

Antibody response to SARS-CoV-2 infection in humans: a systematic review

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KEYWORDS

Immunity, antibody, IgG, IgM, neutralising antibody, cross-reactivity, SARS-CoV-2, COVID-19

LIST OF ABBREVIATIONS

Abbreviation	Full term
ACE2	Angiotensin Converting Enzyme 2
COVID-19	Coronavirus disease (2019)
HCoV	Human coronavirus
ICU	Intensive Care Unit
MEDLINE	Medical Literature Analysis and Retrieval System Online
MERS	Middle East Respiratory Syndrome
N	Nucleocapsid
nAb	Neutralising antibody
NEQAS	National External Quality Assessment Service (UK)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBD	Receptor Binding Domain
S	Spike
SARS-CoV-1	Severe Acute Respiratory Syndrome CoronaVirus-1
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus-2
WHO	World Health Organisation

ABSTRACT

Introduction

Progress in characterising the humoral immune response to Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) has been rapid but areas of uncertainty persist. This review comprehensively evaluated evidence describing the antibody response to SARS-CoV-2 published from 01/01/2020-26/06/2020.

Methods

Systematic review. Keyword-structured searches were carried out in MEDLINE, Embase and COVID-19 Primer. Articles were independently screened on title, abstract and full text by two researchers, with arbitration of disagreements. Data were double-extracted into a pre-designed template, and studies critically appraised using a modified version of the MetaQAT tool, with resolution of disagreements by consensus. Findings were narratively synthesised.

Results

150 papers were included. Most studies (75%) were observational in design, and included papers were generally of moderate quality based on hospitalised patients. Few considered mild or asymptomatic infection. Antibody dynamics were well described in the acute phase, and up to around 3 months from disease onset, although inconsistencies remain concerning clinical correlates. Development of neutralising antibodies following SARS-CoV-2 infection is typical, although titres may be low. Specific and potent neutralising antibodies have been isolated from convalescent plasma. Cross reactivity but limited cross neutralisation occurs with other HCoVs. Evidence for protective immunity in vivo is limited to small, short-term animal studies, which show promising initial results in the immediate recovery phase.

Interpretation

Published literature on immune responses to SARS-CoV-2 is of variable quality with considerable heterogeneity with regard to methods, study participants, outcomes measured and assays used. Antibody dynamics have been evaluated thoroughly in the acute phase but longer follow up and a comprehensive assessment of the role of demographic characteristics and disease severity is needed. The role of protective neutralising antibodies is emerging, with implications for therapeutics and vaccines. Large, cross-national cohort studies using appropriate statistical analysis and standardised serological assays and clinical classifications should be prioritised.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the novel viral pathogen that causes coronavirus disease 2019 (COVID-19) in humans, has spread worldwide since its identification in late 2019. At the time of writing, there have been around 22.3m confirmed cases and 782,456 deaths reported to the WHO.¹ Limited pre-existing immunity is assumed to account for the extraordinary rise in cases worldwide. Characterisation of the human antibody response to SARS-CoV-2 infection is vitally important to inform vaccine development and strategies, and to guide appropriate design, implementation, and interpretation of serological assays for surveillance purposes.

Transmission models used to predict the behaviour of the pandemic and plan non-pharmaceutical interventions assume a degree of protective immunity arising from infection with SARS-CoV-2.^{2,3} A range of clinical and policy interventions to tackle SARS-CoV-2 spread depend on better understanding of the dynamics and determinants of humoral immunity to this virus. These include the proposed use of 'immunity passports', a form of certification for individuals with positive detection of antibodies that can enable them to avoid isolation or quarantine on the assumption they are protected against re-infection;⁴ treatment options such as infusion of convalescent plasma or derived immunoglobulin;⁵ sero-surveillance to monitor progression of the epidemic in the population;⁶ and the nature of the likely response to vaccination and supporting decisions on prioritising use of vaccines.

