize antibody responses to coronaviruses. Assays we encountered in our review fell into two major categories (Table S1). The most commonly used assays were binding assays, including enzyme linked immunosorbent assays (ELISA), immunofluorescence assays (IFA), Western blots, hemagglutination inhibition (HAI), and complement fixation (CF). The second category of assays was neutralization assays. Neutralization assays are typically considered the gold standard for measuring functional antibody responses as they measure biological activity throughout the viral replication process. Researchers have used assays of both types to characterize antibody activity by antibody class (i.e. IgG, IgM, IgA). As these antibodies are known to have different temporal dynamics, we reported when specific classes of antibodies were characterized in figures. If no characterization was specified, we reported the measures of antibody aggregated across all classes. The source of samples in the reviewed studies was almost exclusively serum samples. However, mucosal samples collected by swab or nasal washings were also reported.

Antibody kinetics and association of antibody responses with clinical severity

Initially, 56 studies were classified as relevant to antibody kinetics, and 40 as relevant to the association of antibody responses with clinical severity. Of these, 27 were selected after further review (4 on endemic HCoV, 10 on MERS-CoV, 11 on SARS-CoV-1, and 3, including 2 non-peer-reviewed preprints, on SARS-CoV-2). Table S2 provides summaries of these studies. We digitized data from a subset of 22 studies that included sufficient detail on longitudinal antibody measurements (Supplementary Data File S1). 18% of studies reported cumulative seroconversion only. 73% of the digitized studies provided estimates during the first week after onset of symptoms, while 77% had measurements at least one month after onset of symptoms.

Antibody kinetics post infection

In the studies we shortlisted, antibody responses to infecting coronaviruses were rarely reported during the acute phase of illness (1-7 days)^{19–22}. Many studies reported an immune response, characterized by a robust increment of antibody titers for HCoV-229E, MERS-CoV, SARS-CoV-1, and SARS-CoV-2 after the second or third weeks following the onset of illness^{8,23–30}.

Callow et al.⁸ found similar dynamics in IgA and IgG across 10 individuals experimentally infected with HCoV-229E: antibody levels increased after 8 days and peaked around 14 days, although significant variation between patients was reported. Yang et al.³¹, analyzing data across 67 patients, found higher positive rates of IgM against SARS-CoV-1 than IgG during the first month. They further found that the proportion of patients who seroconverted for IgM peaked 30 days after onset, followed by a gradual decrease of IgM levels, while IgG levels peaked by week 25³¹. Another study on 30 SARS-CoV-1 infected patients³² detected seroconversion of IgG, IgM, and IgA at similar times, indicating that the earliest they reached a peak was on average 15 days. While it is currently too early to characterize how anti-SARS-CoV-2 antibodies will change over prolonged periods of time, preliminary studies have analyzed antibody changes in recent

infections. Tan et al.³³ found that IgM was detected on day 7 and peaked on day 28 (across 28 patients), and IgG appeared by day 10 and peaked on day 49 (45 patients), while Zhao et al.³⁴ determined that seroconversion among 173 patients took place at median times of 12 (IgM), 14 (IgG), and 11 (neutralizing antibodies) days.

Multiple studies reported that while IgM and IgG titers increased during the first weeks following symptom onset, IgM levels gradually waned (while remaining detectable) for SARS-CoV-1 and MERS-CoV in comparison to IgG levels about a month post follow-up^{23,32}. Most studies that examined antibody kinetics over extended periods of time focused on IgG^{32,35-40}. Callow et al.⁸ found among experimental infections with HCoV-229E that after peaks in IgG and IgA, antibody levels waned and between 11 weeks and 1 year post inoculation were at similar levels to those found in inoculated but uninfected patients. Other studies^{35,40} reported detectable IgG levels in recovered MERS-CoV patients, respectively at five months and one year after illness onset, while another³¹ detected IgG antibodies across 67 SARS-CoV-1 patients after 82 weeks, the endpoint of the study. We found few studies that analyzed changes in antibody kinetics over the course of many years after illness onset^{36,37}. Cao et al.³⁷ described similar long-term dynamics in IgG and neutralizing antibodies over the course of a 3-year study on SARS-CoV-1: titers for both peaked at month 4, and while they waned thereafter, 74.2% and 83.9% of patients had detectable levels of IgG and neutralizing antibodies, respectively, at month 36.

Correlation between severe disease and rise in post-infection antibody level

Studies have increasingly explored a potential link between case severity and antibody response; however, the available information analyzing the nature of this relationship is uneven across viruses. Several studies on MERS-CoV as well as the first preliminary analyses on SARS-CoV-2 explicitly explore this connection, while fewer studies on endemic HCoVs and SARS CoV-1 do so. Several studies found that cases of varying severity (e.g., asymptomatic, mild, and severe) developed detectable antibodies against HCoV-229E, SARS-CoV-1, SARS-CoV-2, and MERS-CoV^{33,41-44}. One study⁴⁵ found that the rise in antibodies between acute and convalescent sera correlated positively with symptoms and clinical score in 15 patients experimentally infected with HCoV-229E (Table 1). However, most studies of SARS-CoV-1 did not report symptom severity, and evidence of differences in antibody responses among cases experiencing symptoms of different severity is inconclusive. SARS-CoV-1 survivors with sequelae were found to have lower neutralizing antibodies than patients without sequelae³⁷, although the same study otherwise found no significant differences in kinetics according to disease severity. Another study³⁹ found no evidence of difference in antibody responses between patients who survived or died. In MERS-CoV, on the other hand, Ko et al.⁴⁶ found that both seroconversion rate and peak antibody levels increased with disease severity, while Okba et al.⁴⁷ reported a robust response to severe infections as opposed to low or no seroconversion in asymptomatic and mild cases. Milder infections also appeared to be less likely to elicit serologic responses^{47,48}, although Okba et al. suggests that seroconversion detection may depend on the antibodies being targeted. More severe cases were also found to have slower responses^{24,27}; 75% of patients who died had not seroconverted by week 3⁴⁶. Some authors have hypothesized^{47,49} that seroconversion rates in severe cases may be associated with prolonged viral shedding, and that low antibody responses

in mild cases may be due to short-lived infections. Another study⁴⁰ suggested that weaker antibody responses to endemic HCoVs (specifically HCoV-229E) might be because these mainly infect the upper respiratory tract. Preliminary studies on SARS-CoV-2 point to a possibly contrasting pattern to MERS-CoV: while IgM antibodies appear at the same time in severe and non-severe cases, IgG appears sooner in severe cases³³. On the other hand, neutralizing antibody titers were higher in severe cases³⁴.

The distributions of time points at which antibodies were detected (see Methods) in the digitized data are shown in Figure 3. The median time to detection was similar across different antibodies for SARS-CoV-1 (12 days; IQR 8-15.2 days) and SARS-CoV-2 (11 days; IQR 7.25-14 days), but longer for MERS-CoV (16 days; IQR 13-19 days). Severity appears to be associated with time to detection of IgM in MERS-CoV cases only (2 days longer), and IgG in both MERS-CoV and SARS-CoV-2 (2 to 3 days longer for more severe cases). All data on time to seroconversion was based on symptomatic patients. No data were available for asymptomatic individuals.

Figure 4 provides a broad sense for trajectories of antibodies (also see Figures S2 and S3). Most longer-term studies (>10 weeks) were for MERS-CoV and reported IgG and neutralizing antibodies; these showed the presence of IgG and neutralizing antibodies up to 60 weeks after symptom onset (Figure 4). The studies reporting symptom severity with longer-term data focused on MERS-CoV. Not all of these studies reported a cutoff for the assay used; in those that did, two thirds of patients with mild symptoms had detectable or positive IgG antibodies at six months and one year, while all patients with severe symptoms had detectable IgG antibodies at the same points in time (Table 1).

Correlates of protection

Identification of a correlate of protection requires characterization of immune responses prior to a known exposure or period of risk in which infection or illness outcomes are characterized. In our review, we found that this level of detail was only present in human challenge experiments with HCoVs. We identified 18 studies in which volunteers were exposed to experimental infections with HCoV. Of these, 6 associated pre-infection antibody measurements with either virologic, serologic or illness outcomes upon experimental infection (Table S4).

The earliest identified experimental infection study of coronaviruses found that 7 of 8 with neutralizing titer < 5 excreted virus after experimental exposure compared to only 1 of 4 with pre-exposure titer of 40 or greater¹⁰. Interestingly, this study is one of the few to report illness as a function of dose of viral inoculum given in the challenge experiment and suggests that those given higher doses ($>10^{1.2}$ TCD₅₀) were more likely to experience colds (10/15) than those exposed to lower doses ($<10^{0.7}$ TCD₅₀) (3/11).

Barrow et al.⁵⁰ found lower proportions of individuals with high neutralizing titer experienced 'significant colds' upon viral challenge than individuals with low titer.

Callow¹² characterized IgA, IgG and neutralizing antibody in sera and nasal washings from 33 volunteers before they were experimentally exposed to 229E HCoV. She found that multiple antibody responses were associated with reduced risk of infection, seroconversion, and symptomatic illness upon challenge. Individuals who seroconverted to the experimental viral exposure (defined as a rise in ELISA IgG serum antibodies) had significantly higher serum IgG, neutralizing antibodies, and nasal IgA. Serum and mucosal IgA were associated with the duration of viral shedding post experimental infection, with those shedding for 5 days or more having statistically significantly less mucosal IgA than those shedding less than 5 days (0.6 ng/ml versus 4.7 ng/ml, $p < 0.01$). Serum neutralizing antibody was not found to be significantly associated with viral shedding duration. This study also showed protective associations of pre-infection serum neutralizing antibody, serum IgG and nasal IgA with clinical severity scores and nasal secretion weights (a measure of severity of rhinorrhea symptoms).

Another prospective study⁵¹ reported detection of pre-existing neutralizing antibodies among medical students who had virus isolation (67%, $n=8/12$) or seroconversion to HCoV-229E (25%, $n=3/12$). Pre-existing neutralizing antibodies were inversely associated with increases in neutralizing antibodies after re-infection, but were not associated with reinfection events that were determined by CF seroconversion.

Experimental re-infection or re-challenge

Several studies exposed volunteers to two challenges of virus, some months apart. Reed re-challenged 6 volunteers who had been experimentally infected 8-12 months previously⁹. On the first challenge, all 6 developed symptoms and detectable viruses and 5 of 6 experienced significant rise in titer. In the second, 0/6 experienced illness, detectable virus or significant rise in titer. Callow et al re-challenged volunteers with the same dose of coronavirus, one year apart⁸. Of 9 volunteers who were infected in the first exposure, 6 (67%) were infected in the second exposure. However, none of these individuals developed respiratory illness symptoms and they experienced a mean duration of detectable virus of 2 days compared to a mean of 5.6 in the initial challenge.

Cross-reactivity and antigenic diversity

We identified 73 papers as related to cross-reactivity and/or antigenic diversity (Table S5). Of these studies, 43 were identified as highly important and were described in the text, and data was digitized from 7 studies (Supplementary Data File S2).

General background for this area of focus: Genetic relationships of human coronaviruses and immunogenic proteins

Within the *Coronaviridae* family, the *Coronavirinae* subfamily includes four distinct genera. The **Alphacoronaviruses** include two major human coronaviruses, HCoV-229E and HCoV-NL63. Multiple HCoV-229E-like strains have also been characterized. The **Betacoronaviruses** are categorized into 4 lineages. Lineage A includes HCoV-OC43 and HCoV-HKU1, Lineage B

includes SARS-CoV-1 and SARS-CoV-2, Lineage C includes MERS-CoV and multiple bat coronaviruses, and lineage D contains coronaviruses thus far only identified in bats. HCoV-OC43 and HCoV-229E are documented to cause common cold while the more recent strains (HCoV-HKU1 and HCoV-NL63) infect both the upper and lower respiratory tract, resulting in more severe but rarely fatal disease⁵². Other CoVs have been associated with human disease, including enteric disease in infants and zoonotic infections from livestock, but seem rare and are not described here^{9,53–58}.

Coronaviruses have four structural proteins: the spike protein (S), the nucleocapsid (N), the envelope protein (E) and the membrane protein (M)^{59,60}. The S protein, which protrudes from the virus envelope, is immunodominant and consists of two subunits: the S1 protein, which contains the receptor binding domain (RBD) and the S2 protein, which mediates cell membrane fusion^{61,62}. The nucleocapsid protein, which is also immunogenic, is smaller than S, lacks a glycosylation site, and induces antibodies sooner than to S during infection, making it an attractive protein for diagnostic assay design⁶³. Sequence homology for the N and S of SARS-CoV-1 to other Betacoronaviruses is 33-47% and 29%, respectively, while homology to Alphacoronaviruses is lower (25-29% homology to N and 23-25% for S)⁶³. SARS-CoV-2 is most similar to SARS-CoV-1, harboring sequence homology of 90% in N and 76% in S followed by MERS-CoV (48% and 35%, respectively)⁶⁴.

Natural and experimental infection studies in humans point to cross-reactivity within but minimal reactivity between endemic human Alpha- and Betacoronaviruses.

Individuals experimentally inoculated with HCoV-229E and HCoV-229E-like strain LP experienced a >4-fold rise in neutralizing antibodies to both HCoV-229E and LP, while individuals inoculated with HCoV-OC43 did not⁶⁵. However, while volunteers experimentally inoculated with HCoV-229E-like strains were protected against challenge with the homologous strain at one year (n=6/6; none shed virus, showed symptoms, or had a rise in antibodies), volunteers experienced only partial protection against heterologous HCoV-229E-like strains (n=5/12 protected). Increasing population immunity to HCoV-229E in the population was associated with less clinical disease upon challenge with HCoV-229E-like strains⁹. Studies of serological responses to HCoV N proteins point to cross-reactivity within Alpha-HCoVs (229E and NL63) and Beta-HCoVs (OC43 and HKU1) but not between Alpha- and Beta-HCoVs^{66–68}. Consistent with observations in human challenge studies, children experiencing natural HCoV infections experience 4-fold seroconversions to either HCoV-OC43 or HCoV-229E but not both simultaneously⁶⁹. However, a longitudinal study in newborns found that children seroconverted to either HCoV-NL63 or HCoV-229E but not both, although both viruses are Alpha-HCoVs⁷⁰. A later study in newborns followed from age 0 to 20 months⁷¹ showed asymmetric interactions within Alpha-HCoVs and Beta-HCoVs: seroconversion to HCoV-NL63 was observed after HCoV-229E but no recent HCoV-229E seroconversions had a recent infection by HCoV-NL63, suggesting HCoV-NL63 provides at least short-term protective immunity against HCoV-229E. Similarly, HCoV-HKU1 seroconversion occurred prior to HCoV-OC43 but rarely after, suggesting HCoV-OC43 protected against HCoV-HKU1.

Infection with endemic HCoVs produces little cross-reactivity to emerging CoVs SARS-CoV-1 and MERS-CoV.

Individuals experiencing natural infections with HCoV-OC43 or HCoV-229E did not have detectable antibodies in acute or convalescent samples against SARS-CoV-1 (to N protein⁷²; by IFA or neutralization³⁹). Healthy individuals with antibodies to HCoV-229E, HCoV-OC43, and other endemic HCoVs rarely had detectable antibodies that bound SARS-CoV-1 infected cells or SARS-CoV-1 N protein^{68,73,74}. HCoV-OC43 N and SARS-CoV-1 N proteins have a subset of sites with shared homology, potentially explaining low-level false positive results for N-based assays⁷⁵. Blood donors in Southern China (n=152) and Saudi Arabia (n=130) did not have detectable binding (IFA) or neutralizing antibodies to either MERS-CoV or SARS-CoV-1^{76,77}. Because children experience less severe disease during SARS-CoV-1 infection than adults, it was hypothesized that childhood vaccination with non-CoVs provided cross-protection against SARS-CoV-1. However, binding and neutralizing antibodies and T cell responses induced by routine childhood vaccinations (AMPV, BCG, DPT, HBV, Hib, JEV, MMRV [and MV, RV], OPV, PI, SV, VV [varicella vaccine]) did not cross-react with SARS-CoV-1 in experimentally inoculated mice⁷⁸.

Emerging HCoVs can induce cross-reactive binding antibodies toward endemic and other emerging HCoVs

SARS patients often experience a >4-fold rise in antibody to HCoV-229E, HCoV-NL63, and/or HCoV-OC43 in paired acute/convalescent samples (n=12/20)³⁹. In one study, the number of SARS patients who experienced a >4-fold rise in binding antibodies was greater to HCoV-OC43 (n=10/11) than HCoV-229E (n=5/11)⁷³. Some SARS patients also showed a rise in antibodies to HCoV-229E and HCoV-OC43 N protein⁷³ and HCoV-NL63⁷⁹. Among SARS-CoV-1 patients (n=28), 60% had detectable IFA titers to MERS-CoV and 25% had anti-MERS-CoV neutralizing antibodies. A subset with available paired samples experienced seroconversion to HCoV-OC43, but limited seroconversion to Alpha-CoVs. In the same study, animal handlers at a wildlife market in Guangzhou (n=94) with low-level prevalence of antibodies to SARS-CoV-1 (13.8% by IFA, 4.3% by NT) had detectable antibodies toward MERS-CoV (2.2% by IF)⁷⁶. A follow-up study found that the cross-reactivity between SARS-CoV-1 and MERS-CoV was unlikely to be due to similarity in the receptor-binding domain (RBD), as monoclonal antibodies (mAbs) raised to SARS-CoV-1 RBD did not bind MERS-CoV RBD or neutralize MERS-CoV even at high concentrations⁸⁰. MERS-CoV may produce less cross-reactivity against SARS-CoV-1. A subset of slaughterhouse workers in Saudi Arabia had antibodies to MERS-CoV by IFA as well as to pandemic HCoVs, but none had reactivity to SARS-CoV-1 spike protein. MERS-CoV patients were observed to have low-level cross-reactivity to SARS-CoV-1⁷⁷ and in one study HCoV-HKU1 N protein⁷⁹. Because of this cross-reactivity, researchers have developed diagnostic assays with truncated SARS-CoV-1 S, N, and M proteins^{81–84}. See Figure 5 for associations between homologous and heterologous titers.

There is some evidence for antigenic evolution in the receptor binding domain of emerging CoVs

A study of SARS-CoV-1 strains from the zoonotic phase (palm civets and bats) to early and late in the SARS epidemic revealed that some escaped neutralization by mAbs targeting the spike RBD of SARS-CoV-1⁸⁵⁻⁸⁷. Sera from BALB/c mice immunized with full length S protein from civet strains were ineffective against human SARS-CoV-1 and vice versa⁸⁸. Despite significant cross-reactions between mAbs against conformational epitopes of RBD with multiple mutational differences, single mutations were shown to disrupt neutralizability⁸⁹. In contrast, mAbs targeting regions critical for fusion and entry on the S2 protein are immunogenic and can broadly neutralize SARS-CoV-1 strains^{59,90}. A recent study showed reduced binding of mAbs from SARS patients to the RBD of SARS-CoV-2, especially those that blocked binding to the ACE2 receptor. The only mAb potentially bound to SARS-CoV-2 RBD protein did not compete with the RBD for binding to the ACE2 receptor, suggesting it bound a different, conserved site on the protein⁹¹. Similar studies were conducted to study changes in MERS-CoV. Five recombinant RBD proteins were constructed with mutations detected from MERS-CoV strains isolated in humans (2012-2015) and camels⁹². These RBDs maintained functionality and induced potent neutralizing antibodies. When residues in their receptor binding motifs were mutated to evade neutralization, cross-reactivity persisted but binding affinity to DPP-4 (the main receptor for MERS-CoV) was lost, suggesting limited antigenic escape for MERS-CoV. A study of MERS-CoV isolates with distinct amino acid differences in the S and other replication proteins found differences in replication kinetics, but it is not clear that these were attributable to differences in S⁹³.

Immunopathogenesis

In the initial review, 38 papers were identified as related to immunopathogenesis. Of these, we found 25 sufficiently relevant to review in Table S6, and 16 of those are detailed below and summarized in Figure 6.

Antibody-dependent enhancement (ADE) may be possible

Multiple studies have suggested the possibility that pre-existing antibodies increase disease by facilitating viral entry into cells. This mechanism, a long hypothesized explanation for severe dengue infections, is called antibody-dependent enhancement (ADE). This has also been hypothesized as relevant to coronaviruses specifically in patients who seroconverted early in SARS-CoV-1 infection^{25,94,95}. Reasons why some individuals can mount responses more quickly than others are unknown, but the correlation between greater age and early response with higher titers suggest priming effects from existing antibodies against endemic strains⁹⁵. Authors from another study pointed toward enhancement from antibodies within the episode¹⁷. Nasopharyngeal viral load increased in the first week and declined thereafter but clinical worsening was seen in many of the patients at week two, with virus shedding in stool and urine observed towards the end^{25,94}. Many manifested with new-appearing lesions as original lesions improved. The timing of the appearance of new lesions correlated with IgG seroconversion, suggesting that pathology post week one was driven by the immune response rather than by uncontrolled viral replication.

Others have argued that ADE due to neutralizing antibodies is unlikely as treatment of SARS-CoV-1 with convalescent serum did not result in adverse effects⁹⁵.

Observation of increased risk of disease in infants with mid-levels of maternal antibody to dengue (compared to high or low levels of maternal antibody) is important evidence supporting the role of antibody in pathogenesis for dengue⁹⁶. A similar mechanism has been identified for seropositive and seronegative kittens infected with feline infectious peritonitis virus, a coronavirus that causes fatal disease in cats⁹⁷. One study characterizing endemic HCoV in infants observed the highest lower respiratory tract infection burden (7.8%) at 6-23 months of age (1.5% at <6 months, close to none at 2-5 years) while upper respiratory tract infection burden was close to uniform⁹⁸. The heightened disease burden after maternal immunity waning to medium levels in the lower tract, and the absence of such observation in the upper tract where antibodies do not circulate, subtly supports the possibility of ADE in HCoVs.

Suggestive enhancement mechanisms from in vitro experiments

Controlled *in vitro* experiments have explored the possible enhancing action of antibodies for HCoV infections. A series of studies by Yip et al. demonstrated that opsonization of anti-spike antibodies allowed SARS-CoV-1 to enter non-ACE2 expressing immune cells that bear Fc- γ -RII (CD32)^{99,100}. Though replication is observed after entry, the virus does not exit nor alter the expression of proinflammatory immune mediators (CCL2/MCP-1, CCL3/MIP-1 α , CXCL10/IP-10, TNF- α) and apoptosis inducing ligands (FasL)¹⁰¹. This contrasts with effects in nonhuman primate studies where endocytosis into macrophages stimulated inflammation, which in turn drove severe lung injuries¹⁰². A study by another group in human promonocyte cell line (HL-CZ), which expresses both ACE2 and Fc- γ -RII, demonstrated increased infectivity and virus-induced apoptosis when anti-SARS-CoV-1 sera from patients were added at 100- to 2000-fold dilutions, while at higher concentrations neutralization occurred¹⁰³. Upon infection, TNF- α , IL-4 and IL-6 expressions heightened, while IL-3 and IL-1 β only appeared in trace amounts. The difference could have resulted from the cell line differences or the set of mediators assessed¹⁰⁴. Regarding regions of the spike protein that may induce antibodies with enhancement effects, both anti-S1a and anti-S1b mAbs showed mild to moderate effects¹⁰³. Only one particular anti-S1b clone showed neutralization. No effect was seen for anti-N mAbs. There is limited evidence that these mechanisms are causal to inflammatory gene expression differences among patients with differing severities¹⁰⁵.

Direct damage caused by antibodies

While the link between antibody presence and enhanced severity via infection of immune cells remains unclear, some have suspected a role for auto-reactive responses in increased severity of illness. Prolonged tissue destruction can increase presentation of host proteins to T- or B-cells and result in an adaptive response against self, i.e. epitope spreading⁵². Anti-S2 IgG antibodies targeting uninfected lung epithelial cells (A549) were detected in SARS-CoV-1 patients after twenty days post-symptom onset¹⁰⁶, a reactivity not seen in serum from healthy individuals and non-SARS-CoV-1 pneumonia patients. Complement inactivation only showed cytotoxic effect

when IgG was present/unbounded. Presence of anti-S2 antibodies also increased the binding of immune cells (PBMCs) to A549 cells treated with IFN- γ , replicating the conditions under which a cytokine storm would be observed. A separate study demonstrated colocalization of anti-S2 Abs collected from serum of SARS patients ≥ 50 days post-fever onset with annexin A2 and immunoprecipitated annexin A2 on A549 cell surfaces. Elevated expression of annexin A2 on the surface can be stimulated by IL-6 and IFN- γ , both cytokines induced by SARS-CoV-1, which in turn increases binding of anti-S2 Abs to the cell. However, its pathogenic role was not explored¹⁰⁷. Alternatively, similarity between viral and host epitopes (molecular mimicry) can generate cross-reactive antibodies. In mice¹⁰⁸ and humans¹⁰⁹, there is evidence of anti-N antibodies that cross react with IL-11, an anti-inflammatory cytokine expressed in many tissues, including lung and bone marrow. The authors suggest high anti-N antibodies induced relatively early during infection may be involved in the thrombocytopenia and lymphopenia observed early in SARS-CoV-1 infection¹⁰⁸.

Population seroprevalence

From the paper review, 68 papers were classified as having data on age and seroprevalence or seroincidence, of which 20 studies were confirmed on further review, and 14 had digitizable data. The age range across studies was 0 to ≥ 65 , while the sample size of studies ranged from 69-19,974 (82-6,400 for studies of endemic HCoVs). Table S7 and Supplementary Data File S3 contain details of the studies.

Seroprevalence to endemic coronaviruses increases rapidly during childhood

For endemic coronaviruses, seroprevalence rises sharply in childhood, with little to no change in seroprevalence by age among adults. While exact dynamics from 6 months to 20 years vary between studies, the general trend remains consistent. Figure 7 displays HCoV age-seroprevalence curves for the 7 papers with digitizable data on seroprevalence by age, with the panels representing the four major endemic strains^{74,110-115}. Trends from papers not displayed in the figure are largely the same^{68,70,116,117}. Two studies show a marked decline in seroprevalence with age above 40^{68,111}.

Seroincidence of endemic coronaviruses occurs in all age groups, with no clear trend

Available data sets are more sparse for incidence, and the patterns are inconsistent between studies^{110,118-120}. Figure 8 displays age-incidence curves for the 4 papers with digitizable data on incidence by age, with each panel representing the two strains included in these studies (HCoV-229E and HCoV-OC43). There was an increasing trend in seroincidence with age during an outbreak for HCoV-229E in Tecumseh, Michigan¹¹⁰, but a similar analysis of HCoV-OC43 seroincidence in the same outbreak showed no such increase¹¹⁸. Longitudinal follow-up of 10

families in Seattle found a lower rate of seroconversions among adults compared to children¹¹⁹. A comparison of a cohort of 21-40 year-olds and a cohort of ≥65 year-olds found no clear difference in incidence between the two age groups, as measured by seroconversion or PCR-confirmed, HCoV-associated respiratory illness¹²⁰. Finally, observational studies have shown evidence of coronavirus-associated respiratory illnesses in elderly populations^{121–123} and across all ages¹²⁴.

The force of infection of endemic coronavirus strains is high, and the age at first infection low, but variable across studies. Simple catalytic models fit to the digitized data predict median total force of infection across studies of 0.21 (95% CI 0.09, 0.40) (see Table S8 for estimates by study), corresponding to an average age at first infection with any strain of 4.8 years (95% CI 2.5, 11.2). A cohort of 25 infants followed from birth for an average of two years experienced annual strain-specific incidence rates from 0.12-0.70^{70,71}. Zhou et al.'s serosurvey measured IgG and IgM separately, and showed very different patterns with age¹¹⁵ (Figure 7). While IgG seroprevalence rose to high levels by age 10 and remained high into the adult population, IgM seroprevalence declined to zero for all individuals aged 14 and older. The authors interpreted this as evidence that first infections occurred before the age of 14 for all strains.

Data are incompatible with complete, lifelong homologous immunity to endemic coronaviruses

The rapid rise in seroprevalence with age observed in the literature suggests a force of infection (and thus proportion seropositive to all serotypes at older ages) high enough to preclude significant rates of coronavirus infection among older adults if each serotype confers lifelong homologous immunity (Figure 9, green dotted line). On the other hand, short-term, complete immunity, lifelong partial immunity, and the existence of multiple genotypes within a single serotype with limited cross-immunity could explain the age-seroprevalence and age-incidence curves seen in the literature (Figure 9).

Further observations from review

The review gave rise to several observations that were either consistent or conflicting across papers. Studies that enrolled children less than 6 months detected loss of maternal antibodies, representing a preliminary line of defense for newborn children^{70,71,74,117}. Most studies showed no discernible difference in age-seroprevalence trends or in overall seroprevalence by strain. Gao et al.⁶⁸ found that seroprevalence of HCoV-229E and HCoV-HKU1 was significantly lower than seroprevalence of HCoV-OC43 and HCoV-NL63. In addition, Chan et al.¹¹⁴ found seroprevalence to HCoV-HKU1 to be low (21.6% in 31-40 year olds) in Hong Kong, and stated that this was expected from the low rates of HCoV-HKU1 among respiratory illnesses. Finally, most studies measured the presence of binding antibodies in the blood. Of the studies in Figure 7, only Cavallaro and Monto¹¹⁰ (red) measured seropositivity using a neutralization assay. That the seroprevalence is markedly lower in that study compared to the others could indicate lower test

sensitivity compared to more modern tests, or of the lack of correlation between neutralizing and binding antibodies against endemic coronaviruses.

Regarding the novel coronaviruses, serosurveys of SARS-CoV-1 confirmed that the rate of asymptomatic or subclinical infection was very low¹²⁵. Asymptomatic and subclinical rates of MERS-CoV are generally higher, but available serosurveys lack the power to draw strong inference about age trends. A large serosurvey conducted across Saudi Arabia found that the age of seropositive individuals was significantly lower than the age of clinical cases¹²⁶, while another conducted across multiple countries in Africa and Asia found no trend in seroprevalence with age¹²⁷. Studies of risk factors within camel workers have either not addressed age as a risk factor^{128,129} or not found an association¹³⁰.

Discussion

Key findings

We have presented a broad, comprehensive review of multiple aspects of the literature on antibody immunity to coronaviruses. We identified a number of key findings. The median time to detection was similar across different antibodies for SARS-CoV-1 (12 days; IQR 8-15.2 days) and SARS-CoV-2 (11 days; IQR 7.25-14 days), but longer for MERS-CoV (16 days; IQR 13-19 days). Most long-term studies found that IgG waned over time (typically detectable up to at least a year) while others found detectable levels of IgG three years post symptoms onset. Antibody kinetics varied across the severity gradient with longer durations of detectable antibody associated with more severe symptoms. Human challenge studies with HCoV indicate that serum and mucosal immune responses (serum IgG, IgA, neutralizing titer, mucosal IgA) provide possible correlates of protection from infection and disease. However, repeat human challenge experiments with single HCoV suggest individuals can be infected with the same HCoV one year after first challenge, but with possible lower severity. There is cross-reactivity within but minimal reactivity between Alpha- and Beta-CoVs. While endemic HCoVs rarely induce cross-reactive antibodies against emerging HCoVs, SARS-CoV-1 and MERS-CoV stimulate antibodies induced by prior HCoV infections. Multiple mechanisms for immunopathology have been suggested but no strong causal evidence exists and the extent to which the presence of antibodies affects human disease severity is not known. Seroprevalence with the four major endemic HCoV strains rose rapidly during childhood and remained high in adults. The median age at first infection with any strain was 4.8 years (95% CI 2.5, 11.2). There was no clear trend in seroincidence with age, and many studies have demonstrated incidence of coronavirus infections in elderly populations. These results suggest a measurable impact of immunity to coronaviruses on future risk, but this protection may be transient.

Limitations of systematic review

We have suggested a set of search terms to identify relevant work, and others may expand on this search. Due to the speed of new research being produced, we limited our systematic review

of SARS-CoV-2 papers to before March 20, 2020. Further evidence on immune responses to SARS-CoV-2 is likely contained in work that has since been published. We excluded from the review animal studies and studies of animal CoVs to remain human-focused, but this literature is likely relevant to some areas of the review. We limited the scope of the review to antibody-mediated immunity, meaning that understanding of some areas of the review may be incomplete. Finally, digitized data could be affected by publication bias or other selection bias, meaning that it might not be representative of data from all studies. The aim of the pooled analyses was to summarize the array of studies rather than formally explore hypotheses, and as a result the models used are simple. For example, in estimating force of infection from age-stratified seroprevalence data, we did not consider other features of a model such as assay sensitivity, time- and age-varying force of infections, seroreversion, and cross-reactivity between strains, that might better explain patterns seen in the data.

Implications for SARS-CoV-2 pandemic responses and future outlooks

Serological assay development

There is a **need for development of serological assays with high sensitivity for screening and sufficient specificity to exclude individuals from unneeded interventions**. Evidence from previous emerging CoVs suggests that false negativity is likely to result from waning of antibody levels. As most studies on antibody kinetics are on symptomatic patients, the kinetics in subclinical infections, a significant proportion of SARS-CoV-2 infections¹³¹, remains a key gap in the literature. Indications that less severe illnesses are associated with reduced antibody responses suggests that mild cases may pose challenges to serological assays.

On the other end, the proposed policy of “**immunity passports**” to allow individuals presumed immune to return to work once social distancing measures are relaxed **requires highly specific serological tests** to mitigate adverse outcomes. Evidence from past emerging HCoVs suggests low false positivity from cross-reaction with endemic HCoVs. However, antibody titers do not necessarily translate to immunity. Challenge studies indicate multiple candidates that may serve as correlates of protection including serum and mucosal measures; however, these will need specific evaluation for SARS-CoV-2. The knowledge gap in correlates of protection and their durability must be filled before immunity passports are safe for general use.

Therapeutics, vaccines, and ADE

Pharmaceutical interventions to protect susceptible individuals or improve outcomes among sick individuals will first need to be tested in randomized trials. Vaccines with various antigens are currently under development¹³² and polyclonal antibodies from SARS-CoV-2-recovered patients have been used in some cases for treatment¹³³. Though the evidence for immunopathogenesis remains limited¹³⁴, it will be important to design rigorous trials that can provide valid evidence of positive effect but also detect negative effects if they occur with associated adaptive stopping criteria. Such concerns might extend beyond vaccine development if negative effects are subtle and not or weakly detectable in Phase III studies. In the event of mass vaccination following

successful efficacy studies, surveillance designed to detect waning immunity and adverse events due to vaccine-mediated immunopathogenesis is critical.

Long-term dynamics of SARS-CoV-2 and concluding remarks

Key questions for the long-term dynamics of SARS-CoV-2 include whether it is likely to be eradicated, whether widespread immunity will lead to transient decreases in incidence and how long it will take for another large outbreak to occur. Modeling studies will be crucial in answering these questions, but they will rely on an understanding of immune responses to SARS-CoV-2 and interactions with other coronaviruses to make relevant predictions. Analysis of datasets, specifically of serosurveys, needs to account for the kinetics of waning immunity and effects of imperfect assays to draw meaningful inferences.

Finally, we note that the best evidence for immune responses to SARS-CoV-2 will come from studies of the virus itself. Such studies are being performed and reported with unprecedented speed, but in the absence of firm evidence many are turning to the existing coronaviruses as a model. To that end we have produced this review to aid researchers in understanding the scope of the evidence for immune responses to these coronaviruses.

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Main Text Figure Titles

Figure 1: Aspects of antibody response included in this review.

Figure 2: PRISMA Diagram of Systematic Review.

Figure 3: Distributions of times from symptom onset to detection of antibodies against MERS, SARS-CoV-1 and SARS-CoV-2.

Figure 4: MERS-CoV antibody kinetics.

Figure 5: Antigenic and phylogenetic relationships among HCoV.

Figure 6: A diagrammatic summary of evidence supporting (red) and contradicting (blue) the contributions of antibodies to pathogenesis.

Figure 7: Age-seroprevalence curves for the studies with appropriate, digitizable data on endemic HCoV.

Figure 8: Age-incidence curves for studies with appropriate, digitizable data on endemic HCoV.

Figure 9: Seroprevalence (shaded area, scale indicated by right y-axis) and seroincidence (lines, scale indicated by left y-axis) curves by age for a single strain for four hypothetical models of coronavirus immunity.

Main Text Table Titles

Table 1: Percentage of patients that had detectable antibodies, at different time points post infection, for HCoV-229E and MERS-CoV.

Supplementary Figure Titles

Figure S1: **Cumulative proportion of patients that seroconverted.**

Figure S2: **Antibody time series reported in studies in units of optical density (OD).**

Figure S3: **Antibody time series reported in studies in units of titers.**

Supplementary Table Titles

Table S1: **Summary of serological Assays**

Table S2: **Summary of studies on the kinetics of antibody immunity after infection, and for the association of antibody responses with disease severity.**

Table S3: **Severity ratings used in the studies, and the corresponding standardisations.**

Table S4: **Summary of studies on correlates of antibody immunity and protection against CoVs infection.**

Table S5: **Summary of studies on antigenic diversity, cross-reactivity.**

Table S6: **Summary of immunopathogenesis.**

Table S7: **Summary of studies on population-level seroprevalence of CoV.**

Table S8: **Estimated annual force of infection from digitized age-seroprevalence data for endemic HCoVs.**

Supplementary Data Titles

Supplementary Data S1: **Data digitized on antibody kinetics and association of antibody responses with clinical severity.**

Supplementary Data S2: **Data digitized on cross-reactivity and antigenic diversity.**

Supplementary Data S3: **Data digitized on population seroprevalence.**

References

1. Chinazzi, M. *et al.* The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science* (2020) doi:10.1126/science.aba9757.
2. Read, J. M., Bridgen, J. R. E., Cummings, D. A. T., Ho, A. & Jewell, C. P. Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions. doi:10.1101/2020.01.23.20018549.
3. Kucharski, A. J. *et al.* Early dynamics of transmission and control of COVID-19: a mathematical modelling study. *Lancet Infect. Dis.* (2020) doi:10.1016/S1473-3099(20)30144-4.
4. Casadevall, A. & Pirofski, L.-A. The convalescent sera option for containing COVID-19. *J. Clin. Invest.* **130**, 1545–1548 (2020).
5. Godlee, F. The burning building. *BMJ* m1101 (2020) doi:10.1136/bmj.m1101.
6. Baker, R. E., Yang, W., Vecchi, G. A., Metcalf, C. J. E. & Grenfell, B. T. Susceptible supply limits the role of climate in the COVID-19 pandemic. doi:10.1101/2020.04.03.20052787.
7. Kissler, S. M., Tedijanto, C., Goldstein, E., Grad, Y. H. & Lipsitch, M. Projecting the transmission dynamics of SARS-CoV-2 through the post-pandemic period. *Epidemiology* (2020).
8. Callow, K. A., Parry, H. F., Sergeant, M. & Tyrrell, D. A. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol. Infect.* **105**, 435–446 (1990).
9. Reed, S. E. The behaviour of recent isolates of human respiratory coronavirus in vitro and in volunteers: evidence of heterogeneity among 229E-related strains. *J. Med. Virol.* **13**, 179–192 (1984).
10. Bradburne, A. F., Bynoe, M. L. & Tyrrell, D. A. Effects of a 'new' human respiratory virus in volunteers. *BMJ* vol. 3 767–769 (1967).
11. Tyrrell, D. A. & Bynoe, M. L. CULTIVATION OF A NOVEL TYPE OF COMMON-COLD

VIRUS IN ORGAN CULTURES. *Br. Med. J.* **1**, 1467–1470 (1965).

12. Callow, K. A. Effect of specific humoral immunity and some non-specific factors on resistance of volunteers to respiratory coronavirus infection. *J. Hyg.* **95**, 173–189 (1985).
13. Eyal, N., Lipsitch, M. & Smith, P. G. Human challenge studies to accelerate coronavirus vaccine licensure. *J. Infect. Dis.* (2020) doi:10.1093/infdis/jiaa152.
14. Ferguson, N. M. *et al.* EPIDEMIOLOGY. Countering the Zika epidemic in Latin America. *Science* **353**, 353–354 (2016).
15. Borchering, R. K. *et al.* Impacts of Zika emergence in Latin America on endemic dengue transmission. *Nat. Commun.* **10**, 5730 (2019).
16. He, D. *et al.* Global Spatio-temporal Patterns of Influenza in the Post-pandemic Era. *Sci. Rep.* **5**, 11013 (2015).
17. Peiris, J. S. M. *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* **361**, 1767–1772 (2003).
18. Hens, N. *et al.* Seventy-five years of estimating the force of infection from current status data. *Epidemiol. Infect.* **138**, 802–812 (2010).
19. Chen, X. *et al.* Serology of severe acute respiratory syndrome: implications for surveillance and outcome. *J. Infect. Dis.* **189**, 1158–1163 (2004).
20. Hsueh, P.-R., Huang, L.-M., Chen, P.-J., Kao, C.-L. & Yang, P.-C. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. *Clin. Microbiol. Infect.* **10**, 1062–1066 (2004).
21. Yang, Z. *et al.* Determining SARS sub-clinical infection: a longitudinal seroepidemiological study in recovered SARS patients and controls after an outbreak in a general hospital. *Scand. J. Infect. Dis.* **41**, 507–510 (2009).
22. He, W.-P., Shu, C.-L., Li, B.-A., Zhao, J. & Cheng, Y. Human LINE1 endonuclease domain as a putative target of SARS-associated autoantibodies involved in the pathogenesis of

- severe acute respiratory syndrome. *Chin. Med. J.* **121**, 608–614 (2008).
23. Spanakis, N. *et al.* Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen. *Int. J. Antimicrob. Agents* **44**, 528–532 (2014).
24. Ko, J.-H. *et al.* Serologic responses of 42 MERS-coronavirus-infected patients according to the disease severity. *Diagn. Microbiol. Infect. Dis.* **89**, 106–111 (2017).
25. Hsueh, P.-R. *et al.* Microbiologic characteristics, serologic responses, and clinical manifestations in severe acute respiratory syndrome, Taiwan. *Emerg. Infect. Dis.* **9**, 1163–1167 (2003).
26. Hsueh, P.-R., Huang, L.-M., Chen, P.-J., Kao, C.-L. & Yang, P.-C. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. *Clin. Microbiol. Infect.* **10**, 1062–1066 (2004).
27. Park, W. B. *et al.* Kinetics of Serologic Responses to MERS Coronavirus Infection in Humans, South Korea. *Emerg. Infect. Dis.* **21**, 2186–2189 (2015).
28. Azhar, E. I. *et al.* Evidence for camel-to-human transmission of MERS coronavirus. *N. Engl. J. Med.* **370**, 2499–2505 (2014).
29. Wang, W. L. *et al.* Serological Study of An Imported Case of Middle East Respiratory Syndrome and His Close Contacts in China, 2015. *Biomed. Environ. Sci.* **29**, 219–223 (2016).
30. Al-Abdely, H. M. *et al.* Middle East Respiratory Syndrome Coronavirus Infection Dynamics and Antibody Responses among Clinically Diverse Patients, Saudi Arabia. *Emerg. Infect. Dis.* **25**, 753–766 (2019).
31. Yang, Z. *et al.* Determining SARS sub-clinical infection: a longitudinal seroepidemiological study in recovered SARS patients and controls after an outbreak in a general hospital. *Scand. J. Infect. Dis.* **41**, 507–510 (2009).
32. Hsueh, P.-R., Huang, L.-M., Chen, P.-J., Kao, C.-L. & Yang, P.-C. Chronological evolution

- of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. *Clin. Microbiol. Infect.* **10**, 1062–1066 (2004).
33. Tan, W. *et al.* Viral Kinetics and Antibody Responses in Patients with COVID-19. *medRxiv* (2020).
34. Zhao, J. *et al.* Antibody Responses to SARS-CoV-2 in Patients of Novel Coronavirus Disease 2019. *Preprint with The Lancet* (2020).
35. Van Kerkhove, M. D. *et al.* Transmissibility of MERS-CoV Infection in Closed Setting, Riyadh, Saudi Arabia, 2015. *Emerg. Infect. Dis.* **25**, 1802–1809 (2019).
36. Tang, F. *et al.* Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J. Immunol.* **186**, 7264–7268 (2011).
37. Cao, W.-C., Liu, W., Zhang, P.-H., Zhang, F. & Richardus, J. H. Disappearance of antibodies to SARS-associated coronavirus after recovery. *N. Engl. J. Med.* **357**, 1162–1163 (2007).
38. Liu, W. *et al.* Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *J. Infect. Dis.* **193**, 792–795 (2006).
39. Chan, K. H. *et al.* Serological responses in patients with severe acute respiratory syndrome coronavirus infection and cross-reactivity with human coronaviruses 229E, OC43, and NL63. *Clin. Diagn. Lab. Immunol.* **12**, 1317–1321 (2005).
40. Choe, P. G. *et al.* MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. *Emerg. Infect. Dis.* **23**, 1079–1084 (2017).
41. Cao, W.-C., Liu, W., Zhang, P.-H., Zhang, F. & Richardus, J. H. Disappearance of antibodies to SARS-associated coronavirus after recovery. *N. Engl. J. Med.* **357**, 1162–1163 (2007).
42. Park, W. B. *et al.* Kinetics of Serologic Responses to MERS Coronavirus Infection in Humans, South Korea. *Emerg. Infect. Dis.* **21**, 2186–2189 (2015).