Experience with other human coronavirus species (HCoV) suggests that partial immunity arises following infection with a variable but generally short (1 to 2 year) duration.⁷ Limited data available for the closely related SARS-CoV-1 indicate that antibodies able to block viral infection (neutralising antibodies) may persist for up to 17 years following infection.⁸

Early clinical studies suggest that the dynamics of antibody response following acute infection with SARS-CoV-2 is similar to other HCoVs. Antibody responses are generally detected against the nucleocapsid (N) or spike (S) proteins, the S1 subunit of which contains the receptor-binding domain (RBD): antibodies against different antigens may have differential dynamics and neutralising effect. The presence of neutralising antibodies has been demonstrated in studies of vaccine research and therapeutic use of convalescent plasma.^{7,9} Previous lessons from Severe Acute Respiratory Syndrome (SARS-CoV-1), Middle Eastern Respiratory Syndrome (MERS-

CoV) epidemics and other seasonal human coronaviruses suggest that there is the potential for a decline in population level protection from reinfection over a short period of time, but this is somewhat dependent on initial disease severity.^{7,9} Neutralising antibodies (nAbs) are likely to be a key metric for protection against infection by viruses such as SARS-CoV-2. However, their dynamics and role in long-term population immunity are not well understood.⁷ Furthermore, understanding of the mechanistic correlates of protective immunity in humans remains limited, including the antibody titre and specificity required to confer protection.¹⁰

This is the first of two linked papers reporting results from a systematic review of peer-reviewed and pre-print literature on the immune response to SARS-CoV-2 infection.¹¹ This paper has three aims. Firstly, to characterise the antibody response to SARS-CoV-2 infection over time and explore the effects of potential correlates of immune activity (including age, time since symptom onset, clinical severity and ethnicity) on the nature of this response. Secondly, to consider relationships between these variables and indirect or relative quantification of antibodies to SARS-CoV-2. Thirdly, to consider the duration of post-infection immunity conferred by the antibody response.

METHODS

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was pre-registered with PROSPERO (CRD42020192528).

Identification of studies

Keyword-structured searches were performed in MEDLINE, Embase, COVID-19 Primer and the Public Health England library¹² for articles published from 01/01/2020-26/06/2020. A sample search strategy is in **Supplementary Appendix A**. Subject area experts were consulted to identify relevant papers not captured through the database searches.

Definitions, inclusion and exclusion criteria

We included studies in all human and animal populations, and in all settings (laboratory, community and clinical - encompassing primary, secondary and tertiary care centres) relevant to our research questions. We excluded the following study designs: case reports, commentaries,

correspondence pieces or letter responses, consensus statements or guidelines and study protocols.

We focused on studies reporting measured titres (total antibody, IgA, IgG and/or IgM) with follow-up duration of greater than 28 days (which we defined as the limit of the acute phase of illness). Shorter follow-up studies were included if they reported on protective immunity, or immune response correlates. We defined “correlates” as encompassing, among other factors: primary illness severity - proxied by the WHO’s distinction between “mild”, “moderate”, “severe” and “critical” illness;¹³ subject age; gender; the presence of intercurrent or co-morbid disease e.g. diabetes, cardiovascular and/or chronic respiratory disease; and ethnicity.

Selection of studies

Studies were independently screened for inclusion on title, abstract and full text by two members of the research team (working across 4 pairs), with arbitration of disagreements by one review lead.

Data extraction, assessment of study quality, and data synthesis

Data were extracted in duplicate from each included study. Extraction was performed directly into a dedicated Excel template (**Supplementary Appendix B**). Pre-prints of subsequently published peer reviewed papers were included and results extracted where substantial differences in reported data were identified; if little difference was observed only the peer-reviewed version was retained.

Critical appraisal for each included study was performed in duplicate using a version of the MetaQAT 1.0 tool, adapted for improved applicability to basic science and laboratory-based studies. MetaQAT was selected for its simplicity and versatility in application to studies of all design types.¹⁴ Principal adaptations to the MetaQAT tool are described in **Supplementary Appendix C**.