43. Choe, P. G. *et al.* MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. *Emerg. Infect. Dis.* **23**, 1079–1084 (2017).
44. Ko, J.-H. *et al.* Serologic responses of 42 MERS-coronavirus-infected patients according to the disease severity. *Diagn. Microbiol. Infect. Dis.* **89**, 106–111 (2017).
45. Kraaijeveld, C. A., Reed, S. E. & Macnaughton, M. R. Enzyme-linked immunosorbent assay for detection of antibody in volunteers experimentally infected with human coronavirus strain 229 E. *J. Clin. Microbiol.* **12**, 493–497 (1980).
46. Ko, J.-H. *et al.* Serologic responses of 42 MERS-coronavirus-infected patients according to the disease severity. *Diagn. Microbiol. Infect. Dis.* **89**, 106–111 (2017).
47. Okba, N. M. A. *et al.* Sensitive and Specific Detection of Low-Level Antibody Responses in Mild Middle East Respiratory Syndrome Coronavirus Infections. *Emerg. Infect. Dis.* **25**, 1868–1877 (2019).
48. Choe, P. G. *et al.* MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. *Emerg. Infect. Dis.* **23**, 1079–1084 (2017).
49. Al Hosani, F. I. *et al.* Serologic Follow-up of Middle East Respiratory Syndrome Coronavirus Cases and Contacts-Abu Dhabi, United Arab Emirates. *Clin. Infect. Dis.* **68**, 409–418 (2019).
50. Barrow, G. I. *et al.* The effect of intranasal nedocromil sodium on viral upper respiratory tract infections in human volunteers. *Clin. Exp. Allergy* **20**, 45–51 (1990).
51. Hamre, D. & Beem, M. Virologic studies of acute respiratory disease in young adults. V. Coronavirus 229E infections during six years of surveillance. *Am. J. Epidemiol.* **96**, 94–106 (1972).
52. Perlman, S. & Dandekar, A. A. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat. Rev. Immunol.* **5**, 917–927 (2005).
53. Resta, S., Luby, J. P., Rosenfeld, C. R. & Siegel, J. D. Isolation and propagation of a human enteric coronavirus. *Science* **229**, 978–981 (1985).

54. Gerna, G., Passarani, N., Cereda, P. M. & Battaglia, M. Antigenic relatedness of human enteric coronavirus strains to human coronavirus OC43: a preliminary report. *J. Infect. Dis.* **150**, 618–619 (1984).
55. Han, M. G., Cheon, D.-S., Zhang, X. & Saif, L. J. Cross-protection against a human enteric coronavirus and a virulent bovine enteric coronavirus in gnotobiotic calves. *J. Virol.* **80**, 12350–12356 (2006).
56. Gerdes, J. C., Klein, I., DeVald, B. L. & Burks, J. S. Coronavirus isolates SK and SD from multiple sclerosis patients are serologically related to murine coronaviruses A59 and JHM and human coronavirus OC43, but not to human coronavirus 229E. *J. Virol.* **38**, 231–238 (1981).
57. Kaye, H. S., Yarbrough, W. B., Reed, C. J. & Harrison, A. K. Antigenic relationship between human coronavirus strain OC 43 and hemagglutinating encephalomyelitis virus strain 67N of swine: antibody responses in human and animal sera. *J. Infect. Dis.* **135**, 201–209 (1977).
58. Vlasova, A. N. *et al.* Two-way antigenic cross-reactivity between severe acute respiratory syndrome coronavirus (SARS-CoV) and group 1 animal CoVs is mediated through an antigenic site in the N-terminal region of the SARS-CoV nucleoprotein. *J. Virol.* **81**, 13365–13377 (2007).
59. Zhong, X. *et al.* B-cell responses in patients who have recovered from severe acute respiratory syndrome target a dominant site in the S2 domain of the surface spike glycoprotein. *J. Virol.* **79**, 3401–3408 (2005).
60. Cui, J., Li, F. & Shi, Z.-L. Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiol.* **17**, 181–192 (2019).
61. Bisht, H. *et al.* Severe acute respiratory syndrome coronavirus spike protein expressed by attenuated vaccinia virus protectively immunizes mice. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 6641–6646 (2004).

62. Ren, Y. *et al.* A strategy for searching antigenic regions in the SARS-CoV spike protein. *Genomics Proteomics Bioinformatics* **1**, 207–215 (2003).
63. Meyer, B., Drosten, C. & Müller, M. A. Serological assays for emerging coronaviruses: challenges and pitfalls. *Virus Res.* **194**, 175–183 (2014).
64. Grifoni, A. *et al.* A Sequence Homology and Bioinformatic Approach Can Predict Candidate Targets for Immune Responses to SARS-CoV-2. *Cell Host Microbe* **27**, 671–680.e2 (2020).
65. Bradburne, A. F. Antigenic relationships amongst coronaviruses. *Arch. Gesamte Virusforsch.* **31**, 352–364 (1970).
66. Trivedi, S. U. *et al.* Development and Evaluation of a Multiplexed Immunoassay for Simultaneous Detection of Serum IgG Antibodies to Six Human Coronaviruses. *Sci. Rep.* **9**, 1390 (2019).
67. Agnihothram, S. *et al.* Evaluation of serologic and antigenic relationships between middle eastern respiratory syndrome coronavirus and other coronaviruses to develop vaccine platforms for the rapid response to emerging coronaviruses. *J. Infect. Dis.* **209**, 995–1006 (2014).
68. Gao, X. *et al.* Antibody against nucleocapsid protein predicts susceptibility to human coronavirus infection. *J. Infect.* **71**, 599–602 (2015).
69. Kaye, H. S., Ong, S. B. & Dowdle, W. R. Detection of coronavirus 229E antibody by indirect hemagglutination. *Appl. Microbiol.* **24**, 703–707 (1972).
70. Dijkman, R. *et al.* Human coronavirus NL63 and 229E seroconversion in children. *J. Clin. Microbiol.* **46**, 2368–2373 (2008).
71. Dijkman, R. *et al.* The dominance of human coronavirus OC43 and NL63 infections in infants. *J. Clin. Virol.* **53**, 135–139 (2012).
72. Lehmann, C. *et al.* A line immunoassay utilizing recombinant nucleocapsid proteins for detection of antibodies to human coronaviruses. *Diagn. Microbiol. Infect. Dis.* **61**, 40–48 (2008).

73. Che, X.-Y. *et al.* Antigenic cross-reactivity between severe acute respiratory syndrome-associated coronavirus and human coronaviruses 229E and OC43. *J. Infect. Dis.* **191**, 2033–2037 (2005).
74. Liang, F.-Y. *et al.* Immunoreactivity characterisation of the three structural regions of the human coronavirus OC43 nucleocapsid protein by Western blot: implications for the diagnosis of coronavirus infection. *J. Virol. Methods* **187**, 413–420 (2013).
75. Patrick, D. M. *et al.* An Outbreak of Human Coronavirus OC43 Infection and Serological Cross-reactivity with SARS Coronavirus. *Can. J. Infect. Dis. Med. Microbiol.* **17**, 330–336 (2006).
76. Chan, K.-H. *et al.* Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests. *J. Infect.* **67**, 130–140 (2013).
77. Aburizaiza, A. S. *et al.* Investigation of anti-middle East respiratory syndrome antibodies in blood donors and slaughterhouse workers in Jeddah and Makkah, Saudi Arabia, fall 2012. *J. Infect. Dis.* **209**, 243–246 (2014).
78. Yu, Y. *et al.* Children's vaccines do not induce cross reactivity against SARS-CoV. *J. Clin. Pathol.* **60**, 208–211 (2007).
79. Trivedi, S. U. *et al.* Development and Evaluation of a Multiplexed Immunoassay for Simultaneous Detection of Serum IgG Antibodies to Six Human Coronaviruses. *Sci. Rep.* **9**, 1390 (2019).
80. Du, L., Ma, C. & Jiang, S. Antibodies induced by receptor-binding domain in spike protein of SARS-CoV do not cross-neutralize the novel human coronavirus hCoV-EMC. *The Journal of infection* vol. 67 348–350 (2013).
81. Yu, F. *et al.* Evaluation of inapparent nosocomial severe acute respiratory syndrome coronavirus infection in Vietnam by use of highly specific recombinant truncated nucleocapsid protein-based enzyme-linked immunosorbent assay. *Clin. Diagn. Lab.*

- Immunol.* **12**, 848–854 (2005).
82. Mu, F. *et al.* The expression and antigenicity of a truncated spike-nucleocapsid fusion protein of severe acute respiratory syndrome-associated coronavirus. *BMC Microbiol.* **8**, 207 (2008).
83. He, Y., Zhou, Y., Siddiqui, P., Niu, J. & Jiang, S. Identification of immunodominant epitopes on the membrane protein of the severe acute respiratory syndrome-associated coronavirus. *J. Clin. Microbiol.* **43**, 3718–3726 (2005).
84. Carattoli, A. *et al.* Recombinant protein-based ELISA and immuno-cytochemical assay for the diagnosis of SARS. *J. Med. Virol.* **76**, 137–142 (2005).
85. Rockx, B. *et al.* Structural basis for potent cross-neutralizing human monoclonal antibody protection against lethal human and zoonotic severe acute respiratory syndrome coronavirus challenge. *J. Virol.* **82**, 3220–3235 (2008).
86. Zhu, Z. *et al.* Potent cross-reactive neutralization of SARS coronavirus isolates by human monoclonal antibodies. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 12123–12128 (2007).
87. Yang, Z.-Y. *et al.* Evasion of antibody neutralization in emerging severe acute respiratory syndrome coronaviruses. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 797–801 (2005).
88. Liu, L. *et al.* Natural mutations in the receptor binding domain of spike glycoprotein determine the reactivity of cross-neutralization between palm civet coronavirus and severe acute respiratory syndrome coronavirus. *J. Virol.* **81**, 4694–4700 (2007).
89. He, Y. *et al.* Cross-neutralization of human and palm civet severe acute respiratory syndrome coronaviruses by antibodies targeting the receptor-binding domain of spike protein. *J. Immunol.* **176**, 6085–6092 (2006).
90. Elshabrawy, H. A., Coughlin, M. M., Baker, S. C. & Prabhakar, B. S. Human monoclonal antibodies against highly conserved HR1 and HR2 domains of the SARS-CoV spike protein are more broadly neutralizing. *PLoS One* **7**, e50366 (2012).
91. Tian, X. *et al.* Potent binding of 2019 novel coronavirus spike protein by a SARS

- coronavirus-specific human monoclonal antibody. *Emerg. Microbes Infect.* **9**, 382–385 (2020).
92. Tai, W. *et al.* Recombinant Receptor-Binding Domains of Multiple Middle East Respiratory Syndrome Coronaviruses (MERS-CoVs) Induce Cross-Neutralizing Antibodies against Divergent Human and Camel MERS-CoVs and Antibody Escape Mutants. *J. Virol.* **91**, (2017).
93. Agnihothram, S. *et al.* Evaluation of serologic and antigenic relationships between middle eastern respiratory syndrome coronavirus and other coronaviruses to develop vaccine platforms for the rapid response to emerging coronaviruses. *J. Infect. Dis.* **209**, 995–1006 (2014).
94. Peiris, J. S. M. *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* **361**, 1767–1772 (2003).
95. Ho, M.-S. *et al.* Neutralizing antibody response and SARS severity. *Emerg. Infect. Dis.* **11**, 1730–1737 (2005).
96. Kliks, S. C., Nimmanitya, S., Nisalak, A. & Burke, D. S. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. *Am. J. Trop. Med. Hyg.* **38**, 411–419 (1988).
97. Weiss, R. C. & Scott, F. W. Antibody-mediated enhancement of disease in feline infectious peritonitis: comparisons with dengue hemorrhagic fever. *Comp. Immunol. Microbiol. Infect. Dis.* **4**, 175–189 (1981).
98. Talbot, H. K. *et al.* The pediatric burden of human coronaviruses evaluated for twenty years. *Pediatr. Infect. Dis. J.* **28**, 682–687 (2009).
99. Jaume, M. *et al.* Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent FcγR pathway. *J. Virol.* **85**, 10582–10597 (2011).

100. Yip, M. S. *et al.* Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus. *Viol. J.* **11**, 82 (2014).
101. Yip, M. S. *et al.* Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. *Hong Kong Med. J.* **22**, 25–31 (2016).
102. Fu, Y., Cheng, Y. & Wu, Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: From Mechanisms to Potential Therapeutic Tools. *Viol. Sin.* (2020) doi:10.1007/s12250-020-00207-4.
103. Wang, S.-F. *et al.* Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. *Biochem. Biophys. Res. Commun.* **451**, 208–214 (2014).
104. Yip, M. S. *et al.* Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. *Hong Kong Med. J.* **22**, 25–31 (2016).
105. Cameron, M. J., Bermejo-Martin, J. F., Danesh, A., Muller, M. P. & Kelvin, D. J. Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Res.* **133**, 13–19 (2008).
106. Lin, Y. S. *et al.* Antibody to severe acute respiratory syndrome (SARS)-associated coronavirus spike protein domain 2 cross-reacts with lung epithelial cells and causes cytotoxicity. *Clin. Exp. Immunol.* **141**, 500–508 (2005).
107. Fang, Y.-T. *et al.* Annexin A2 on lung epithelial cell surface is recognized by severe acute respiratory syndrome-associated coronavirus spike domain 2 antibodies. *Mol. Immunol.* **47**, 1000–1009 (2010).
108. Cheng, M. *et al.* Cross-reactivity of antibody against SARS-coronavirus nucleocapsid protein with IL-11. *Biochem. Biophys. Res. Commun.* **338**, 1654–1660 (2005).
109. Yasmon, A., Ibrahim, F., Bela, B. & Sjahrurachman, A. Potential cross-reactivity of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) nucleocapsid (N)-based IgG ELISA assay for plasma samples from HIV-1 positive intravenous drug users (IDUs). *Acta Med. Indones.* **44**, 193–198 (2012).

110. Cavallaro, J. J. & Monto, A. S. Community-wide outbreak of infection with a 229E-like coronavirus in Tecumseh, Michigan. *J. Infect. Dis.* **122**, 272–279 (1970).
111. Sarateanu, D. E. & Ehrengut, W. A two year serological surveillance of coronavirus infections in Hamburg. *Infection* **8**, 70–72 (1980).
112. Shao, X., Guo, X., Esper, F., Weibel, C. & Kahn, J. S. Seroepidemiology of group I human coronaviruses in children. *J. Clin. Virol.* **40**, 207–213 (2007).
113. Severance, E. G. *et al.* Development of a nucleocapsid-based human coronavirus immunoassay and estimates of individuals exposed to coronavirus in a U.S. metropolitan population. *Clin. Vaccine Immunol.* **15**, 1805–1810 (2008).
114. Chan, C. M. *et al.* Examination of seroprevalence of coronavirus HKU1 infection with S protein-based ELISA and neutralization assay against viral spike pseudotyped virus. *J. Clin. Virol.* **45**, 54–60 (2009).
115. Zhou, W., Wang, W., Wang, H., Lu, R. & Tan, W. First infection by all four non-severe acute respiratory syndrome human coronaviruses takes place during childhood. *BMC Infect. Dis.* **13**, 433 (2013).
116. Hovi, T., Kainulainen, H., Ziola, B. & Salmi, A. OC43 strain-related coronavirus antibodies in different age groups. *J. Med. Virol.* **3**, 313–320 (1979).
117. Ukkonen, P., Hovi, T., von Bonsdorff, C. H., Saikku, P. & Penttinen, K. Age-specific prevalence of complement-fixing antibodies to sixteen viral antigens: a computer analysis of 58,500 patients covering a period of eight years. *J. Med. Virol.* **13**, 131–148 (1984).
118. Monto, A. S. & Lim, S. K. The Tecumseh study of respiratory illness. VI. Frequency of and relationship between outbreaks of coronavirus infection. *J. Infect. Dis.* **129**, 271–276 (1974).
119. Schmidt, O. W., Allan, I. D., Cooney, M. K., Foy, H. M. & Fox, J. P. Rises in titers of antibody to human coronaviruses OC43 and 229E in Seattle families during 1975-1979. *Am. J. Epidemiol.* **123**, 862–868 (1986).

120. Walsh, E. E., Shin, J. H. & Falsey, A. R. Clinical impact of human coronaviruses 229E and OC43 infection in diverse adult populations. *J. Infect. Dis.* **208**, 1634–1642 (2013).
121. Falsey, A. R., Walsh, E. E. & Hayden, F. G. Rhinovirus and coronavirus infection-associated hospitalizations among older adults. *J. Infect. Dis.* **185**, 1338–1341 (2002).
122. Falsey, A. R. *et al.* Long-term care facilities: a cornucopia of viral pathogens. *J. Am. Geriatr. Soc.* **56**, 1281–1285 (2008).
123. Gorse, G. J., Donovan, M. M. & Patel, G. B. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. *J. Med. Virol.* **92**, 512–517 (2020).
124. Gaunt, E. R., Hardie, A., Claas, E. C. J., Simmonds, P. & Templeton, K. E. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. *J. Clin. Microbiol.* **48**, 2940–2947 (2010).
125. Leung, G. M. *et al.* Seroprevalence of IgG antibodies to SARS-coronavirus in asymptomatic or subclinical population groups. *Epidemiol. Infect.* **134**, 211–221 (2006).
126. Müller, M. A. *et al.* Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study. *Lancet Infect. Dis.* **15**, 559–564 (2015).
127. Degnah, A. A. *et al.* Seroprevalence of MERS-CoV in healthy adults in western Saudi Arabia, 2011-2016. *J. Infect. Public Health* (2020) doi:10.1016/j.jiph.2020.01.001.
128. Sikkema, R. S. *et al.* Risk Factors for Primary Middle East Respiratory Syndrome Coronavirus Infection in Camel Workers in Qatar During 2013-2014: A Case-Control Study. *J. Infect. Dis.* **215**, 1702–1705 (2017).
129. Alshukairi, A. N. *et al.* High Prevalence of MERS-CoV Infection in Camel Workers in Saudi Arabia. *MBio* **9**, (2018).

130. Khudhair, A. *et al.* Risk Factors for MERS-CoV Seropositivity among Animal Market and Slaughterhouse Workers, Abu Dhabi, United Arab Emirates, 2014-2017. *Emerg. Infect. Dis.* **25**, 927–935 (2019).
131. Wu, J. T. *et al.* Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. doi:10.21203/rs.3.rs-17453/v1.
132. Thanh Le, T. *et al.* The COVID-19 vaccine development landscape. *Nat. Rev. Drug Discov.* (2020) doi:10.1038/d41573-020-00073-5.
133. Jiang, S., Hillyer, C. & Du, L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. *Trends Immunol.* (2020) doi:10.1016/j.it.2020.03.007.
134. Cao, X. COVID-19: immunopathology and its implications for therapy. *Nat. Rev. Immunol.* (2020) doi:10.1038/s41577-020-0308-3.
135. Zhang, W. *et al.* Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg. Microbes Infect.* **9**, 386–389 (2020).
136. Tsao, K.-C. *et al.* False positive antibody results against human T-cell lymphotropic virus in patients with severe acute respiratory syndrome. *J. Med. Virol.* **77**, 331–336 (2005).
137. Chen, X. *et al.* Serology of severe acute respiratory syndrome: implications for surveillance and outcome. *J. Infect. Dis.* **189**, 1158–1163 (2004).
138. Hsueh, P.-R. *et al.* Microbiologic characteristics, serologic responses, and clinical manifestations in severe acute respiratory syndrome, Taiwan. *Emerg. Infect. Dis.* **9**, 1163–1167 (2003).
139. Chan, K.-H. *et al.* Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests. *J. Infect.* **67**, 130–140 (2013).
140. Haynes, L. M. *et al.* Recombinant protein-based assays for detection of antibodies to severe acute respiratory syndrome coronavirus spike and nucleocapsid proteins. *Clin. Vaccine Immunol.* **14**, 331–333 (2007).

141. Viruses, C. S. G. of T. I. C. on T. of & Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology* vol. 5 536–544 (2020).
142. Al-Abdely, H. M. *et al.* Middle East Respiratory Syndrome Coronavirus Infection Dynamics and Antibody Responses among Clinically Diverse Patients, Saudi Arabia. *Emerg. Infect. Dis.* **25**, 753–766 (2019).
143. Alshukairi, A. N. *et al.* Antibody Response and Disease Severity in Healthcare Worker MERS Survivors. *Emerg. Infect. Dis.* **22**, (2016).

Table 1: Proportion of patients that had detectable antibodies, at different time points post symptom onset or infection, for HCoV-229E and MERS-CoV. Results for HCoV-229E are from Kraaijeveld et al.⁴⁶, and report the number of individuals experiencing symptoms of a given severity that had significant antibody rises post infection. Results for MERS-CoV are taken across studies in which a cutoff for the assay being used was provided, and gives the number of patients for which IgG levels were above the respective cutoffs, at different time points (also see Figure 4). For example, at week 26, there were 12 patients with mild symptoms from studies that reported a cutoff, and 8 of those patients had IgG levels above that cutoff. MERS-CoV data were digitised from six studies^{35,40,46,47,142,143}

	Asymptomatic	Mild symptoms	Severe symptoms
HCoV-229E			
3 weeks	20% (1 of 5)	100% (10 of 10)	
MERS-CoV			
13 weeks		67% (10 of 15)	95% (18 of 19)
26 weeks		67% (8 of 12)	100% (10 of 10)
52 weeks		67% (8 of 12)	100% (8 of 8)

Figure 1: Aspects of antibody response included in this review. This figure shows the areas of focus of our review within our conceptualisation of the stages of exposure and infection at which we believe antibody mediated immunity may play a role in the dynamics of SARS-CoV-2. At the individual level (left), antibody response following the first infection/exposure increases and then declines (**Antibody kinetics**). Sometime later individuals may be exposed to SARS-CoV-2 again. They may be protected from infection by their acquired immunity (**Correlates of protection**). Their acquired immunity may also moderate the severity of infection with some possibility that pre-existing immunity may lead to **immunopathogenesis** (relevant to both first and second exposure). These individual-level dynamics aggregate to form the **population-level seroprevalence** (right-top). Measures of seroprevalence may imperfectly measure past exposure to infection due to **antigenic diversity** of future SARS-CoV-2 viruses and **cross-reactivity** of endemic human coronaviruses (HCoVs) with SARS-CoV-2. Measures of seroprevalence may also be inconsistent across times as antibodies-levels within individuals wane.

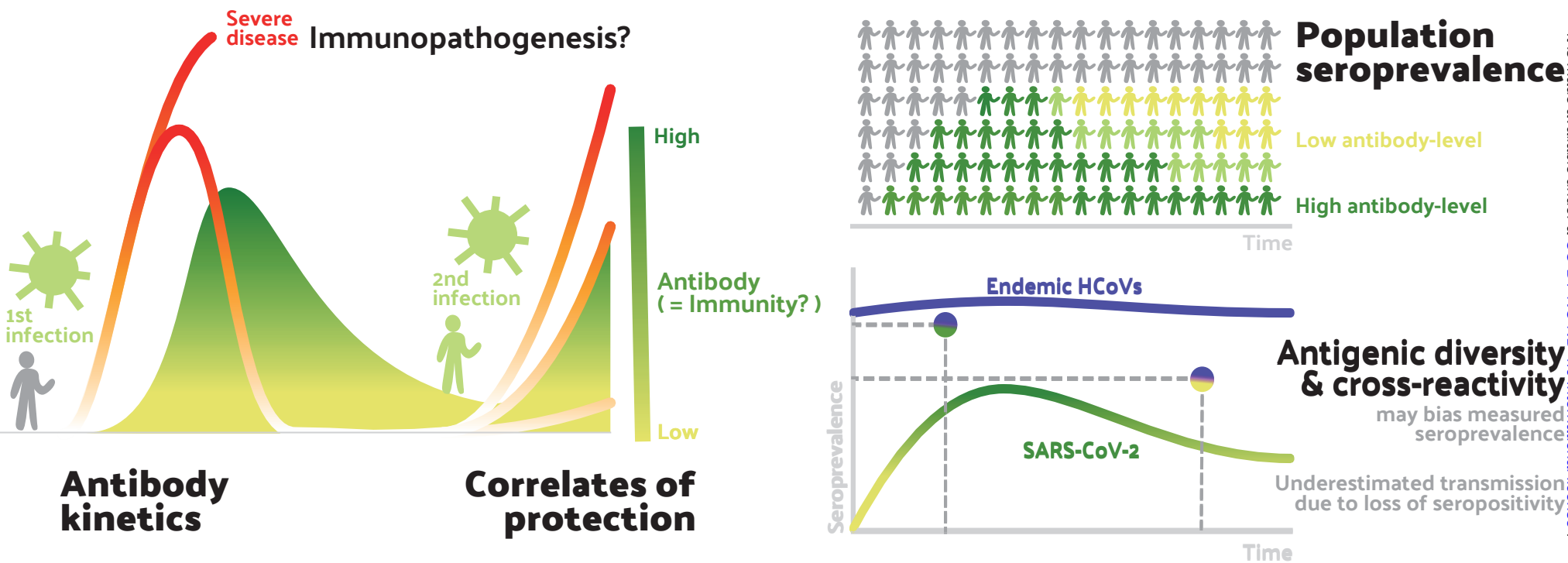


Figure 2: PRISMA diagram of systematic review process

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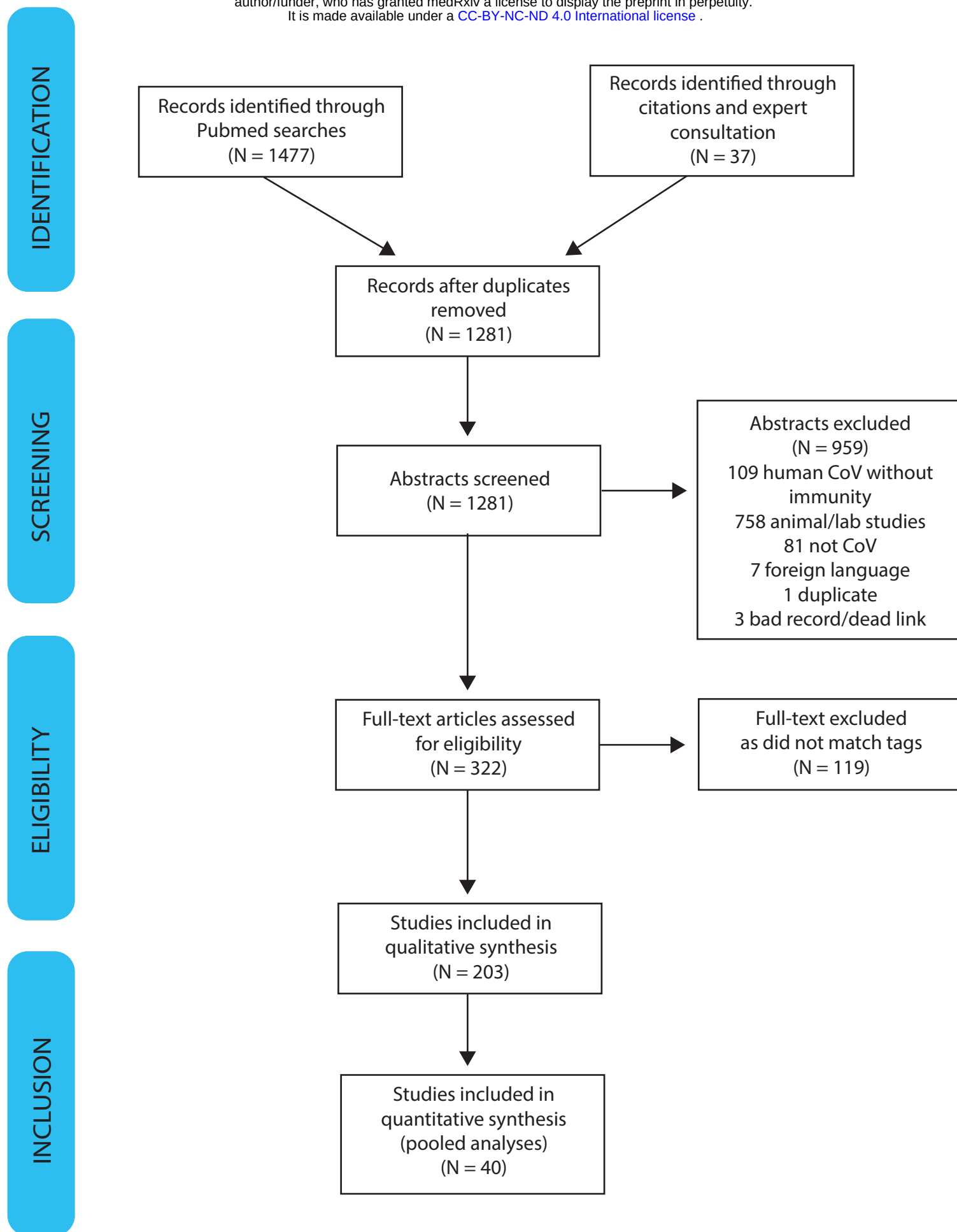


Figure 3: Distributions of times from symptom onset to detection of antibodies against MERS, SARS-CoV-1 and SARS-CoV-2. Times between symptom onset and the detection of IgG (top row), IgM (middle row) and neutralizing antibodies (bottom row). Black vertical lines indicate the median values across all severity ratings, while dashed coloured lines are the median values for mild (blue), severe (orange) illnesses as well as illnesses of unreported severity (grey). Data were digitized from 12 studies^{23,27,29,30,32,34,40,44,135–138}.

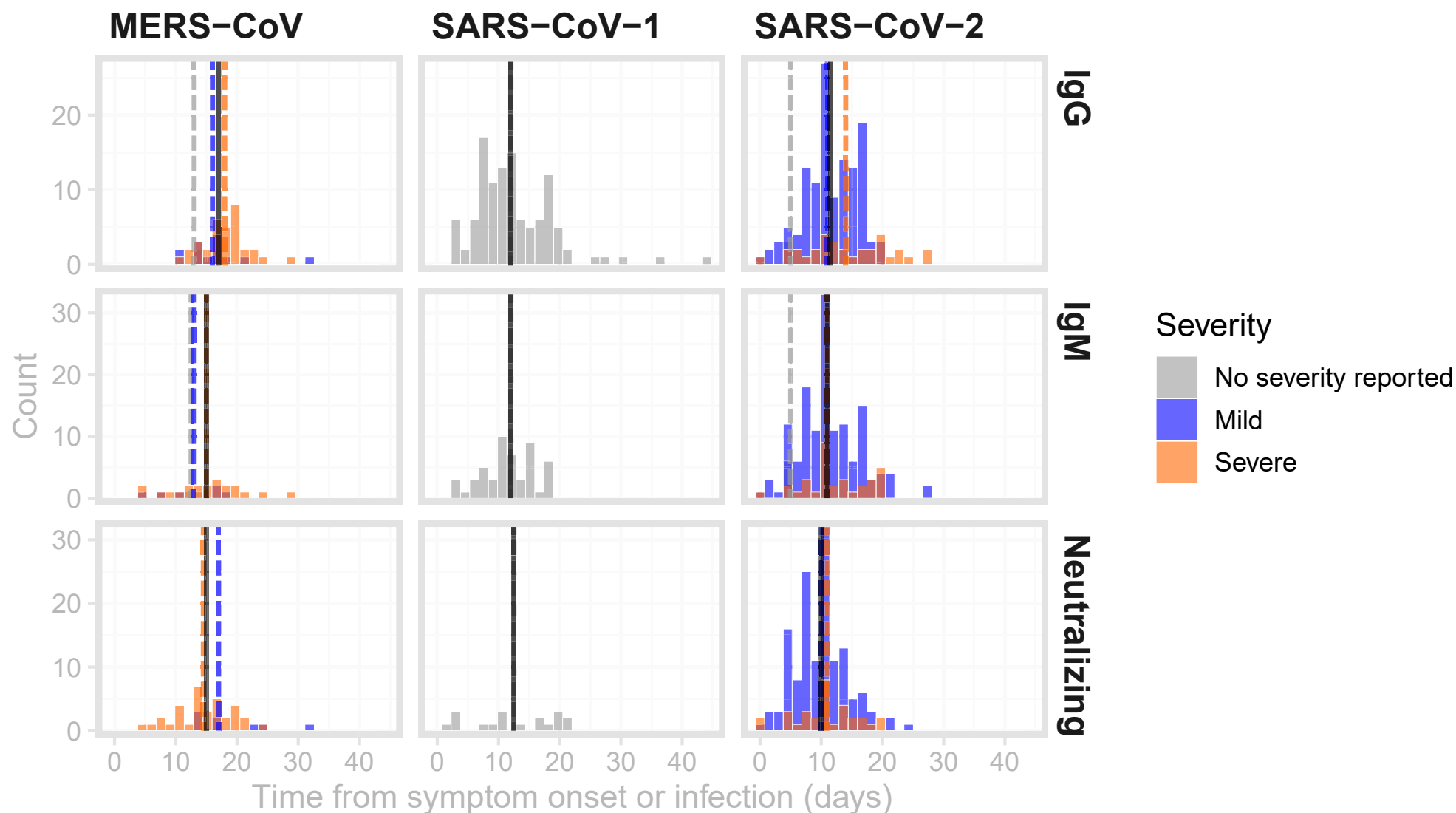


Figure 4: MERS-CoV antibody kinetics. The left panel shows data for studies reporting IgG concentration in units of optical density, while the right panel shows data for studies reporting neutralizing antibodies in units of titers. The plotting symbols indicate whether a measurement was above the cutoff for the assay being used, if reported in the study. Some studies reported titers that were lower than or greater than some threshold value; those are here plotted at those values (e.g., for ≥ 320 , the value is assumed to be 320). Some studies may report kinetics of different antibodies or using different assays (and different units) for the same patient. Note that while these are plotted on the same axes, values may not necessarily be comparable across studies within each panel, as each lab may have different assay conditions resulting in different scales. See Figures S2 and S3 for (more limited) data on SARS-CoV-1 and IgA.

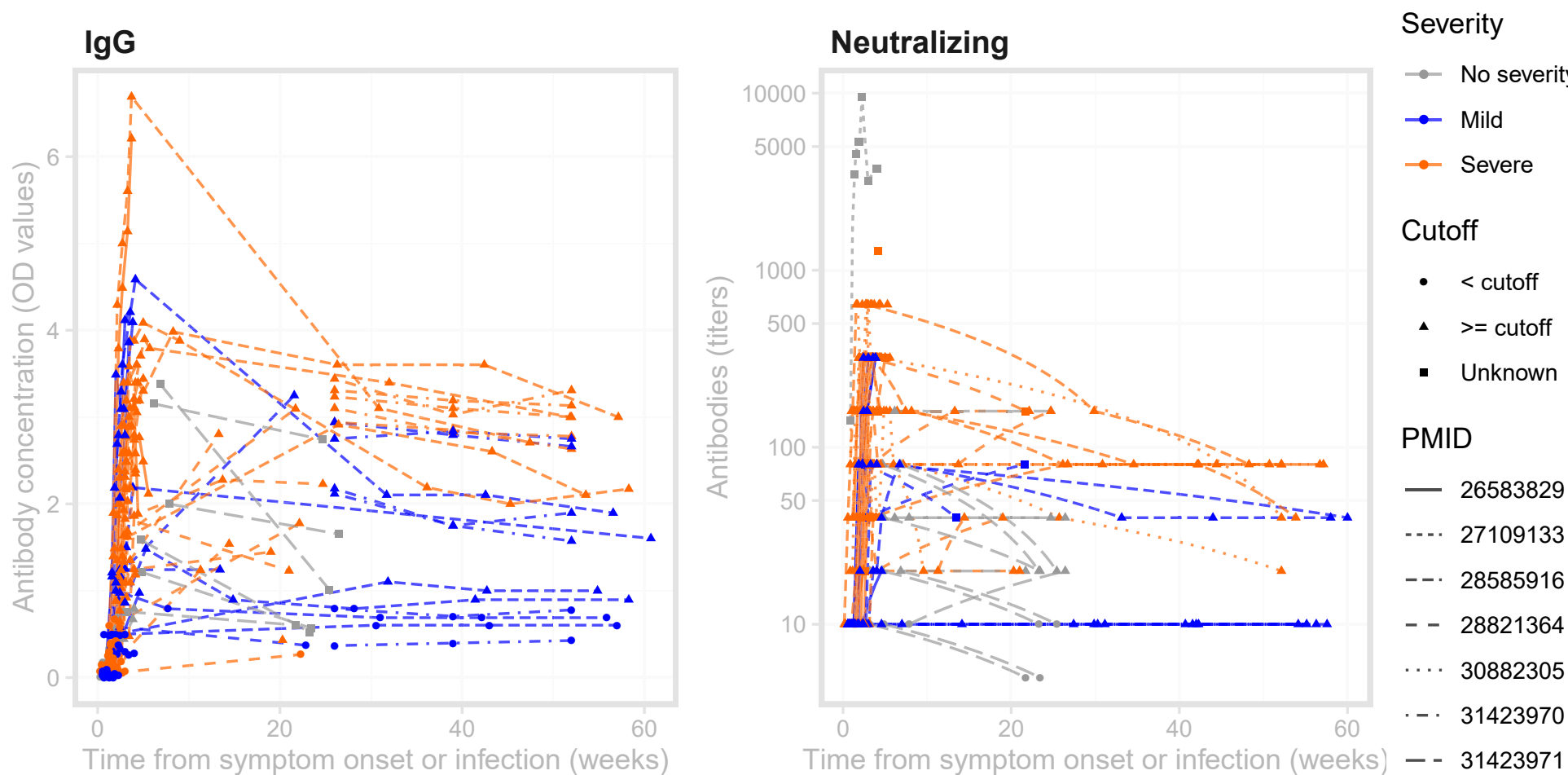


Figure 5: Antigenic and phylogenetic relationships among human coronavirus strains (Top) Read with isopartition (which is taken from individuals) with the confirmed infections of each human coronavirus against a panel of Phas are used and say (circles) for display. It is made available under a CC-BY-NC-ND 4.0 International license. (Bottom) Bracket of reported convalescent-to-acute titer fold-rise upon infection. Data extracted from 7 studies^{39,65,69,72,73,139,140}. Phylogeny modified from¹⁴¹.

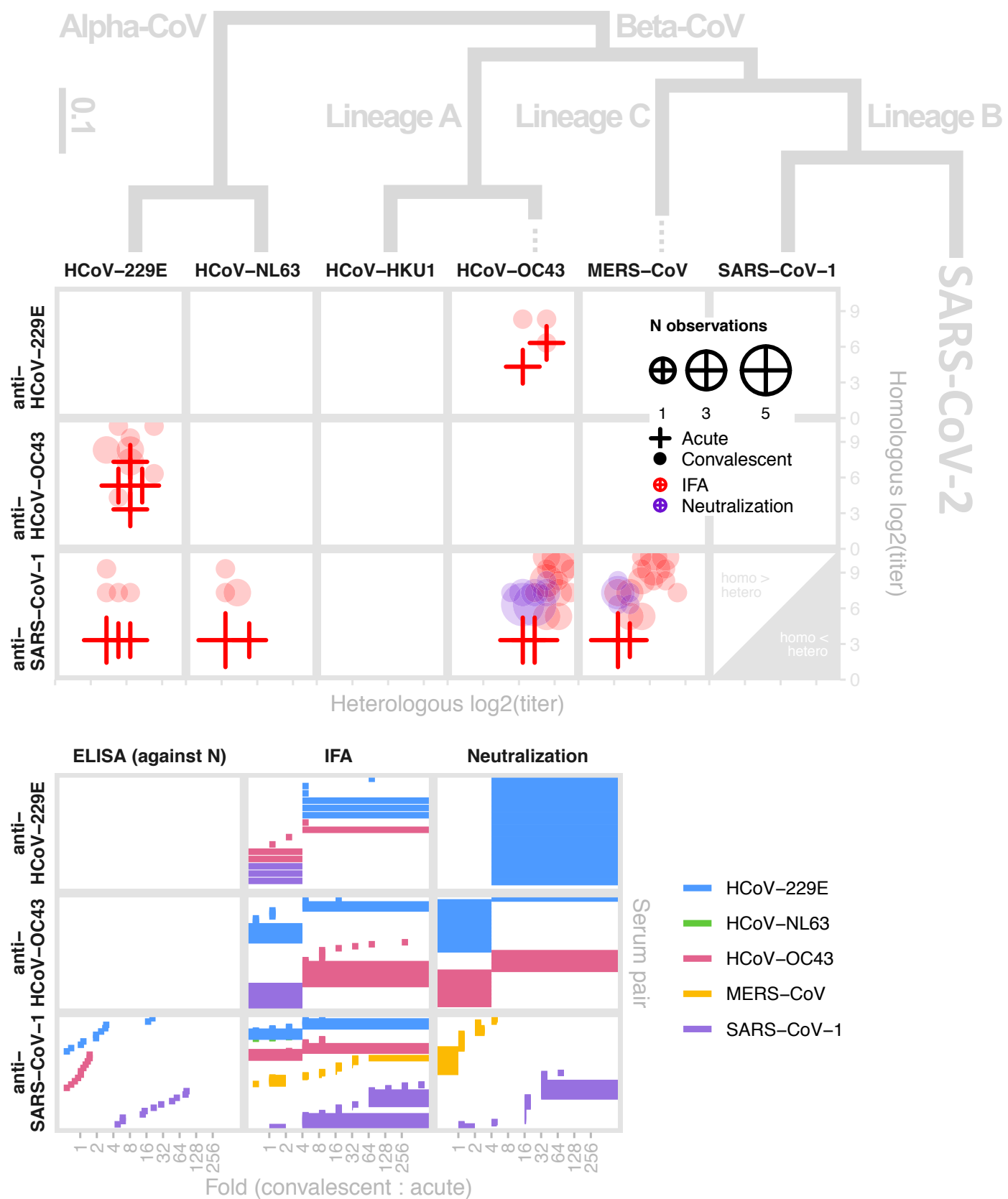


Figure 6: A diagrammatic summary of evidence supporting (red) and contradicting (blue) the contributions of antibodies to the pathogenesis of SARS-CoV-1. Anti-S1 antibodies triggered upon infection may facilitate entry into immune cells at later stages of the infection if concentration is low. Replication happens but no virus is released. Consequential induction of cytokines are inconclusive, but if they occur, they are associated with severe disease. Roles of anti-S2 and anti-N antibodies are supported by binding observations. Items shown in grey are weaker evidence given as speculations in the literature.