The adapted MetaQAT tool was used to gather both qualitative feedback on study quality, and scaled responses (yes/no/unclear) for answers to key questions around study reliability, internal and external validity, and applicability, among other fields. Scaled responses were converted into weighted scores for each paper. Accordingly, studies were assigned a “high”, “medium” or “low” quality grading.

Study heterogeneity precluded formal meta-analysis. Results were instead synthesised narratively.

RESULTS

The PRISMA flowchart for the review is given in **figure 1**.

General characteristics of included studies

150 studies were included, of which 108 (72%) contained data pertaining to antibody response, and 70 (47%) to protective immunity (descriptive statistics for included studies are given in **table 1**). The vast majority focused on hospitalised patients (i.e. higher severity disease). Eleven studies considered antibody responses in asymptomatic individuals in the community and only five investigated protective immunity in this group. Most studies were of moderate quality. Assays used to detect and quantify antibody response were diverse, with target antigens including spike (S), S1 and S2 subunits, receptor binding domain (RBD) and nucleocapsid (N). Details of assays used, and an overview of strengths and limitations of these is provided in **Supplementary Appendix D**.

Kinetics of the antibody response

Time to seroconversion

The majority of individuals in the included studies mounted a SARS-CoV-2-specific antibody response during the acute phase of illness, with many studies reporting 100% seroconversion. Overall seroconversion rates depended on the timepoint at which testing was conducted in the disease course, the populations under study, the serology assay platforms used and their specific target proteins. Studies considered time to seropositivity for total antibody and/or individual antibody classes (IgA/IgG/IgM) (**figure 2**), although this was often not clearly defined with respect to symptom onset or first positive PCR test. In addition, whilst some studies described specific target proteins of assays used, others were either non-specific or not described. This limited assessment of dynamics of antibodies against specific viral targets, in particular anti-N versus anti-S, the latter of which may be more closely related to protection.

A number of studies reported seroconversion for total antibody (combined IgG, IgM and/or IgA),^{15–21} however the focus of findings presented is for specific antibody isotypes. For IgG, mean or median time to seroconversion ranged from 12 - 15 days post symptom onset,^{7,9,15,22–26} with wide variation in first to last detection of IgG from 4 - 73 days post symptom onset although reporting methods varied by study.^{15,27–33} For IgM, mean or median time to seroconversion ranged from 4-14 days post symptom onset,^{7,9,15,22–24,26,31,34} again with variations in reporting methods, study quality, and sample size giving rise to uncertainty around findings. Time to seroconversion for IgA was measured in fewer studies, ranging from 4 - 24 days post symptom onset, although most were within 4-11 days,^{23,35,36} with some outliers, including two reports of 24 days to first detection.^{37,38}

Sequential antibody response

In line with the expected sequential appearance of antibody isotypes, the majority of studies reported detection of IgM followed by IgG.^{15,23,39,40} Nevertheless, this finding was not consistent across all studies. One study measured time to seroconversion for IgA, IgM, and IgG and demonstrated detection of IgA and IgM simultaneously, followed by IgG.²³ . One study detected IgG seroconversion in advance of IgM,²⁶ and a study involving African green monkeys reported simultaneous IgM and IgG responses.⁴¹ These disparities may reflect the use of differing antibody assays across a range of species and without standardisation.

Antibody dynamics over time

IgG dynamics appeared to follow a pattern of peak, plateau, and persistence at lower levels (**figure 3**). After appearance, IgG titres rose to a peak between three and seven weeks post symptom onset,^{7,23,30,42–48} with studies recording the presence of IgG in and beyond weeks four,^{40,49} five,⁵⁰ six,^{23,51} seven,^{52,53} and eight^{17,45,54–56} post symptom onset. Some studies reported a plateau in virus-specific IgG beyond week three but levels beyond the peak were not well described.^{32,57–59} A decrease in antibody levels was reported in the eighth week post symptom onset by two studies,^{17,38} while another reported a decline from the second month after symptom onset.⁵⁸ Evidence from a cohort of 40 UK patients suggests a decline in titres after eight weeks,⁵⁸ although persistence of virus-specific IgG has been described at varying levels up to 12 weeks post symptom onset,⁴³ the longest follow up period among included studies. Dates of last detection were limited by the length of the study follow-up period, rather than confirmation of disappearance of detectable antibody titres.

IgM dynamics follow a ‘rise and fall’ pattern, with a peak two to five weeks post symptom onset^{7,26,30,34,43,46,47,53,60,61} then decline over time to below the detection limit.^{38,43,62} Beyond the peak, IgM is consistently reported to decrease from as early as two to three weeks,^{53,61} to as late as eight weeks⁵⁵ post symptom onset, with the majority of studies reporting this decline to occur at between three to five weeks.^{40,43,62,63} Virus-specific IgM became undetectable in almost all cases by around six weeks after disease onset in two small but high quality cohort studies.^{53,64}

Fewer studies describe IgA dynamics compared to IgM or IgG. IgA levels are reported to peak between 16 - 22 days post symptom onset, although there is no consensus on trends over time.^{23,61}

Correlates of Antibody Response

Key findings regarding correlates of the antibody response to SARS-CoV-2 infection are summarised in **table 2**. Included papers addressed clinical factors (disease severity, co-morbid disease status and symptom profile) and demographic factors (age, sex and ethnicity) although results for many of these factors were conflicting or inconclusive. Across all papers, the definitions of comparator groups were highly variable, including disease severity classifications (severe/mild), outcomes (deceased/mild), and treatment categories (ICU/Non-ICU). The lack of consistency in methods, comparison groups and study design means it is not possible to determine whether or how disease severity affects, or is affected by, the antibody response. Most studies showed no association between antibody response and age or sex, and, when taken together, studies that did show associations had inconclusive results and lacked statistical analysis to relate these findings to disease severity. There were virtually no data to describe the immune response according to ethnicity.

Protective immunity

Neutralising antibody kinetics

Across the included studies, the majority of subjects developed detectable neutralising antibodies in response to SARS-CoV-2 infection in both human^{7,18,22,29,65–88} and animal^{41,89–92} participants. However, neutralising antibody titres were low in a substantial minority of participants. A high

quality cohort study found almost all participants (94%, n=19) generated an antibody response capable of neutralising 42-99% of pseudovirus in a carefully validated assay 14 days after exposure.⁸³ Another high-quality cohort study also found most patients (91%, n=22) developed a neutralising antibody response by 21 days after disease onset.⁸⁴ However only three quarters developed titres over 1:80. A larger case-control study including a sample of largely non-hospitalised convalescent patients demonstrated most participants (79%, n=149) had low neutralising antibody titres (<1:1000) after an average of 39 days following disease onset, while only 3% showed titres >1:5000.⁸⁷ Notably, RBD-specific antibodies with potent antiviral activity were found in all individuals tested, suggesting specific neutralising antibodies are produced following infection despite low overall plasma neutralising ability.⁸⁷

Neutralising antibodies were generally detectable between 7 - 15 days following disease onset,^{7,18,75,84,85,88,93,94} increasing over days 14 - 22 before plateauing^{22,68,69,88,93,94} and declining over a period of six weeks.^{69,85,88,95} Evidence from one medium-quality pre-print study suggests neutralising antibody titres reduced significantly among 27 convalescent patients around six weeks following disease onset to a mean neutralisation half maximum inhibitory dilution (ID50) of 596.⁵¹ A second medium quality preprint found neutralising antibodies became undetectable in four of 11 previously detectable cases.⁸⁵ Further high-quality evidence is required to fully evaluate the apparent waning of the neutralising antibody response over time. There were no high-quality studies investigating the dynamics of protective immunity over time in a cohort identified in this review. To date no studies have determined neutralising titres in upper respiratory tract samples.