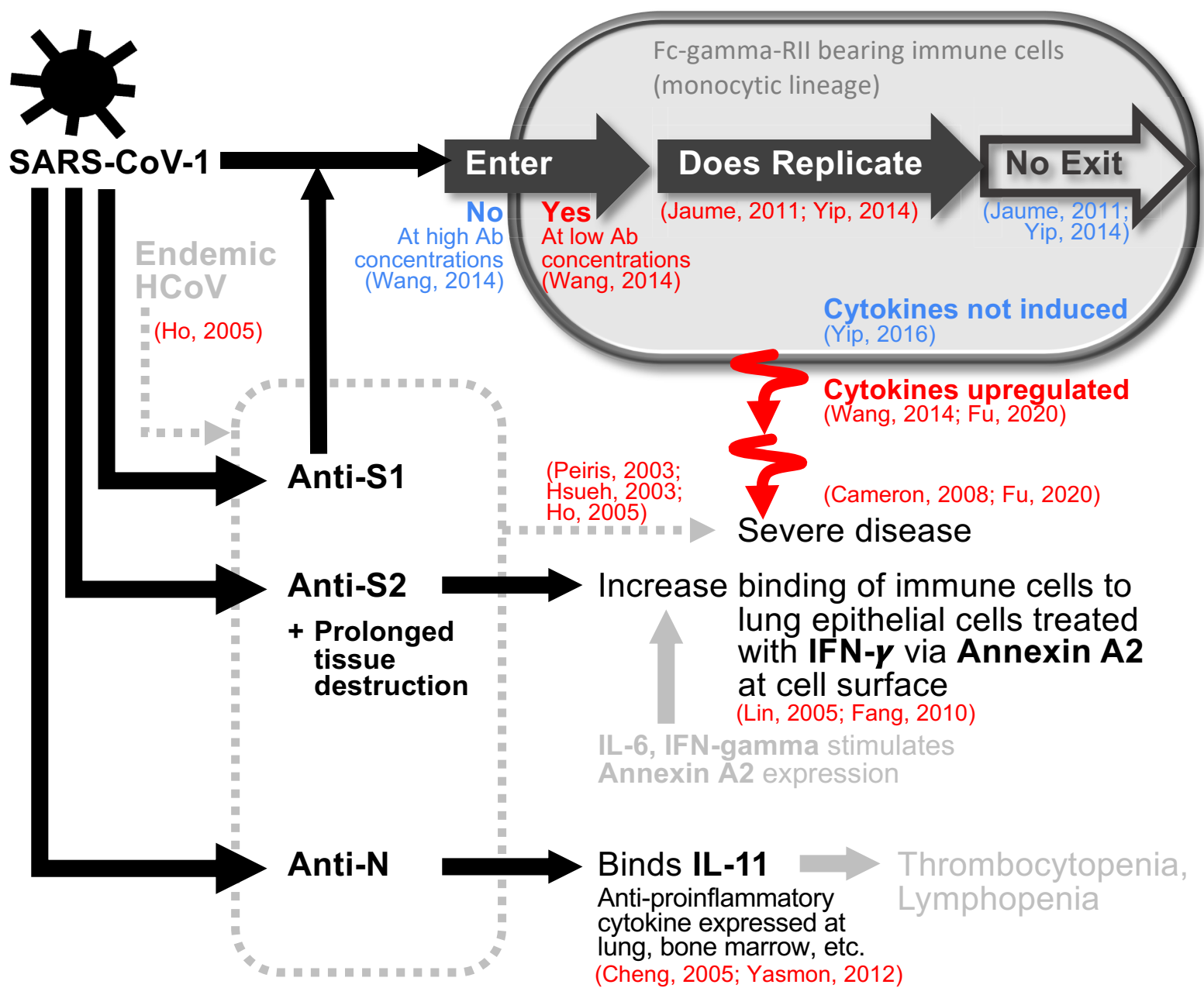


Figure 7: Age-seroprevalence curves for the studies with appropriate, digitizable data on endemic HCoV. The color denotes the study, and the point type denotes the assay and antibody measured. Data from Sarateanu et al is averaged over two serosurveys conducted in 1975 and 1976. Data from Liang et al. were measured in cord blood samples and adults aged 18-25, and do not represent the change in seroprevalence across childhood. Therefore we have not connected these two points with a line.

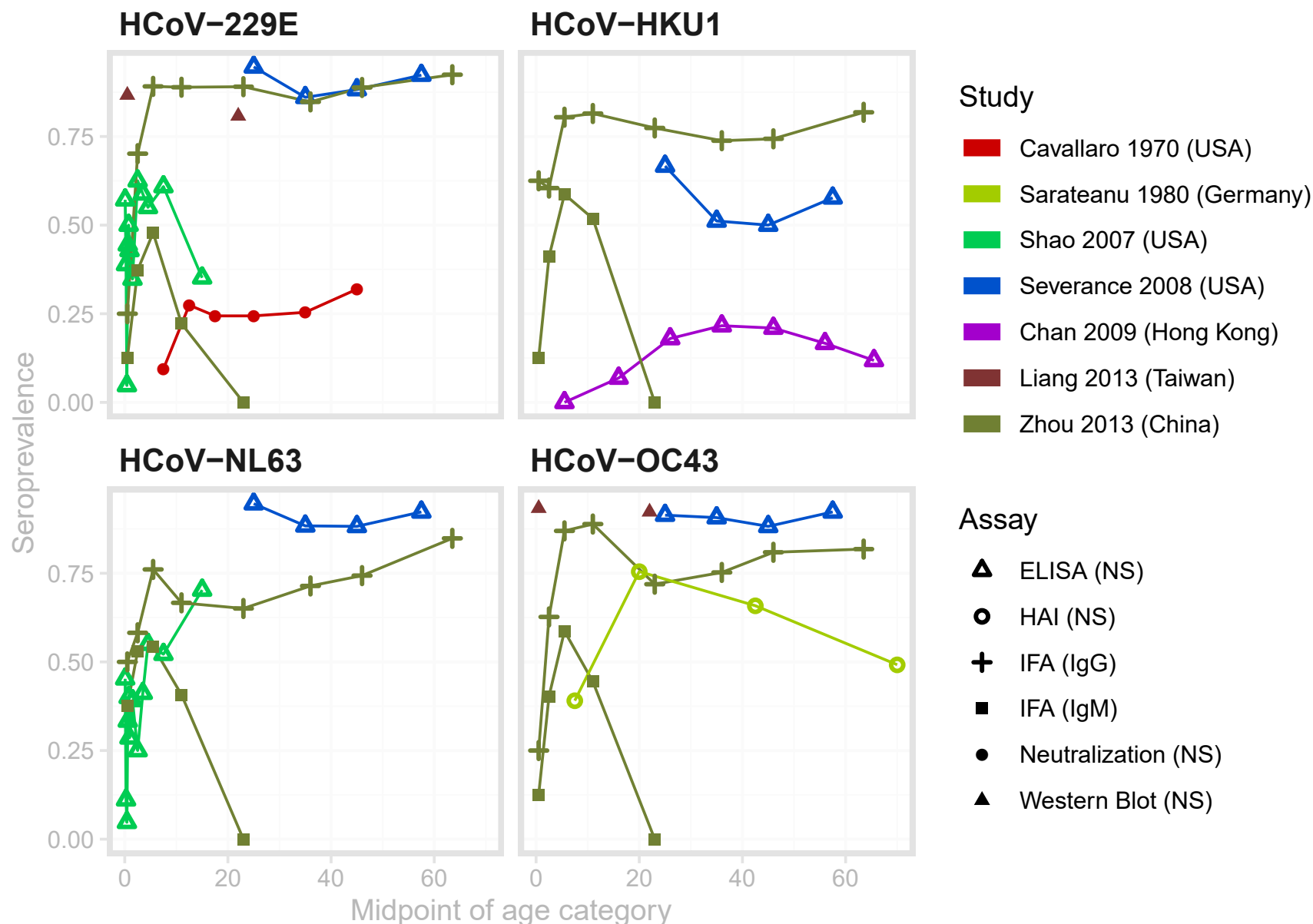


Figure 8: Age-incidence curves for studies with appropriate, digitizable data on endemic HCoV. The color denotes the study, the point type denotes the assay and antibody measured, and the line type represents the number of years between successive serosample

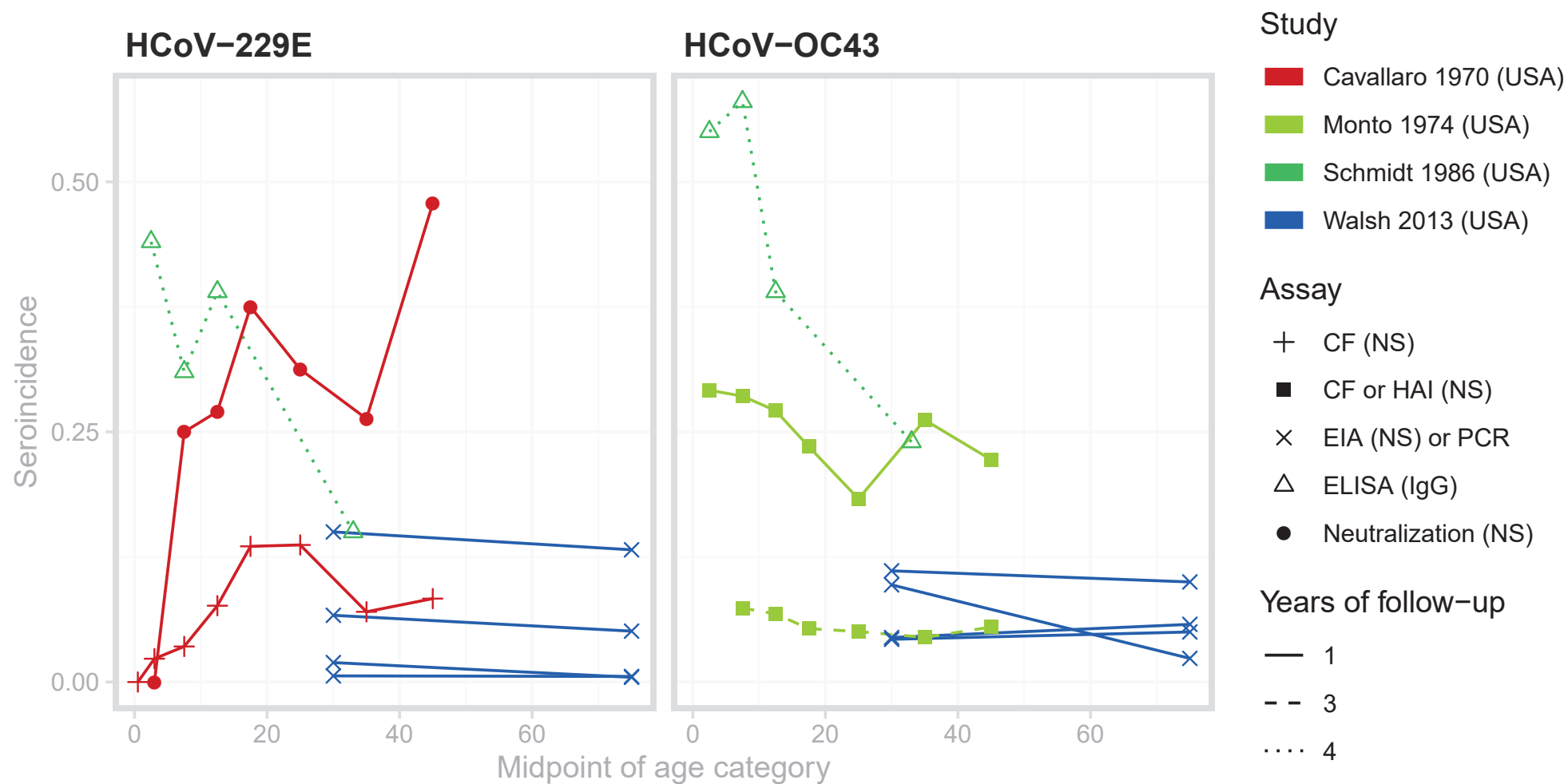
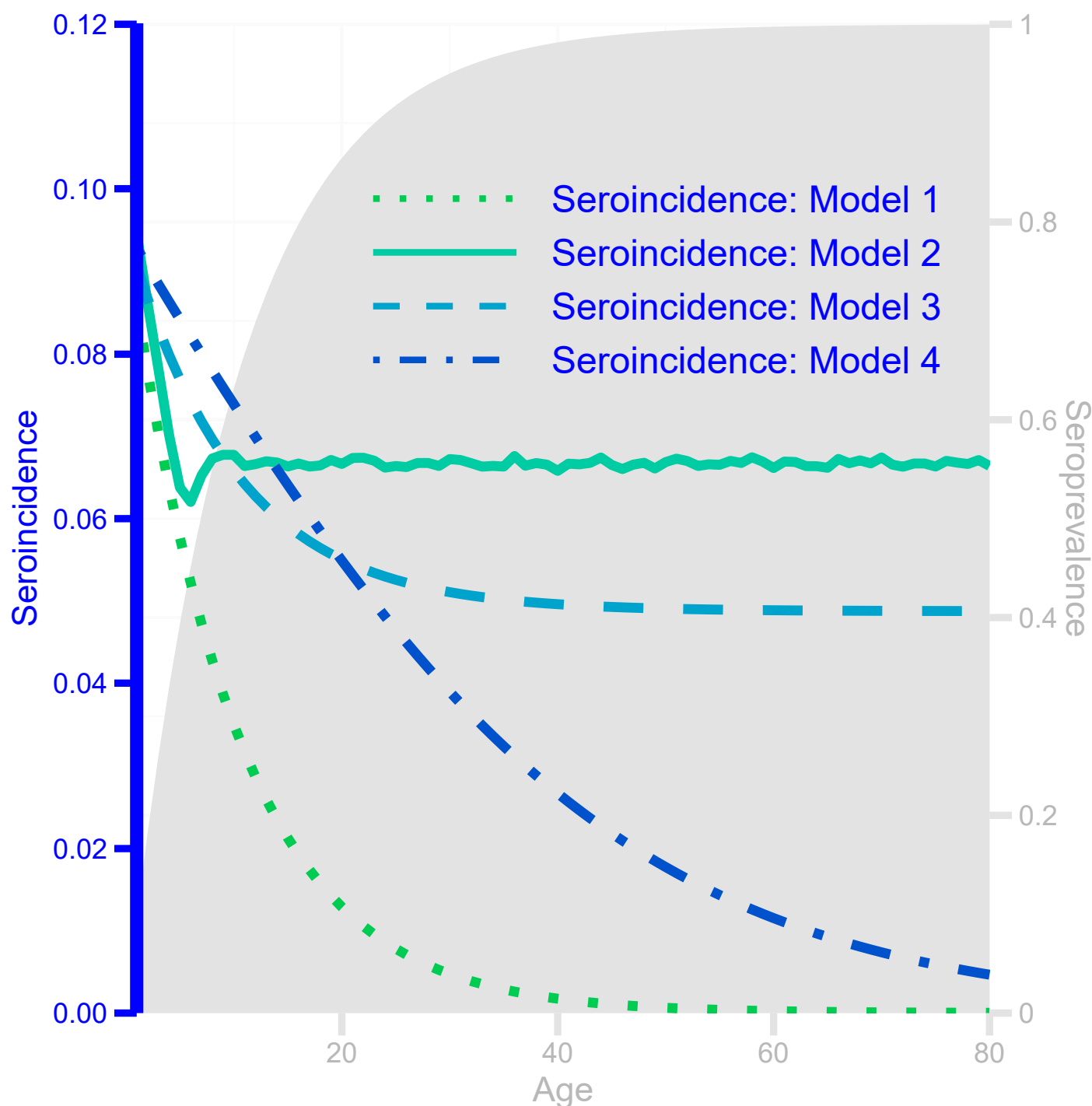


Figure 9: Seroprevalence (shaded area, scale indicated by right y-axis) and seroincidence (lines, scale indicated by left y-axis) curves by age for a single strain for four hypothetical models of coronavirus immunity: complete homologous immunity (Model 1), complete homologous immunity for 5 years, then reversion to full susceptibility (Model 2), partial homologous immunity for life after the first infection (Model 3), and 4 genotypes within a strain, conferring lifelong genotype-specific immunity but no within-strain cross-immunity (Model 4).



Supplementary Appendix

Methods

Data Abstraction

Antibody kinetics and association of antibody responses with clinical severity

We shortlisted papers that met the following criteria for data digitization: (i) antibody responses were provided for at least two distinct points in time and were relative to a point of infection or symptoms onset; or (ii) explicitly discussed severity of symptoms in relation to antibody response. Data could consist of multiple measures of antibody kinetics: serological responses for individual patients (either quantified antibody levels or binary metric of seropositivity), and (cumulative) proportion of a group of patients that was seropositive or had seroconverted at different time points. Most studies used more than one assay and targeted more than one antibody; in these cases, we digitized all the data provided across assays and antibody types. For the pooled-analysis, we excluded studies that summarized antibody responses across patients, but we nonetheless discussed their main findings. Where possible, severity associated with different (groups of) patients were extracted, and standardized (Table S3). Finally, we also digitized cutoff points for the assays when given to define limits of detection or thresholds for positivity and refer to these as limits of detection. When not explicitly stated, but a category defined as less than some value exists, we assumed the value to be the limit of detection (e.g. cutoff of 1:10 is assumed when “<1:10” was present).

Correlates of protection

Studies on correlates of protection targeted for inclusion required a defined exposure, pre-existing antibody level (either antibody concentrations and/or serostatus) and outcomes as either virologically confirmed or serologically confirmed infection.

Cross-protection and antigenic diversity

Instances of human infections with a particular HCoV and titers against itself and the others were summarized. Acute, convalescent and fold rise in titers were digitized as brackets of possible values along with the number of individuals associated with those data points (e.g., a titer reported as 1:160 with the next serial dilution tested at 1:320 could take a value from 1:160 to 1:320). For MERS-CoV and SARS-CoV-1, acute titers were assumed to be the lowest reported in that study (either <1:10 or <1:20) as prior exposure was unlikely (Leung et al. 2006; Degnah et al. 2020). If not reported, fold rises were calculated using lower ends of both time points. If measurements included the lowest reported we assumed a titer of 5 to avoid having a zero as the denominator. All data points are accompanied by the type of test/assay performed.

Population seroprevalence

We determined papers which reported the number of positive tests out of the number sampled in at least two age groups in a population (by seroconversion with/without symptoms or PCR-confirmed symptomatic infections) if sampling was performed independently of symptoms.

Data extracted from text, tables, or figures includes: strain/virus tested for; whether seropositivity, seroconversion, or incidence was measured; time period of study for seroincidence studies; assay type; target antigen; cut-point for defining

seropositivity/seroconversion; bounds of age category; number of samples; number of positive samples. In plotting the data, if the upper bound of the highest age category could not be identified, we assumed it was 20 years above the lower bound based on inspection of the highest age categories in other studies.

For diagnostic serological assays and immunopathogenesis, we compiled and summarized findings from the categories without data extraction. Data extracted for correlates of protection and antigenic diversity were summarized and visualized without the attempt to draw a pooled conclusion.

Supplementary Table 1. Summary of Serological Assays

Assay	Antibody Class	Description	Antigen	Limitations/Comments
Enzyme Linked Immunosorbent Assay (ELISA)	Detects IgG, IgM, IgA	Measures intensity of enzyme-mediated signal of antibody bound to viral antigen.	Viral sub-component or whole virus	Seroconversion not until week 2. Useful for confirming cases that are PCR negative. Cross reactivity with respiratory coronaviruses
Indirect Immunofluorescence Assay (IFA)	Detects IgG, IgM, IgA	Measures fluorescent activity of antibody bound to viral antigen.	Viral sub-component or whole virus	Compares well with WB and Immunodot, but more expensive. Prone to subjective interpretation, requires BSL3
Western Blot (WB)	Detect IgG, IgM, IgA	Measures presence of antibody-virus antigen complexes through size exclusion.	Viral sub-component or whole virus	Useful for confirming cases. Synthetic peptides offer improved specificity. Also known as immunoblotting.
Complement fixation (CF)	Aggregate activity	Measures inhibition of a fixed amount of complement to lyse cells by uptake of complement by antibody-virus complexes.	Whole virus	Human sera express an inhibitor mimicking some plaquing factors, leading to false positives. Antibody detected may be time dependent
Hemagglutination Inhibition (HI)	Aggregate activity	Measures interference of virus-red blood cell binding by antibody binding of virus.	Whole virus	Potential for false positives. Relatively quick, simple, inexpensive.
Neutralization	Aggregate activity	Measures ability of sera to inhibit viral entry and replication.	Whole virus	Gold standard and used often for confirmatory testing. Labor-intensive, expensive, requires BSL3

Supplementary Table 2. Summary of studies on the kinetics of antibody immunity after infection, and for the association of antibody responses with disease severity.