Correlates of neutralising antibody production

Clinical and demographic correlates of the neutralising antibody response are described in **table 3**. Neutralising antibody responses correlated with disease severity in all studies in which this association was tested.^{7,43,49,66,76,85,87,96-98} Importantly, the few studies that investigated asymptomatic cases found those individuals were considerably less likely to develop detectable serum neutralising antibody responses than cases with symptoms. With regard to age and sex, evidence was mixed and a limitation across all papers was a lack of statistical adjustment for severity.

Correlation of neutralisation with specific antibodies

The level of neutralisation was found to correlate with a wide range of specific antibodies. Most studies, including all those considered high quality, suggested that neutralisation ability broadly

correlated with total virus-specific IgG.^{29,49,67,74,87,99–101} Specifically, high quality studies found that neutralisation ability correlated positively with anti-S IgG^{49,72,87,99} or anti-RBD IgG.^{72,74,87,102} There was more limited evidence for correlation with anti-RBD IgM, including one high quality study,^{51,84} and IgA.^{93,99}

A number of basic science studies also identified specific neutralising antibodies. The majority of these studies were medium quality, and heterogeneity between assays limits comparability of findings. A high quality study by Rogers et al highlighted the important role of RBD binding antibodies in neutralisation in a pseudovirus assay, with findings supported by an effective animal re-challenge model.¹⁰³ This study also reported that SARS-CoV-2 infection elicited a strong response against the S protein. However, few of these antibodies were neutralising, in agreement with other results.^{104,105} RBD-specific antibodies were also shown to have potent neutralising activity in a range of other small studies,^{70,104,106–112} including one using an IgA isotype.¹¹³ Neutralising ability correlated in particular with competition for the angiotensin converting enzyme - 2 (ACE2) receptor.^{70,72,106} Two studies demonstrated a lack of association with affinity,^{73,106} although a moderate correlation with binding affinity was reported in one study.¹⁰⁷ Potently neutralising N specific antibodies were isolated in other studies,^{73,109} and the potential for antibodies binding to protease cleavage sites as alternatives to RBD isolated from convalescent plasma has also been identified,¹¹⁴ suggesting an important role in preventing antibody dependent enhancement of viral entry.

Few studies investigated B cell responses in detail. A study by Galson et al of 19 hospitalised patients demonstrated clonal expansion and induction of a B cell memory response (possibly to other circulating coronaviridae) but that the predominant expansion was in the naïve B cell population.¹¹⁵ Strong convergence of response emerged across different participants, which was judged to be associated with disease severity, and these findings were consistent with another high quality study.⁸⁷

Correlation of antibodies with viral load

Several studies investigated the relationship between SARS-CoV-2-specific IgG and viral load^{116,117} or the co-existence of antibodies and viral RNA.^{15,24,25,38,42,46,62,64} In a large cohort study, the presence of SARS-CoV-2 anti-N IgG was significantly correlated with reduced viral load (measured as cycle threshold (Ct) >22, which was also associated with lower mortality).¹¹⁶ This was consistent with a study by To et al which correlated increasing anti-N IgG titres with

decreasing median viral load from 6.7 to 4.9 log₁₀ copies per mL between weeks one to three.¹¹⁷ Another high-quality cohort study had similar findings but did not quantify viral load.²⁴ Together these findings suggest the persistence of detectable RNA despite clinical recovery, and although viral loads generally reduced in the convalescent phase, co-existence of SARS-CoV-2 specific IgG and detectable SARS-CoV-2 RNA could be identified in a small number of patients for up to 50 days following seroconversion.²⁵ Other studies were mixed, with one finding higher levels of specific antibodies correlated with viral clearance within 22 days,³⁸ and another finding weaker IgG response correlated with viral clearance within seven days after antibodies become detectable,⁴² although both of these findings are subject to a number of limitations. Importantly, one included study attempted to associate re-detection of viral RNA with the presence of specific antibodies, finding that IgG titres began to decrease immediately following recovery although this was not associated with whether RNA was re-detected. Across all included studies, high quality evidence for re-infection or lasting immunity was lacking.

Re-exposure to SARS-CoV-2

Studies exploring re-exposure to SARS-CoV-2 virus were limited to seven animal studies of variable quality. Broadly, two areas were explored; exposure following a primary infection with SARS-CoV-2^{89–91,118} and re-exposure following passive transfer of neutralising antibodies.^{92,103}

Following primary infection, timing of re-challenge varied between 20–43 days post inoculation. All studies but one⁹⁰ demonstrated some level of protection from reinfection with a high-quality study in nine macaques showing a significant reduction in viral titres ($p < 0.00001$) and reduced clinical symptoms.⁸⁹ Similar findings were reported in a hamster model.^{92,118} In a smaller ferret study, clinical findings following reinfection were mixed with the re-challenged group demonstrating increased weight loss compared to naive ferrets. However, the authors acknowledged that the sample size ($n=4$) was too small to draw wider inference.⁹⁰

Two studies examined protection from SARS-CoV-2 infection following the passive transfer of neutralising antibodies in Syrian hamster models.^{92,103} Following transfer of highly potent neutralising antibodies 12 hours prior to infection, hamsters showed lower viral titres and fewer clinical symptoms of COVID-19. However, following transfer of less potent neutralising antibodies, 1–2 days prior to infectious challenge, results were mixed demonstrating their inability to fully neutralise the virus.¹⁰³ Data on protection from re-infection in humans was not identified in the included papers, therefore conclusions on protective immunity are limited.

Cross-reactivity with other coronaviruses

There is limited evidence on the cross-reactivity of antibodies specific to other coronaviruses.^{49,51,94,119–121} Using a variety of assays, several in-vitro studies explored both cross-reactive antibody-binding responses and cross-neutralisation between SARS-CoV-2 and seasonal coronaviruses, MERS-CoV and SARS-CoV-1. Cross-reactive antibody-binding responses appear to be highest between SARS-CoV-1 and SARS-CoV-2, however cross-neutralisation is rare and where reported is weak.^{49,94,119} Whilst seasonal HCoV-229E are more common in the population, only 10% of sera exposed to HCoV-229E demonstrated cross-reactivity again with very little neutralisation activity.¹²⁰ A study comparing cross reactivity in children and older participants found children had elevated CoV-specific IgM compared to more mature class-switched specific IgA and IgG.¹²² All studies were performed in-vitro and recognised the need for in-vivo investigation.

DISCUSSION

Summary of findings

Most people who experience symptomatic SARS-CoV-2 infection undergo seroconversion to produce a detectable, specific antibody response in the acute phase (≤ 28 days). The kinetics of the antibody response to SARS-CoV-2 follow typical immunological paradigms: virus-specific IgM rises in the acute phase to a peak around two to five weeks following disease onset, then declines over a further three to five weeks before becoming undetectable in many cases; IgG peaks later (three to seven weeks following disease onset), then plateaus, persisting for at least eight weeks with some evidence suggesting a moderate decline over that period. However, understanding of IgG dynamics over time is limited by the understandably short duration of follow up in studies published to date.