PMID, Author, Year Published	Year of study	Country/Region	Study type	Participants	Virus	Key findings
6262459 Riski and Hovi, 1980	1977 - 1980	Finland	Prospective	Patients with suspected viral infections (n=14,000)	HCoV-OC43	● Suggestive association between high titer to HCoV-OC43 and disease other than common cold, including pneumonia. ● Patients with high or decreasing titer to HCoV-OC43 antibodies could also develop other diseases, including pneumonia.
6252244 Kraaijeveld et al., 1980	Appx 1980	United Kingdom	Challenge experiment	Adults (n=15)	HCoV-229E	● Significant antibody rises correlated well with symptoms, clinical score, and virus shedding.
2170159 Callow et al., 1990	1990	United Kingdom	Challenge experiment	Adults (n=15)	HCoV-229E	● IgG and IgA antibody levels increased after day 8 in 10 infected individuals. ● IgG and IgA peaked, on average, on day 14. ● IgG and IgA waned but were detectable after 1 year.
24896817 Azhar et al., 2014	2013	Saudi Arabia	Case report	Confirmed case (n=1)	MERS-CoV	● First serum sample collected on day 1 was negative for MERS-CoV.
31423970 Okba et al., 2019	2013	The Netherlands, Qatar, South Korea	Laboratory	Serum from confirmed cases (n=11)	MERS-CoV	● Serum collected on day 14 detected MERS-CoV antibodies. ● IgG antibodies were detectable and maintained in all severe (n=5) and most non-severe (n=6) cases, after one year, though some lacked detectable neutralizing antibodies. ● Antibody responses tended to be higher among severe cases.
27192543 Alshukairi et al., 2016	2014	Saudi Arabia	Retrospective	Survived HCWs (n=9)	MERS-CoV	● Antibodies detected at month 18 in 2 of 9 patients with severe symptoms. ● More variable antibody longevity among patients with milder symptoms.
25288266 Spanakis et al., 2014	2014	Greece	Case report	Confirmed case (n=1)	MERS-CoV	● IgG titers peaked 3 weeks after onset of illness, and declined during weeks 4-5. ● IgM titers remained consistently elevated during weeks 2-5.
26583829 Park et al., 2015	2015	South Korea	Cross-sectional	Confirmed cases (n=17)	MERS-CoV	● Robust antibody responses by week 3 of illness for most patients. ● Delayed antibody responses with the neutralization test were associated with more severe disease.
27109133 Wang et al., 2016	2015	China	Retrospective	Confirmed case (n=1; 52 close contacts)	MERS-CoV	● IgM and IgG levels plateaued at day 15, and neutralizing antibody titer peaked during this time.
28821364 Ko et al., 2017	2015	South Korea	Prospective	Confirmed cases (n=42)	MERS-CoV	● No seroconversion among asymptomatic patients (n=3). ● Seroconversion rate grew with increasing disease severity. ● Symptomatic patients without pneumonia (n=10) had a robust increase in antibody titer by week 3. ● Delayed rise in antibodies among patients with pneumonia that progressed to respiratory failure. ● 75% of deceased patients did not seroconvert by week 3, compared to 0% of survivors.
28585916 Choe et al., 2017	2015	South Korea	Prospective	Confirmed cases (n=11)	MERS-CoV	● Severe cases tended to have higher antibody responses compared to mild cases.

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PMID, Author, Year Published	Year of study	Country/Region	Study type	Participants	Virus	Key findings
30882305 Al-Abdely et al., 2019	2015 - 2016	Saudi Arabia	Prospective	Confirmed cases (n=33)	MERS-CoV	• 5 of 5 patients with severe disease and 2 of 6 patients with mild disease, had detectable antibodies at year 1. • MERS antibodies decreased throughout the 6 months following disease onset. • Antibody titers in 4 of 6 mild cases were undetectable, even if most had pneumonia.
31423971 Van Kerkhove et al., 2019	2015 - 2016	Saudi Arabia	Cross-sectional	Serum from confirmed cases (n=19)	MERS-CoV	• Patients who died (n=6) exhibited robust neutralizing antibody responses by weeks 2-3, but these were Insufficient for recovery. • For all 9 of 19 cases for which a second sample was collected at month 5, IgG antibody levels had waned but were detectable.
14519257 Hsueh et al., 2003	2003	Taiwan	Prospective	Probable cases (n=7)	SARS-CoV-1	• IgG antibodies detected as early as by day 9 in all 6 patients that had detectable antibodies. • Elevated antibody levels lasted from month 1 up to >2 months. • Antibody level plateaued in all patients during days 4-10. • An upsurge of antibody response was associated with the aggravation of respiratory failure.
15030702 Wu et al., 2004	2003	Taiwan	Laboratory	Probable cases (n=138)	SARS-CoV-1	• Antibodies during days 1-7 were detected in 10% (14 of 138) of probable patients. • Proportion of patients that tested positive was 50% at week 3, and peaked at over 70% at week 10.
15031782 Chen et al., 2004	2003	China	Prospective	Probable cases (n=36)	SARS-CoV-1	• Appearance of IgM and IgG ranged from 3-42 and 5-47 days, respectively. • 5.6% of probable infections were still positive for IgG, but negative for IgM up until day 60.
16173022 Tsao et al., 2005	2003	Taiwan	Laboratory	Probable cases (n=26)	SARS-CoV-1	• Antibody titers in five patients were high after 100 days of disease onset.
16275947 Chan et al., 2005	2003	Hong Kong	Prospective	Confirmed cases (n=20)	SARS-CoV-1, HCoV-OC43, 229E	• IgM still detectable in 8 of 11 patients at month 7. • IgGAM and IgG remained stable over the same period. • No significant difference in the kinetics of antibody responses between patients that survived or died.
18466680 He et al., 2008	2003	China	Laboratory	Confirmed cases (n=22)	SARS-CoV-1	• Most sera became positive by day 7. • Inconclusive for differences in antibody responses between recovered and died cases.
17517191 Liao et al., 2007	2003 - 2004	China	Retrospective	Confirmed cases (n=18; including 4 reemerging cases)	SARS-CoV-1	• Neutralizing antibody titers for 14 cases remained high between days 17-181. • Neutralizing antibody titers for all 4 reemerging SARS cases peaked within 11-13 days then rapidly dropped.
17855683 Cao et al., 2007	2003 - 2006	China	Prospective	Confirmed cases (n=56)	SARS-CoV-1	• Titers peaked at month 4. • 100% of participants were seropositive until month 16.

Supplementary Table 2. Summary of studies on the kinetics of antibody immunity after infection, and for the association of antibody responses with disease severity.

PMID, Author, Year Published	Year of study	Country/Region	Study type	Participants	Virus	Key findings
15606632 Hsueh et al., 2004	2004	Taiwan	Laboratory	Confirmed cases (n=30)	SARS-CoV-1	● IgG and neutralizing antibodies were undetectable in 19.4% and 11.1% of serum samples, respectively, at month 30, and in 25.8% and 16.1%, respectively, at month 36. ● Patients with subsequent aseptic femoral neck necrosis had significantly lower neutralizing antibody levels than those without the sequela. ● IgG, IgM, and IgA were detectable for at least 19 days. ● On average it took 15 days for all three antibodies to peak. ● Levels of IgA and IgM waned during weeks 3-4, remaining low on month 3. ● IgG remained positive for > 28 days.
19396666 Yang et al., 2009	2004 – 2006 ?	China	Prospective	Confirmed cases (n=67)	SARS-CoV-1	● 7.7% of samples were positive for IgM after 1 week. ● IgM antibodies peaked at month 1 and had a higher positive rate than IgG during this period, followed by a gradual decrease. ● IgG levels peaked after week 25, and slowly declined but remained detectable at week 83.
21576510 Tang et al., 2011	2020?	China	Prospective	Confirmed cases (n=23; 22 close contacts)	SARS-CoV-1	● 2 of 23 patients maintained low levels of IgG at year 6. ● 1 patient's IgG antibodies were high after being discharged from the hospital, but decreased substantially by month 72. ● Another patient's IgG antibody remained low but stable.
32065057 Zhang et al., 2020	2020	China	Laboratory	Confirmed cases (n=16)	SARS-CoV-2	● Increase in antibodies was detected in nearly all patients by day 5. ● 81% (13 of 16) of patients were IgM positive by day 5. ● 100% (16 of 16) were IgG positive by day 5.
Zhao et al., 2020	2020	China	Prospective	Confirmed cases (n=173)	SARS-CoV-2	● Antibody levels increased rapidly during the first 2 weeks. ● Cumulative seroconversion reached 100% for IgG and neutralizing antibodies at around month 1. ● Seroconversion of neutralizing antibodies was significantly quicker than that of IgM and IgG (possibly also due to the assay used).
Tan et al., 2020	2020	China	Prospective	Confirmed cases (n=67)	SARS-CoV-2	● Positive rate for IgM peaked at 57.1% by day 28, and declined to 33.3% at day 42. ● Positive rate for IgG reached 74.3% by day 28 and increased to 86.7% at day 42. ● Results suggest that antibody response may be associated with disease severity.

Supplementary Table 3. Severity ratings used in the studies, and the corresponding standardizations

PMIDs	Severity rating used in study	Standardized rating ¹
Kraaijeveld et al. 1980; Alshukairi et al. 2016	Asymptomatic	Asymptomatic
Okba et al. 2019; Park et al. 2015; Kraaijeveld et al. 1980	Mild	Mild
Kraaijeveld et al. 1980	Moderate (HCoV-229E)	
Abbasi et al. 2018	Group 1: Mild - no pneumonia	
Alshukairi et al. 2016	Upper respiratory tract infection	
Choe et al. 2017; Tan et al. 2020	Non-severe	
Zhao et al. 2020	Non-critical	
Al-Abdely et al. 2019	Group 1: Received air throughout hospitalization	Severe
Al-Abdely et al. 2019	Group 2: Required ventilator support and survived	
Al-Abdely et al. 2019	Group 3: Required ventilator support and died	
Abbasi et al. 2018	Group 2: Medium - pneumonia, no respiratory failure	
Abbasi et al. 2018	Group 3: Severe - pneumonia and respiratory failure	
Alshukairi et al. 2016	Severe pneumonia	
Okba et al. 2019; Choe et al. 2017; Tan et al. 2020	Severe	
Park et al. 2015	Severe, requiring supplemental oxygen therapy	
Park et al. 2015	Severe, requiring mechanical ventilation	
Zhao et al. 2020	Critical	

¹ We define “mild” as symptomatic cases not requiring hospitalization, and “severe” as symptomatic cases requiring hospitalization. We necessarily made assumptions on what conditions may have likely required hospitalization, e.g., we assume a participant with pneumonia due to a viral infection (and who has been included in these studies) is more likely to have been hospitalized than not.

Supplementary Table 4. Summary of studies on correlates of antibody immunity and protection against CoV infection.

PMID Author and Year	Year of study	Country/ Region	Study type	Participants	Virus	Key findings
2991366 (Callow 1985)	NA	UNITED KINDOM	Challenge experiment	Adults (n=33)	HCoV-229E	• Individuals who seroconverted to 229E (defined as a 1.5 or higher rise in ELISA IgG serum antibodies) had significantly higher serum IgG and neutralizing antibodies as well as nasal IgA. • Serum and mucosal IgA were associated with the duration of viral shedding post experimental infection, with those shedding for 5 days or more having statistically significantly less mucosal IgA than those shedding less than 5 days (0.6 ng/ml versus 4.7 ng/ml, $p<0.01$). • Serum neutralizing antibody was not statistically significantly associated with the duration of viral shedding. • Protective associations of pre-infection serum neutralizing antibody, serum IgG and nasal IgA with clinical severity scores and nasal secretion weights (a measure of severity of rhinorrhea symptoms)
2170159 Callow et al., 1990	NA	United Kingdom	Challenge experiment	Adults (n=15)	HCoV-229E	• Volunteers who were infected had lower pre-existing antibodies. • All 5 uninfected volunteers were infected and showed symptoms during the re-infection challenge one year later. • 6 of 9 infected volunteers were re-infected without developing into colds during the re-infection challenge one year later.
4626012 Hamre and Beem, 1972	1961-68	United States	Prospective	Medical students (n=12)	HCoV-229E	• 67% (8 of 12) of students with virus isolation had detectable pre-season neutralizing antibodies. • 25% (3 of 12) of medical students who seroconverted to 229E had detectable pre-season neutralizing antibodies. • Pre-season neutralizing antibody level inversely associated with the frequency of significant increase in neutralizing antibody titer after re-infection. • No association between pre-season neutralizing antibody and reinfection determined by CF seroconversion.
6262459 Riski and Hovi, 1980	1977-80	Finland	Prospective	Probable cases (n=28)	HCoV-OC43	• Detectable pre-existing CF antibodies were found in 64% (18 of 28) of people who had common cold/pneumonia and increased CF antibodies. • Patients with high pre-existing antibodies or decreasing titer to OC43 antibodies could also develop other respiratory diseases, including pneumonia.
18495857 Dijkman et al., 2008	2004	The Netherlands	Prospective, cross-sectional	Newborns and children (n=13 longitudinally; 139 cross- sectionally)	HCoV-NL63, HCoV-229E	• All (n = 13) newborns had maternal antibodies to NL63 and 229E at birth, which disappeared within 3 months. • 53.8% and 13.4% of the newborns seroconverted to NL63 and 229E, respectively. • All newborns who later had seroconversion had low pre-infection antibodies. • 75% and 65.0% of the children aged 2.5 to 3.5 years were NL63 and 229E seropositive, respectively.

Supplementary Table 4. Summary of studies on correlates of antibody immunity and protection against CoV infection.

PMID Author and Year	Year of study	Country/ Region	Study type	Participants	Virus	Key findings
6319590 Reed	1984	United Kingdom	Challenge experiment	Adults (n=18)	HCoV-229E, HCoV-OC43	● Re-challenged (n = 6) volunteers who had been experimentally infected 8-12 months previously. On the first challenge, all 6 developed symptoms and detectable virus and 5 of 6 experienced significant rise in titer. In the second season, 0/6 experienced illness, detectable virus or significant rise in titer. ● Re-challenged (n=12) volunteers with heterologous virus (not identical to first experimental infection) 8-14 months after first infections. 7/12 developed cold symptoms
Cohen	1991	United Kingdom	Challenge experiment	Adults (n=54)	HCoV-229E	● Challenge study focused on psychological-stress and its impact on response to experimental infection with coronavirus. ● Suggested that serological status (having above or below median value) was associated with risk but lacks details broken out for just coronavirus.
Barrow	1990	United Kingdom	Challenge experiment	Adults (n=53)	HCoV-229E	● Found lower proportions of individuals with high neutralizing titer experienced 'significant colds' upon viral challenge than individuals with low titer.

Supplementary Table 5. Summary of studies on antigenic diversity and cross-reactivity

Study	Year of study	Country/ Region	Study type	Participants	Viruses/assay	Key findings
Bradburne 1970	1970	United Kingdom	Human challenge study	volunteers challenged with LP (n=18), 229E (n=20), B814 (n=10), OC43 (n=OC43)	HCoV-229E, LP, B814, OC43, neutralization test	- Volunteers inoculated with LP (n=16/18) or 229E (20/20) experienced a ≥ 4-fold rise in neutralizing antibodies to both viruses. - Individuals inoculated with B814 (n=0/10) or OC43 (n=1/14) did not have a ≥ 4-fold rise to 229E or LP.
Kaye, Ong, and Dowdle 1972	1965-1972	United States	Paired serum in a longitudinal survey of children (=104)	Paired serum in a longitudinal survey of children (=104)	HCoV-OC43, -229E, hemagglutination assay	Of 104 paired serum of children in a longitudinal survey which showed 4-fold seroconversions by indirect hemagglutination assay (IHA), 41 were risen to only HCoV-OC43, 62 to only -229E, and only one that was risen to both.
(Reed 1984)	1974-1976; 1971-1981	United Kingdom	<i>In vitro and human challenge study</i>	Volunteers 18-50 yo (n=18) challenged at approximately one-year with the exact homologous strain	HCoV-229E, LP, and 229E-like strains, -OC43 and related strains	- Recent HCoV-OC43-like strains caused different disease manifestations from -229E-like strains did not induce a rise in antibodies (neutralization or HI) to -229E-like viruses or -OC43. - Endemic circulation of HCoV-229E resulted in higher pre-inoculation neutralizing antibodies of new participants against a lab adapted 229E-like strain and decreased clinical disease. - Study participants (n=18) challenged at approximately one-year with the exact homologous strain (6/6) were protected, while 7/12 challenged with a heterologous 229E-like strain developed symptoms and shed virus.
Dijkman et al. 2008	1999-2003	The Netherlands	Longitudinal serological study	Children born to HIV 1 positive mothers (n=13)	HCoV-NL63 and -229E, ELISA	Longevity of anti-coronavirus antibodies in newborns and cross reactivity. Did not find cross-reactivity between HCoV-NL63 N-direct antibodies and -229E N-direct antibodies.
Dijkman et al. 2012	1993-2012	The Netherlands and United Kingdom	Serological Survey	(n=12 males and n=13 females) born to HIV 1 positive mothers (NL63 and 229E in infants followed 20 months (n=25)) hospitalized infants (n=1471)	ELISA to N protein, NL63 and 229E in infants followed 20 months (n=25) and hospitalized infants (n=1471)	Anti-HCoV-NL63 neutralizing antibodies against the spike protein may partially protect against HCoV-229E but not the vice versa. This is also the case for antibodies to HCoV-OC43 and protection against HCoV-HKU1. This may also account for the higher frequency of

(Lehmann et al. 2008)	2008	Germany	Serological Assay	Acute and convalescent sera (n=6 HCoV-OC43 infection, n=6 HCoV-229E infection) n=25 healthy donor sera n=49 sera from convalescent SARS sera	HCoV-229E, OC43, HKU1, NL63, SARS-CoV-1, developed line immunoassay	HCoV-OC43 and -NL63 among hospitalized infants. Supports cross-reactivity among endemic strains within alpha- and beta-CoVs, but not with SARS-CoV-1 N protein.
(Haynes et al. 2007)	2007	United States	Comparison of serological assay detection of N and S proteins	Baby hamster kidney and n=61 patients from Vietnam and Taiwan SARS-CoV-1 positive	SARS-CoV-1, ELISA	Found false-positive to SARS N/S recombinant ELISA but unknown whether it is due to cross-reactivity with other CoVs or are they just nonspecific reactivity.
(Che et al. 2005)	2003-2005	China	Serological study	n=11 paired serum samples from patients with SARS-CoV-1, n=100 random samples were collected from healthy adult donors, n=34 SARS-CoV-1 patients 8-81 days after onset	SARS-CoV-1, IFA, Western Blot, ELISA	- Only 2/100 healthy donor samples had SARS-CoV nucleocapsid reactivity, as compared to 97% with positivity to HCoV-229E and 99% positivity to HCoV-OC43. - SARS patients (n=34) had strong reactivity to nucleocapsid from HCoV-229E (97%), HCoV-OC43 (100%) and SARS-CoV (100%). Similar trends were observed when instead the samples were tested by IgG responses to CoV-infected cells. 10/11 SARS patients showed >=4-fold rise to HCoV-OC43 and 5/11 to 229E by IFA in paired acute/convalescent samples, but more limited seroconversion to the nucleocapsid of -229E (2/11) and -OC43 (0/11).
(Chan et al. 2013)	2013	Hong Kong	Serological study	Animal handlers (n=94), SARS-CoV-1 patients (n=28), healthy blood donors (n=152)	SARS-CoV-1, IF and neutralization	100% of SARS-CoV-1 patients had IF titers >1:10 and 96.4% had neutralizing titers >1:10 against SARS-CoV-1, while 60.7% had IF titers and 25% had neutralizing antibodies to MERS-CoV. - The proportion of cross-reactivity was lower for animal handlers at high risk of exposure to SARS-like CoVs (SARS-CoV: 13.8% IF >1:10, 4.3% with NT >1:10; MERS-CoV: 2.2% IF >1:10, 0% NT >1:10). - None of the healthy donors had any reactivity to either MERS-CoV or SARS-CoV-1. - Among animal handlers and SARS patients with positivity to MERS-CoV by IF, 7/19 had NT to MERS-CoV. All had high levels