Evidence suggests the majority of those infected with SARS-CoV-2 develop nAbs – a finding that is consistent with previous findings for SARS-CoV-1 and MERS-CoV.⁷ The size of this response appears to correlate with disease severity. Neutralising antibodies are initially detectable from around seven to ten days, peaking at around three weeks and then declining. Further evidence is required to evaluate comprehensively the apparent waning of the nAb response over time. Although nAb may be detectable, high quality studies suggest that titres are generally low, and

the response is short lived. This is supported by recently published data (beyond the date cut off for inclusion in this study) from a UK cohort of healthcare professionals.¹²³

A number of potent, specific nAbs have been identified – in line with findings for other HCoVs. This is particularly the case for neutralising anti-RBD antibodies,¹²⁴ and is consistent with data emerging from vaccine development studies showing that protective antibodies can be induced.^{125–127} Ongoing vaccine research has, however, highlighted a need for evidence of longer-term protection due to nAbs, and the titres at which these effects are achieved – neither of which were fully addressed by studies included in this review. This is a significant gap in the evidence base on the immune response to SARS-CoV-2.

Data on correlates of the antibody response is incomplete, inconsistent or contradictory. It is not possible to draw robust conclusions on the associations of antibody response with age, sex, ethnicity or comorbidities, and although disease severity positively correlated with higher IgG antibody titres in a number of studies, distinguishing causation from correlation is not possible. The size of the detectable nAb response appears to be associated with male sex (although the effect of disease severity was not controlled for); this is a surprising finding given the now well-recognised association between male sex and poor COVID-19 outcomes.¹²⁸

Available data on protection following primary infection are limited to small scale animal models which consider re-exposure rather than reinfection. Primary infection appears to provide a degree of protection to reinfection up to day 43 post primary inoculation but no further data are available at later time points. The success of passive transfer of nAbs for protection against SARS-CoV-2 infection appears to be dose dependent, although no data exist around the importance of affinity, isotype or immunoglobulin subclass. Given the probable reduction in nAb titre over time, the protection they provide is likely to be limited. Limited cross reactivity is evident between SARS-CoV-2 and other HCoVs, but cross-neutralisation is rare and when it does occur, fails to fully neutralise the SARS-CoV-2 virus.

Strengths and limitations

Our review is the first to provide an overview and critical appraisal of literature published since the beginning of 2020 on the immune response in the round. Our findings are nevertheless limited both by aspects of the review methodology and by shortcomings in the included literature. The comprehensiveness of systematic reviews is always dependent on search strategy, and some

results relevant to the research question may have been missed. As with all systematic reviews, our findings cannot account for unpublished negative results.

Limitations of the underlying evidence base were considerable. A majority of included studies were of moderate quality. Study populations were highly variable, as were the assays used, along with the rigour with which they were described, verified and validated against their target populations. There are efforts in the UK to standardise laboratory SARS-CoV-2 assays use through the National External Quality Assessment Service (NEQAS), but these are early stage and no comparable international initiatives yet exist to support comparability of research findings. Longitudinal follow-up for durations greater than 50-60 days was rare. Many studies did not perform statistical analysis of findings; in particular, studies of putative correlates of immune response usually failed to control for the effects of potential confounders. Small sample sizes were common, as were study populations selected by convenience which, although common for clinical cohort studies, are prone to bias. Additionally, a large body of the evidence drew from pre-print publications which have not been subject to peer-review. While efforts were made to account for this during synthesis and reporting, reporting standards in these publications were highly variable and there is no validated system at this time for weighting evidence from pre-print publications relative to peer-reviewed papers. Finally, reporting of ethical approval was limited or absent in many studies.

Implications for policy

We identify two main policy implications arising from this work. At individual level, continuing uncertainty concerning the nature of the humoral response to SARS-CoV-2 makes it difficult to determine what the practical meaning of serologically-detected antibody response is with respect to sterilising immunity. Short follow-up periods, as well as the use of binary (positive/negative) serological tests in many studies continue to limit what can be said about the granularity of the immune response over time – and by implication, how best to interpret the results of serological testing with respect to individual susceptibility to infection.¹²⁹ We did not identify any studies considering risk of re-infection with SARS-CoV-2, which might provide an alternative perspective on susceptibility to infection.