(Chan et al. 2005)	2003-2005	Hong Kong	Serological cohort study	n=20 SARS-CoV-1 patients in the first month of illness. Patients who survived (n=14), patients who died (n=6)	SARS-CoV-1, HCoV-229E, -OC43, -NL63, IFA and neutralization	of NT to OC43. SARS-CoV-1 patients with paired acute/convalescent sera (n=4) experienced seroconversion by (IF and NT) to SARS-CoV; some had positivity by IF to MERS-CoV in either acute (n=1) or convalescent (n=2) samples. All showed >2-fold rise to betacoronavirus OC43 by IF, while only 1 seroconverted to alpha coronaviruses 229E and NL63 by IF. • Infections with HCoV-OC43 and HCoV-229E did not lead to antibodies (acute or convalescent phase) against SARS-CoV by IFA or neutralization. • Total Ig (IgG, IgA, and IgM) and IgG to endemic HCoVs (-229E, -OC43) measured by IF showed a 4-fold rise after SARS-CoV-1 infection in 12/20 patients. A subset also had a rise in antibodies to NL63. • Neutralization titers to SARS-CoV remained stable for 7 months.
(Fung and Liu 2019)	2019	China	Review	Vaires	Human coronaviruses, various	• Review study of of human coronavirus pathogenesis
(Zhong et al. 2005)	2003-2005	China	Serological cohort study	n=40 patients who recovered from SARS-CoV-1 1 month after discharge (20-65 yo)	SARS-CoV-1, ELISA, Western Blot	• While most neutralizing antibodies against CoVs target epitopes in the S1 region, the only identified surface immunodominant site in a study identifying immunogenic epitopes from convalescent samples of twenty SARS survivors through biopanning against phage display dodecapeptide library resides in the S2 domain.
(Cui et al. 2019)	2019	United States	Review	Varies	Human coronaviruses	• Review on coronavirus evolutionary history
(Ren et al. 2003)	2003	China	Serological study	SARS-CoV-1 sera (n=4) Healthy sera (n=2)	SARS-CoV-1, ELISA	• Characterized antigenic regions on recombinant S1 and S2 protein by Western Blot and ELISA
(Bisht et al. 2004)	2004	United States	Mouse challenge study	2 groups of 8 BALBc mice 0-4 weeks received MVA/S or MVA i.m.	Attenuated modified vaccinia virus Ankara (MVA) and SARS-CoV-1, Western Blot, ELISA, neutralization	• Characterization of the SARS-CoV S protein

(Wang et al. 2005)	2005	Taiwan	ADE and cell infectivity study	Anti-SARS-CoV-1 sera were collected from SARS-CoV-1 patients	Immunoblotting and RT PCR	Investigated the timing of IgG reactivity up to and after 3 weeks demonstrated stronger immunogenicity/antigenicity of N and S3 protein compared to S1 and S2.
(Meyer et al. 2014)	2014	Germany	Serological assay development Review	Varies	HCoV-229E, -NL63, OC43, HKU1, SARS-CoV-1, MERS-CoV, IFA, ELISA, Western Blot	Review of serological assays for SARS-CoV-1, MERS-CoV, and newly emerging CoVs
(Patrick et al. 2006)	2003-2006	Canada	Serological study	n=95/142 residents n=53/160 staff experienced symptoms of SARS-CoV-1	SARS-CoV-1, RT PCR, IFA, ELISA, neutralization, Western Blot, Euroimmun indirect	- A study screening 220 ten amino acid peptides covering the full length of HCoV-OC43 N protein (with eight residues running overlaps) and 207 peptides of SARS-CoV-1 N revealed four sites with shared homology - The study was conducted to explain false-positives to SARS-CoV-1 in multiple assays. Supported by non-seroconversion in the neutralization assay and RT-PCR positive results for HCoV-OC43, these were likely HCoV-OC43 infections with cross-reactive results driven by these potentially cross-reactive sites.
(Du et al. 2013)	2013	United States and China	Serological study	SARS-CoV-1 S-RBD protein-vaccinated mice	SARS-CoV-1, neutralization	- Find whether the cross-reactivity between SARS-CoV and MERS-CoV was due to antibodies targeting the RBD. They found monoclonal antibodies raised to SARS-CoV RBD did not bind the MERS-CoV RBD even at high concentrations (10ug/mL) and all had low or no neutralizing activity against MERS-CoV pseudoviruses. - There is an absence of cross-neutralization of MERS-CoV isolates by antiserum to S glycoprotein HKU 4 or 5 (animal CoVs in the same subgroup). For SARS-CoV, there is also an absence of cross-neutralization by antiserum to HKU 3 and BtCoV 279 S glycoprotein. - Between SARS-CoV and MERS-CoV, all mAbs generated that have high affinity to conformational or linear epitopes in the RBD of SARS-CoV does not neutralize nor bind to the RBD and S1 proteins of MERS-CoV even at high concentrations (10 mg/ml).

(Aburizaiza et al. 2014)	2012	Saudi Arabia	Serological study	healthy individuals (n=130) slaughterhouse workers (n=226)	MERS-CoV, IFA and neutralization	- None of the healthy individuals had IFA positivity to MERS-CoV, while 8/226 slaughterhouse workers had some cross-reactivity by IFA to MERS-CoV and 2 had reactivity to the MERS-CoV spike protein, as well as some reactivity to 229E, NL63, OC43 and/or HKU1 in immunofluorescence assay (IFA). None had a response to the SARS-CoV spike protein, although, antisera from confirmed MERS patients in Germany high PRNT90 titers (1:320 and 1:640) to MERS-CoV showed slight cross-reactivity with SARS-CoV-1 by IFA. - Low positivity among healthy blood donors (10/4719 tested, n individuals ages 19-88 years), contacts of confirmed MERS patients (1/135 tested, 14-49 years; mean age 31 years), while 3/4 confirmed MERS cases were positive (30-70 years; mean age 52), but random testing of the blood donors using an IgM assay revealed some false negative results, suggesting the assay was underestimated prevalence. Blood donors that were positive and negative for MERS antibodies had high prevalence of antibodies to HCoV-229E, -NL63, -OC43, and -HKU1. - Reactivity of human positive control antisera to each of the various strains (HCoV-NL63, -229E, -OC43, -HKU1, SARS-CoV-1, MERS-CoV) as well as antiserum to EV68 as negative control were measured against nucleocapsid (N) of these strains across a gradient of concentrations. SARS-CoV-1 showed no cross-reactivity. Comparing the reactivity patterns, HCoV-HKU-1 appeared antigenically close to -OC43, and -229E appeared close to -NL63, but the distance was non-symmetric. - Measured the mean fluorescent intensity (MFI) of reactions between positive control sera and recombinant N of those strains. Group 1 HCoVs (alpha-HCoV-229E and
(Al Kahlout et al. 2019)	2012-2016	Qatar	Serological Study	4858 plasma samples (n=4719 blood donors 19-88yo), (n=135 close contacts to 4 confirmed cases 14-49 yo), (n=4 confirmed patients 30-70yo)	recombinant S1 protein IgG ELISA kit	
(Gao et al. 2015)	2015	Turkey and United Kingdom	Seroprevalence study	n=695 healthy adults and n=492 healthy children for seroprevalence and to test the relationship between anti-N-IgG and HCoV infection n=361 serum samples from children with LRI were used	HCoV-229E, -NL63, -OC43, -HKU1, SARS-CoV-1, and MERS-CoV Western Blot, ELISA	
(Trivedi et al. 2019)	2019	United States	Development and Evaluation of Immunoassay	Positive for HCoV-229E (n=4), HCoV-NL63 (n=9), HCoV-OC43 (n=21), HCoV-HKU1 (n=14), SARS-CoV-1 (n=5), MERS-CoV (n=7)	HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV-1, MERS-CoV, RT	

					PCR, ELISA, multiplex immunoassay	-NL63) cross-reacted with other group 1 CoVs but did not cross-react with strains from group 2 (beta-HCoV-OC43 and -HKU1). Antiserum against SARS-CoV-1 (from group 2b) reacted with HCoV-229E and -NL63. Antiserum against HCoV-OC43 (from group 2a) reacted with -HKU1 (also in 2a). Antiserum against MERS-CoV (group 2c) reacted with HCoV-HKU1.
(Agnihothram et al. 2014)	2012-2014	United Kingdom	Serological Study	MERS-CoV was isolated from a 49yo patient	MERS-CoV, ELISA, neutralization	- Antiserum against MERS-CoV (group 2c) reacted with HCoV-HKU1 were consistent with cross-reactivity of epitopes in the N protein between subgroups but not between those observed in polyclonal sera generated through mice immunization. - It is unclear how much of the in vitro fitness and plaque morphology differences can be attributed to the antigenic differences observed between strains. - Examined cross-reactivity (binding by ELISA and Western Blot) among CoV N proteins between SARS-CoV-1 N and animal CoV N proteins (porcine CoVs gastroenteritis CoV [TGEV] and porcine respiratory CoV [PRCV], feline infectious peritonitis virus [FIPV], and canine CoVs). - Found cross-binding by serum from SARS patients against SARS-CoV-1 and porcine CoVs N protein sites while healthy human samples showed no binding to SARS-CoV porcine CoV N proteins. Both groups had high reactivity to HCoV-NL63.
(Vlasova et al. 2007)	2007	United States	Serological study and protein reactivity	SARS patients (n=6, convalescent samples collected 18-50 days post-symptom onset) healthy human samples (n=24)	SARS-CoV-1, s, HCoV-NL63, ELISA, Western Blot	

(Yu et al. 2005)	2003-2005	Japan and Vietnam	Serological study	n=149 healthcare workers, 37 probable SARS-CoV-1 cases n=175 healthy volunteers	SARS-CoV-1, ELISA, Western Blot, neutralization	• Showed nonspecific reaction to N protein by ELISA was reduced through the use of N constructs with 121 amino acid deletions at the N-terminus compared to four residue deletions. • When tested against sera from healthy volunteers and SARS-CoV-1 patients in Vietnam, the resulting titers were higher than that of SARS-CoV-1-infected cell lysate-based ELISA. Of those include four inapparent SARS-CoV-1 infections confirmed by virus neutralization. • Explored recombinant S and N protein as diagnostic tools for identifying SARS-CoV-1 patients and found an ELISA testing positivity to a truncated S-N protein (N321-422 and S264-680) proteins from SARS-CoV could discriminate between SARS-CoV-1 patients and healthy donors, nearly as well as SARS-CoV-1 lysate and better than S or N alone. SARS-CoV-1 patients showed more positivity to full N proteins of HCoV-229E and -OC43 than truncated versions of N. • No cross-reactivity with SARS-CoV nor HCoV-229E was observed. Immunoblotting assessment on three structural regions of the NP showed strongest reactivity at the central-linker region (aa174-300) followed by the C-terminal domain (aa301-448), and low at the N-terminal domain (aa1-173). Western blot assay against the recombinant protein in sera from adults (92.3% positive), patients with respiratory infection symptoms (82.3%), and cord blood samples (93.3%), showed no reaction to SARS-CoV-1 NP but 81% reacted to HCoV-229E NP. • The reaction (quantified in 38 of the 52 HCoV-OC43 positive sera) to the three structural regions showed three distinct patterns. All patterns reacted highly to the central-linker region, another pattern was
(Mu et al. 2008)	2003-2008	China	Serological challenge study	SARS patients (n=457/460+, 35-114 days post-symptom onset) healthy donors (n=650/650-)	Immunoblot analysis, IFA, ELISA, neutralization test,	
(Liang et al. 2013)	2013	Taiwan	Serological study	n=26 human serum samples from young healthy adults 18-26 yo, n=17 serum samples people 50-80 yo who reported to the hospital with respiratory tract infection, n=15 cord blood samples	HCoV-OC43, other human coronaviruses (HCoV-229E, SARS-CoV-1) Western blot	

(Carattoli et al. 2005)	2005	Italy and Germany	Serological assay development (protein-based) for SARS-CoV-1 diagnosis	n=6 SARS-CoV-1 Controls= (n=20 healthy donors) and (n=73 patients with non-SARS-CoV-1 infections)	SARS-CoV-1, ELISA, immunocytochemical assay	also reactive to the C-terminal region, and the last pattern strongly reacted to all. Membrane protein could be used to distinguish serum from SARS-CoV-1 patients who had strong responses and low inter-subject variability in responses to the M2 antigen. Healthy controls did not show a response.
(He et al. 2005)	2003-2005	United States and China	Serological study recognizing epitope	n=40 convalescent SARS-CoV-1 patients 30-60 days after onset, n=30 healthy blood donors Passive immunization was conducted on 10-12 week old BALBc mice Human monoclonal antibody generation were described in: Traggiai et al. (2004)	SARS-CoV-1, ELISA	Showed the membrane protein can induce antibodies in experimental animal inoculation.
(Rockx et al. 2008)	2008	United States	Mouse challenge study		SARS-CoV-1, Neutralization, ELISA,	Found escapes from mAbs targeting the spike receptor-binding domain (RBD) of SARS-CoV.
Zhu et al. 2007	2007	China	Immunogenicity study	n=6 bats showing positive or negative cross-reactivity with SARS-CoV-1	SARS-CoV-1, HIV-pseudotyped S proteins (SARS-CoV-1), ELISA, neutralization	While investigating broadly neutralizing antibodies, escapes from mAbs targeting the spike receptor-binding domain (RBD) of SARS-CoV were observed from zoonotic (palm civets and bats) to early to late human strains.
(Liu et al. 2007)	2002-2007	China	Phylogenetic and cross-neutralization study	Convalescent sera 3-12 months post-recovery (n=20) in SARS-CoV-1 pseudovirus study Full-length civet S gene Immunization of 6-8 week BALBc mice Other convalescent sera collected 2002-2003 at 3-12, 24 month post-recovery	SARS-CoV-1, HIV-pseudovirus for contranfecting viral entry assay, neutralization assay and civet viruses	Sera from BALB/c mice immunized with full length S protein in civet strains were ineffective against human SARS-CoV and vice versa.
(He et al. 2006)	2002-2006	United States	RBD study	SARS-CoV-1 isolates from both 2002-2003 and 2003-2004 outbreaks and palm civet isolate SZ3 Immunized mice and rabbits	SARS-CoV-1, ELISA, neutralization	Single mutations were shown to disrupt neutralizability even though there was significant cross-reactions between mAbs against conformational epitopes of RBD with multiple mutational differences.
(Elshabrawy et al. 2012)	2012	United States	Immunotherapy study	Produced and characterized human monoclonal antibodies that neutralized SARS-CoV-1 by binding the S2 protein	SARS-CoV-1, and pseudovirus generated with methods from (Coughlin et al. 2007) ELISA	Monoclonal antibodies targeting regions critical for fusion and entry on the S2 protein appeared broadly neutralizing against SARS-CoV strains.

(Tian et al. 2020)	2019-2020	China	RBD study	Antibody CR3022 isolated from convalescent SARS-CoV-1 patient	SARS-CoV-2, SARS-CoV-1, MERS-CoV Biolayerinterferomtry binding assay, ELISA	- Differential binding of monoclonal antibodies from SARS patients to the receptor binding domain (RBD) of SARS-CoV-1 and SARS-CoV-2. Differences between SARS-CoV and SARS-CoV-2 are largely located at C-terminus residues of the RBD, with structural differences that affect sensitivity to neutralizing antibodies but does not diminish the ability to bind to the ACE2 receptor (suggested by sequence analysis). One antibody potently bound to SARS-COV-2 RBD protein but did not compete with the RBD for binding to the ACE2 receptor or with other RBD-directed antibodies for binding to the RBD - Five recombinant receptor binding domains (rRBD) proteins were constructed with mutations detected from MERS-CoV strains detected in humans (2012-2015) and camels. - These rRBDs maintain functionality and do induce potent neutralizing antibodies. When residues in their receptor binding motifs were mutated to evade neutralization, cross-reactivity persisted but binding affinity to DPP-4 was lost suggesting limited antigenic escape for MERS-CoV. 2/29 amino acid differences between MERS Eng1 isolated from a patient transferred to London and MERS SA1 from Saudi Arabia were on the S glycoprotein. - Evaluated whether antibodies (binding and neutralizing) and T cell responses induced by childhood vaccination (AMPV, BCG, DPT, HBV, HIB, JEV, MMRV [and MV, RV], OPV, PI, SV, VV [varicella vaccine]) cross-reacted with SARS-CoV-1. They found no cross reactivity in any assay. They did find serum from children with prior SARS-CoV-1 infections cross-reacted to vaccine antigens, likely because the children received these vaccines.
(Tai et al. 2017)	2012-2017	China	RBD Study	n=20 human and camel isolates from GenBank database	MERS-CoV and MERS-pseudovirus, Western blot, coimmunoprecipitation assay, ELISA,	
(Yu et al. 2007)	2007 Vaccine produced 2002-2003	China	Pooled vaccine study	Pooled positive sera from people with SARS-CoV-1 Antisera from group of inbred mice immunized with childhood vaccines	SARS-CoV-1, ELISA	

(Resta et al. 1985)	1982-1985	United States	Isolation study	Stool samples from infants with necrotizing colitis (n=12) and Control samples (n=14)	Human enteric coronavirus, HCoV-OC43 and -229E, mouse hepatitis virus, ELISA	- Infants with necrotizing enterocolitis were found to have coronavirus particles by electron microscopy. Serum from infants did not cross react with common human CoVs (OC43, 229E), mouse hepatitis virus (MHV) or strains identified as Breda 1 and 2. - Identified greater prevalence human enteric coronaviruses in infants with acute gastroenteritis compared to age-matched controls and that virus and antiserum showed antigenic cross-reactivity (immune electron microscopy) to HECV-24, HECV-35, and HCoV-OC43.
(Gerna et al. 1984)	1984	Italy	Antigenic relatedness study	acute gastroenteritis (n=34/208) age-matched controls (n=3/182)	Human enteric coronavirus and HCoV-OC43	
(Han et al. 2006)	2006	United states	Challenge study	Child with acute diarrhea, gnotobiotic calves (n=4)	Human enteric coronavirus and bovine enteric coronavirus, ELISA	Identified an HCoV from a child with acute diarrhea as a variant of a bovine CoV.
(Gerdes et al. 1981)	1980-1981	United States	Serological cross-neutralization study	n=2 multiple sclerosis patients	HCoV-229E and -OC43, plaque assay and plaque neutralization	- Two HCoV strains extracted from brain tissue of multiple sclerosis patients were cross-neutralized by antiserum against HCoV-OC43 but not -229E. - Sera positive for HCoV-OC43 were also positive for hemagglutinating encephalomyelitis virus (HEV) while HCoV-229E and HCoV-B814 positive sera were not.
(Kaye et al. 1977)	1960-1977	United States	Serological assay study	n=345 sera from adults with and without respiratory illness, n=213 sera were from adult men in a chronic bronchitis study, n=88 acute and convalescent sera with URI, n=44 sera from influenza vaccine study n=104 acute and convalescent serum pairs from children in longitudinal study of respiratory illness	HCoV-229E and -OC43, indirect hemagglutination, and CF	- Individuals with and without possible contact with swine had significant differences in their HCoV-OC43 and HEV responses while sera collected from swine with Abs to HEV were not positive for HCoV-OC43. - Suggest cross-reaction between the two viruses but did not preclude the possibility of uncharacterized CoV. - Three different antigens for coronaviruses.
(Schmidt and Kenny 1981)	1981	United States	Immunogenicity and Antigenicity study	Paired sera (acute collected close to onset and convalescent 25-58 days later) from pneumonia patients	HCoV-229E and -OC43, CF, HI, neutralization	Samples from pneumonia patients had high reactivity to the 'slow' migrating antigen (Two-dimensional immunoelectrophoresis) of HCoV-OC43 than -229E (probably spike) suggesting it was highly immunogenic.

(McIntosh et al. 1970)	1965-1970	United States	Seroepidemiological study	Acute sera and nasopharyngeal washing from NIH employees with respiratory tract disease on or before fourth day of illness and coronavirus convalescent sera three weeks later (n=466) Throat and nasal swabs from pediatric patients on admission and three weeks later (n=565) Human embryonic tracheal organ cultures were used for diploid cell culture	HCoV-229E, -OC43, -OC38, and MHV, CF	The highest percentage of dual responses (n=91) involved children with -OC38 and -OC43 in coronavirus antigen tests. Some overlap between MHV and -OC38 and/or -OC43. No or few dual response with -229E and MHV or -229E and -OC38 and/or -OC43
Monto and Lim 1974	1966-1974	United States	Prospective study	Families where parents were under 46 yo	HCoV-OC43CF and HAI	Showed low agreement between CF and HI for HCoV-OC43 in sync with a large outbreak of HCoV-229E. Agreement was higher in 1966 and late-1968 to 1969 and showed increased agreement with neutralization test results in selected subsets (66.7%) compared to 28.6% in the other time periods.
(Tuan et al. 2007)	2003-2007	Vietnam	Retrospective cohort study	n=63 SARS-CoV-1 cases (n=53 primary cases, n=37 healthcare workers) n=252 close contact of primary 45 cases	SARS-CoV-1, ELISA and RT PCR	Cross-reactivity between HCoV-OC43 and SARS-CoV-1 was found in one individual while cross-reactivity between HCoV-229E and -OC43 were not found.
(Richardson et al. 2004)	2004	Canada	Diagnostic review	varies	SARS-CoV-1, review of assays and diagnostics	Immunological cross-reactivity has not been detected in SARS-CoV-1 and coronaviruses in antigenic groups 1 and 2. However, after antibody testing for an outbreak of HCoV-OC43, some positive results for SARS-CoV-1 suggest there may be cross-reactivity. This may impact assay development.
(Severance et al. 2008)	2008	United States	Seroprevalence and immunoassay study	n=196 between 18-65 yo served as control Seropositivity assay cutoffs were determined from n=10 seronegative children from a vaccine study	HCoV-229E, -HKU1, -NL63, -OC43, and feline coronavirus ELISA	- Correlations between antibody levels with the highest association were within the same group. - Cross-reactivity in this study may be due to using the whole nucleocapsid sequence. However, because there was an absence of reactivity to the feline coronavirus this cannot be fully explained by groups and may be due to exposure to the particular virus.

(Kossvakis et al. 2015)	2014-2015	Greece	Laboratory investigation	An imported case of MERS-CoV to Greece (69 yo male)	MERS-CoV, RT PCR	Implications for receptor binding efficiency were found in unique amino acid substitution in the spike receptor binding domain.
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Supplementary Table 6. Summary of Immunopathogenesis

Study	Year of study	Country/Region	Study type	Participants	Viruses/assay	Key findings
(Peiris et al. 2003)	2003	Hong Kong	Prospective study	Residents of a housing estate. Patients meeting WHO SARS definition (n=75)	SARS-CoV-1, RT PCR	The timing of IgG (starts approximately day 10) is linked to decreasing viral load but severe clinical worsening. Report enhancement of Abs within episode. This points to the host's response and not viral replication and ADE.
Ho et al. 2005)	2003	Taiwan	Retrospective study of patient data	All patients with probable SARS-CoV-1 (n=665) with (n=347) positive cases	SARS-CoV-1, RT PCR and ELISA	Longer hospital stays and death were associated with early seroconversions of neutralizing Abs to SARS-CoV-1 spike protein, week 5 vs week 8 post fever onset. Worsening pulmonary function was associated with decreasing viral load. This plus clinical studies on cytokines, suggests activation of the Th1 cell-mediated immunity and a hyper-innate inflammatory response lead to severe infection. Suggests ADE and priming effect from existing antibodies against endemic strains of coronavirus.
(Hsueh et al. 2003)	2003	Taiwan	Serological study	Hospitalized patients (n=7, n=6 male) who met the CDC and WHO case definition for SARS-CoV-1	SARS-CoV-1, IFA, RT PCR	There was an upsurge of IgG antibodies, which correlated with ARDS progression. This may be due to host response rather than viral load and suggests ADE.

Supplementary Table 6. Summary of Immunopathogenesis

Study	Year of study	Country/Region	Study type	Participants	Viruses/assay	Key findings
(Cameron et al. 2008)	2008	Varies	Review	Varies. One study cited included well-defined SARS-CoV-1 patients from Toronto (n=50)	SARS-CoV-1	• Expression of a group of proinflammatory cytokines and chemokines is associated with acute and possibly progressing SARS. IFN and ISG are critical in SARS clinical evolution. Non-severe, severe, and fatal patients expressed differences IFN and ISG compared to healthy controls. The study supported prolonged levels of proinflammatory chemokines due to absence of effective adaptive response for virus clearance but the mechanism which led to the malfunctional switch between innate and adaptive is unknown.
(Talbot et al. 2009)	1977-2001	United States	Longitudinal cohort study	children <5 years old LRI (1977-2001) (n=1830, 3958 child-year) (n=948 LRI), (n=553 nasal wash specimens) URI (1982-2001)(n=1481 children and n=6724 episodes) (n=2082 URI specimens)	HCoV-229E, -NL36, and -OC43, RT PCR	• RSV-associated LRI occurs in children <6 months while LRI with HCoV was in children 6-23 months. This may be due to the presence of maternal antibodies in the LRT or immunopathogenesis. URI infection burden was close to uniform with regard to age.
(Jaume et al. 2011)	2011	Hong Kong	<i>In vitro study</i>	Various cell lines and 6-8 week old BALB/c mice (n= 4 to 5 per group)	SARS-CoV-1, IF, ELISA, neutralization, and RT PCR	• Anti-Spike immune serum inhibited viral entry in permissive cell lines but potentiated infection of immune cells by SARS-CoV-1 particles. Antibody-mediated infection was dependent on Fc-gamma-RII but did not use the pathway used by ACE2. None of the non-neutralizing responses elicited towards different immunogens involved IgG2a. ADE for SARS-CoV-1 uses a novel entry method into immune cells.
(Yip et al. 2014)	2014	Hong Kong	<i>In vitro study</i>	Healthy samples were collected from Hong Kong Red Cross Blood Transfusion Service and BALBc mice were immunized	SARS-CoV-1, IF, ELISA and RT PCR	• Human macrophages can be infected by SARS-CoV as a result of IgG-mediated ADE. This indicates that this infection route requires signaling pathways activated downstream of binding to FcγRII receptors. In monocytes, macrophages, and monocyte-derived dendritic cells, virus replicates up to six hours but does not exit the cell.

Supplementary Table 6. Summary of Immunopathogenesis

Study	Year of study	Country/Region	Study type	Participants	Viruses/assay	Key findings
(Fu et al. 2020)	2020	Varies	Review	Varies	SARS-Cov-1 and 2 and HNL36	In a SARS-CoV-1 macaque model it was found that S-IgG present in lungs can cause severe lung injury. In vaccinated macaques acute lung injury was more pronounced than those unvaccinated. This suggests that ADE may be why patients who produce neutralizing antibodies early experience persistent inflammation, ARD, and succumb to SARS-CoV-1.
(Wang et al. 2014)	2014	Taiwan	<i>In vitro study</i>	Anti-SARS-CoV-1 sera was collected from SARS-Cov-1 infected patients in Taiwan BALBc mice were immunized	SARS-CoV-1, IF and RT PCR	Upon infection, TNF-alpha, IL-4 and IL-6 expressions increased while only trace amounts of IL-3 and IL-1beta appeared. Mild to moderate enhancement by various anti-S1a and anti-S1b murine mAbs generated except one particular anti-S1b clone that neutralized it. No effect was seen for anti-N mAbs. ADE is mediated by diluted antibodies against envelope spike proteins not nucleocapsid proteins. HL-CZ cells express ACE2 receptors and display a cytopathic effect caused by SARS-CoV-1.
(Yip et al. 2016)	2009-2011	Hong Kong	<i>In vitro study</i>	6-8 week BALBc mice were immunized (n=4-5 per group)	SARS-CoV-1, IF and RT PCR	Antibody-dependent enhancement (ADE) allows SARS-CoV-1 to infect primary human macrophages, but it does not sustain productive viral replication in the infected cells. ADE of SARS-CoV-1 infection does not change pro-inflammatory gene expression profile of primary human macrophages. TNF-alpha, IL-4 and IL-6 expressions heightened while IL-3 and IL-1beta only appeared in trace amounts. This could be due to the cell line differences or the set of mediators assessed.
(Perlman and Dandekar 2005)	2005	Varies	Review	Varies	SARS-CoV-1	Prolonged tissue destruction can heighten presentation of host proteins to T- or B-cells and result in adaptive response against self, i.e. epitope spreading.

Supplementary Table 6. Summary of Immunopathogenesis

Study	Year of study	Country/Region	Study type	Participants	Viruses/assay	Key findings
(Lin et al. 2005;)	2003	Taiwan	Serological study	Sera was collected from SARS-CoV-1 positive patients (n=80 < 20 days after fever onset) and n=41 >=20 day after fever) n=10 controls	SARS-CoV-1, Preabsorption and binding assays, ELISA	- Autoantibodies reacted with A549 cells - Evidence of pathogenesis when anti-S2 Abs in SARS-CoV-1 cause cytotoxic injury as well as enhanced immune cell adhesion to epithelial cells.
Fang et al. 2010	2003	Taiwan	Proteomic study	Sera was collected from SARS-CoV-1 positive patients (n=5 late stage >=20 days after fever onset)	SARS-CoV-1, ELISA, IF, WB	Evidence of SARS-CoV-1 pathogenesis was found in upregulated expression of annexin A2 by SARS-associated cytokines and the cross-reactivity of anti-SARS-CoV-1 S2 antibodies to annexin A2.
(Cheng et al. 2005)	2005	Hong Kong	<i>In vitro study</i>	The SARS-CoV genomic library was used and mice were infected	SARS-CoV-1, Phage ELISA	- Evidence of anti-N antibodies that cross react with IL-11 including lung and bone marrow. - High anti-N antibodies induced relatively early during infection may be involved in the thrombocytopenia and lymphopenia observed early in SARS-CoV-1 infection.
(Yasmon et al. 2012)	2012	Germany	Serological study	n=20 health sera were used as control n=129 (n=61 HIV-1 negative and n=68 HIV-1 positive) were collected from IDU in Jakarat, Indonesia <21 yo	SARS-CoV-1 and HIV, IgG ELISA	Show anti-N antibodies that cross react with IL-11.
(Ksiazek et al. 2003)	2003	United States	Serological Study	Clinical specimens=serum from SARS-CoV-1 patients in Singapore, Bangkok, and Hong Kong (n=19). Healthy blood from the US CDC And patients with known OC43 and 229E	Group 1 coronaviruses, SARS-CoV-1 RT PCR, IFA, ELISA, suckling ICR mice were used to isolate virus	- Did not show cross-reactivity with the same immune human serum sample and feline infectious peritonitis virus 1 antigen. - Paired human serum samples with diagnostic increases (by a factor >=4) in antibody (with very high titers to the homologous viral antigen in the convalescent-phase serum) to the two known human coronaviruses, HCoV-OC43 (13 pairs) and -229E (14 pairs), showed no re-activity in either acute- or convalescent-phase serum with the newly isolated coronavirus.

Supplementary Table 6. Summary of Immunopathogenesis

Study	Year of study	Country/Region	Study type	Participants	Viruses/assay	Key findings
(Gorse et al. 2020)	2009-2013		Serological study	Group 1: 99 of age ≥ 60 with underlying chronic lung and heart disease; Group 2: 101 healthy adults of age 21-40 years old	HCoV-229E, -NL63, -OC43	Baseline binding antibody titers to all strains (by ELISA) were higher in the older adults. Post infection, neutralizing Abs were more efficiently triggered in the older group to HCoV suggesting the role of cross-reacting Abs from past exposures. Antibody-dependent enhancement of SARS-CoV and feline infectious peritonitis virus infectivity has been reported and can be mediated by antibodies to S protein epitopes. studies of the S protein sequence and neutralization antigenicity suggest that serum antibodies may not cross-react as well with the laboratory strains of HCoV that were used in our neutralization assays, affecting the sensitivity of the neutralization assay used in the study.
(Bermingham et al. 2004)	2004	United Kingdom	Review	Various	Review of molecular detection, targets, diagnostics, and assays	Demonstrates limited cross reactivity with antibodies to human group 1 or group 2 coronaviruses and group 1 animal coronaviruses
(Yang et al. 2005)	2004	United States and Switzerland	Neutralization test	Purified immune IgG came from vaccine candidates 5 female BALBc mice per group (6-8 weeks old)	SARS-CoV-1 and hACE-2, human and civet S proteins	Abs that neutralized most human S glycoproteins enhanced entry mediated by the civet virus S glycoproteins. The mechanism of enhancement involved the interaction of Abs with conformational epitopes in the hACE-2-binding domain Entry of SARS-CoV-1 can be enhanced by Abs.
(De Groot 2003)	2003	United States	Review	Varies	SARS-CoV-1 and HIV	Antibody seroconversion occurs around day 10. Observed antibody-mediated exacerbation in feline and bovine coronaviruses. SARS-CoV-1, like HIV, is an RNA virus that has an error-prone replication mechanism, which may explain mutations in the SARS-CoV genome in the S protein along with response to immune pressure.
(Subbarao et al. 2004)	2003	United States	Mouse model study	Female BALBc mice 4-6 weeks old	SARS-CoV-1, neutralization assay	Challenge with SARS-CoV-1 revealed primary infection provided high levels of resistance to replication of the challenge virus or immune serum. Neutralizing Abs were developed 28 days later. Rapid time course for SARS-CoV-1 replication in mice.

Supplementary Table 6. Summary of Immunopathogenesis

Study	Year of study	Country/Region	Study type	Participants	Viruses/assay	Key findings
(Weiss and Scott 1981)	1980	United States	Serum challenge Study	12 week old specific-pathogen-free kittens	Feline infectious peritonitis virus (FIPV), IF,	Non-immune kittens passively immunized with high titer serum developed enhanced disease. Kittens with FIPV antibodies developed clinical signs earlier and died more rapidly compared to kittens non-sensitized that did not show clinical signs or die of FIPV revealing evidence of ADE.
(Yang et al. 2004)	2004	United States	Vaccine Study	Female BALBc mice 6-8 weeks old Protein expression was confirmed with recovered patients	SARS-CoV-1, ELISA	DNA vaccine encoding the S protein of SARS-CoV-1 induces T cell and neutralizing antibodies as well as protective immunity. Mice vaccinated with an expression vector encoding S elicited neutralizing antibodies.
(Rockx et al. 2008)	2008	United States	Mouse challenge study	Passive immunization was conducted on 10-12 week old BALBc mice Human monoclonal antibody generation were described in: Traggiai et al. (2004)	SARS-CoV-1, neutralization, ELISA,	The majority of human mAbs recognize a set of overlapping epitopes, since reactivity was lost by denaturation of the antigen (as seen in a cited hepatitis B study). Escape mutant analysis to identify key residues in neutralizing activity of two cross-neutralizing mAb.
(Dawson et al. 2019)	2019	United States	Review	n=407 articles reviewed and n=208 included	MERS-CoV, various diagnostic assays	The main route of entry for MERS is di-peptidyl peptidase 4 (CD26) and like SARS-CoV-1 uses a spike protein as the RBD.

Supplementary Table 7. Summary of studies on population-level seroprevalence of CoV

Author and Year	Virus	Assay	Figures Digitized	Notes
Dijkman et al, 2008	HCoV NL63 and 229E	ELISA	n/a	Finds that majority of HCoV-NL63 seroconversion occurs before 3.5 years of age
Severance et al, 2009	HCoVs 229E, HKU1, NL63, OC43	ELISA	Table 1	Cross-sectional survey of children (10) and adults (96)
Dijkman et al, 2012	HCoVs 229E, HKU1, NL63, OC44	ELISA	Table 1	Longitudinal follow-up of 25 healthy infants from birth to 24 months
Müller et al, 2015	MERS	ELISA IgG, IFA, neutralization	Supplement	Cross-sectional serosurvey for MERS in Saudi Arabia from general population
Chan et al, 2004	SARS	IgG (assay unclear)	Text	The authors attributed the seropositivity differences to some patients in the older age groups not available for convalescent blood sample (died/moved wards)
Falsey et al, 2002	HCoV 229E and OC43	EIA for IgG	n/a	Respiratory infection hospitalization surveillance
Sarateanu et al, 1980	HCoV OC43	HI	Table 1	Serosurveillance over 2 years in Hamburg, Germany
Hovi et al, 1979	HCoV OC43	CF, HI, RIA	n/a	Serosurvey of CoV across age groups and assays
Walsh et al, 2013	HCoV 229E and OC43	EIA	Table 2	Seroincidence of three cohorts varying in age and health status
Gao et al, 2016	Six HCoVs (incl SARS)	ELISA/WB	n/a	Examines cross-reactivity between HCoVs
Ukkonen et al, 1984	HCoV OC43	CF	n/a	Complement fixation antibody responses across 16 respiratory pathogens of 58,000+ patients and 8 years
Liang et al, 2013	HCoV OC43	WB	Table 1	HCoV exploration of N protein and immunoreactivity
Cavallaro et al, 1971	HCoV 229E	CF and neutralization	Figures 2 & 3	Population level surveillance of 229E already in place during a 229E outbreak in Tecumseh, Michigan
Monto et al, 1974	HCoV OC43	HAI and CF	Tables 1 & 3	Population level surveillance of OC43 already in place during a 229E outbreak in Tecumseh, Michigan
Degnah et al, 2020	MERS	ELISA, ppNT, MNT	Table 3	Seroprevalence of MERS in Saudi Arabia indicating possible asymptomatic infections
Zhou et al, 2013	HCoV 229E, OC43, NL63, HKU1	IFA for IgG and IgM	Figures 3 & 4	Serosurvey providing further evidence of early onset of first infection
Chan et al, 2009	HCoV HKU1	anti-S ELISA+WB	Figure 6	Assay development and testing across CoV serum samples

Shao et al, 2007	HCoV 229E and NL63	ELISA	Table 1	Seroprevalence study among individuals <20 years old
Cereda et al, 1986	HCoV OC43 and 229E	indirect immuno- peroxidase staining	n/a	Seroprevalence among individuals hospitalized for any cause
Schmidt et al, 1986	HCoV OC43 and 229E	ELISA IgG	Table 2	Seroprevalence lower among adults in 10 families in Seattle

Supplementary Table 8. Estimated annual force of infection from digitized age-seroprevalence data for endemic HCoVs

Strain	Author and year	Annual force of infection (95% CI)
HCoV-229E	Zhou et al, 2013	0.06 (0.03,0.10)
	Shao et al, 2007	0.16 (0.09,0.26)
	Severance et al, 2009	0.06 (0.04,0.09)
	Cavallaro et al, 1971	0.01 (0.008,0.02)
HCoV-OC43	Zhou et al, 2013	0.05 (0.03,0.09)
	Severance et al, 2009	0.06 (0.04,0.09)
	Sarateanu et al, 1980	0.03 (0.01,0.05)
HCoV-NL63	Zhou et al, 2013	0.04 (0.02,0.08)
	Shao et al, 2007	0.12 (0.09,0.16)
	Severance et al, 2009	0.06 (0.04,0.09)
HCoV-HKU1	Zhou et al, 2013	0.05 (0.02,0.08)
	Severance et al, 2009	0.02 (0.01,0.03)
	Chan et al, 2009	0.004 (0.003,0.006)

Supplementary Figure Titles

Figure S1: **Cumulative proportion of patients that seroconverted**, digitised from four studies (Z. Yang et al. 2009c; P-R Hsueh et al. 2004e; X. Chen et al. 2004c; Zhao et al. 2020). Studies on SARS-CoV-1 did not provide information on severity of symptoms.

Figure S2: **Antibody time series reported in studies in units of optical density (OD)**. Some studies may report time series of different antibodies for the same patient. The plotting symbols indicate whether a measurement was above the cutoff for the assay being used, if reported in the study. Note that while these are plotted on the same axis, values may not necessarily be compared across studies as each may employ different scales.

Figure S3: **Antibody time series reported in studies in units of titers**. Some studies may report time series of different antibodies or using different assays for the same patient. The plotting symbols indicate whether a measurement was above the cutoff for the assay being used, if reported in the study. Some studies reported titers that were lower than or greater than some threshold value; those are here plotted at those values (e.g., for ≥ 320 , the value is assumed to be 320). Note that while these are plotted on the same axis, values may not necessarily be compared across studies as each may use different scales.

Figure S1.

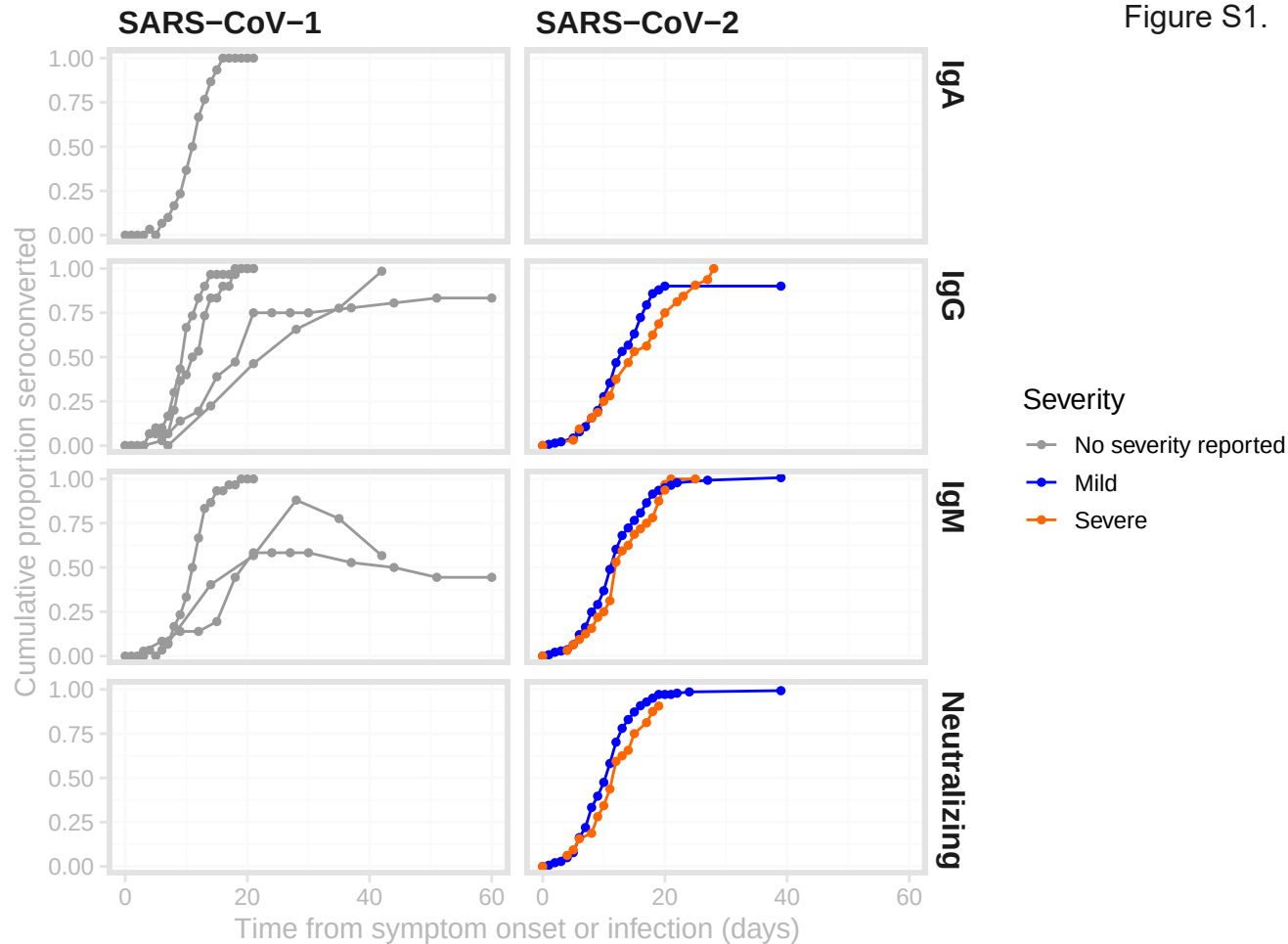


Figure S2.