At population-level, important policy implications arising from these data on antibody response relate to both surveillance and control. Reliance in the published literature on serological tests that have been evaluated predominantly in acutely unwell, hospitalised patients (without

appropriate validation against mild disease or in people with asymptomatic infection) means that seroprevalence estimates from this work should be treated with caution. A recent Cochrane review emphasises the risk of false-positive and false-negative results under different population prevalence scenarios.¹³⁰ However, in the UK, nationally validated assays have been evaluated with convalescent samples from community participants and a number of large-scale sero-surveys now use these.^{131–133} Clear understanding of the kinetics of the response, particularly for the specific N and S antigens, is important for the interpretation of seroprevalence studies.

With regard to control, the evidence here for lasting protective immunity, or lack thereof, may suggest it is too early to recommend the use of ‘immunity passports’. A range of promising data have been identified to support further investigation of treatment with convalescent plasma or immunoglobulin, and the basic science underlying the antibody/virus/host cell interaction is starting to be described, with promising findings related to vaccine development. For vaccines, beyond development, strategies for implementation will also require a thorough understanding of the likely impact in different population groups.

Onward research questions

Investigating the relationship between antibody response and correlates including age, sex, ethnicity and disease severity through high-quality, large-sample studies using well validated assays and incorporating appropriate statistical testing of results should be prioritised. The limited amount of data on antibody dynamics for mild and asymptomatic cases, which are likely to make up a significant proportion of infections, is a particularly important gap in the literature that will need to be addressed to improve understanding and definition of the varied clinical phenotypes associated with SARS-CoV-2 infection.

Evidence on immunity beyond three months following primary infection or vaccination is urgently needed. Evidence of immunity following vaccination is being explored through various vaccine trials (e.g. ChAdOx1 nCoV-19).¹²⁵ However, longitudinal studies of those already infected with SARS-CoV-2 is required to examine the degree of protection arising from prior infection.

Conclusions

Studies on the immune response to SARS-CoV-2 is of variable quality, and comparison of findings is difficult. A longer-term view and a more comprehensive assessment of the role of demographic characteristics and disease severity is required. Larger, high-quality, longitudinal studies, with

appropriate statistical analysis, consistent use of established and well-validated serological assays matched to clearly defined clinical phenotypes should be prioritised.

Author contributions (CRediT author statement)

NP – investigation, writing – original draft, writing – review and editing

DE – conceptualisation, investigation, project administration, writing – original draft, writing – review and editing

CH – investigation, writing – original draft, writing – review and editing

MCIVS – conceptualisation, investigation, methodology, writing – original draft, writing – review and editing

MS – investigation, writing – original draft, writing – review and editing

DL – investigation, writing – review and editing

SR – investigation, writing – review and editing

SVW – investigation, writing – review and editing

WHB – validation, writing – review and editing

PK – conceptualisation, validation, writing – review and editing

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AMS – validation, writing – review and editing

GA – conceptualisation, supervision, validation, writing – review and editing

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SAI – conceptualisation, investigation, methodology, project administration, writing – original draft, writing – review and editing

Acknowledgements

We thank Professor Mike Ferguson from the School of Life Sciences, University of Dundee, for comments on the research questions and initial outputs from this work; and Professor Mark Petticrew from the Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine for advice on methodological aspects of this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. MCIVS is funded by a NIHR Doctoral Fellowship (Ref NIHR300156). JM acknowledges the support of the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. SAI is supported by a Wellcome Trust Clinical Research Training Fellowship (Ref No 215654/Z/19/Z). The views expressed in this paper are those of the authors and not necessarily those of the NHS, the NIHR, PHE or the Department of Health.

Competing interests

JM is chief scientific officer, shareholder and scientific founder of Leucid Bio, a spinout company focused on development of cellular therapeutic agents. The authors report no other competing financial interests or conflicts of interest.

Ethics

This was a systematic review based on analysis of openly published secondary data. No ethical approval was required.

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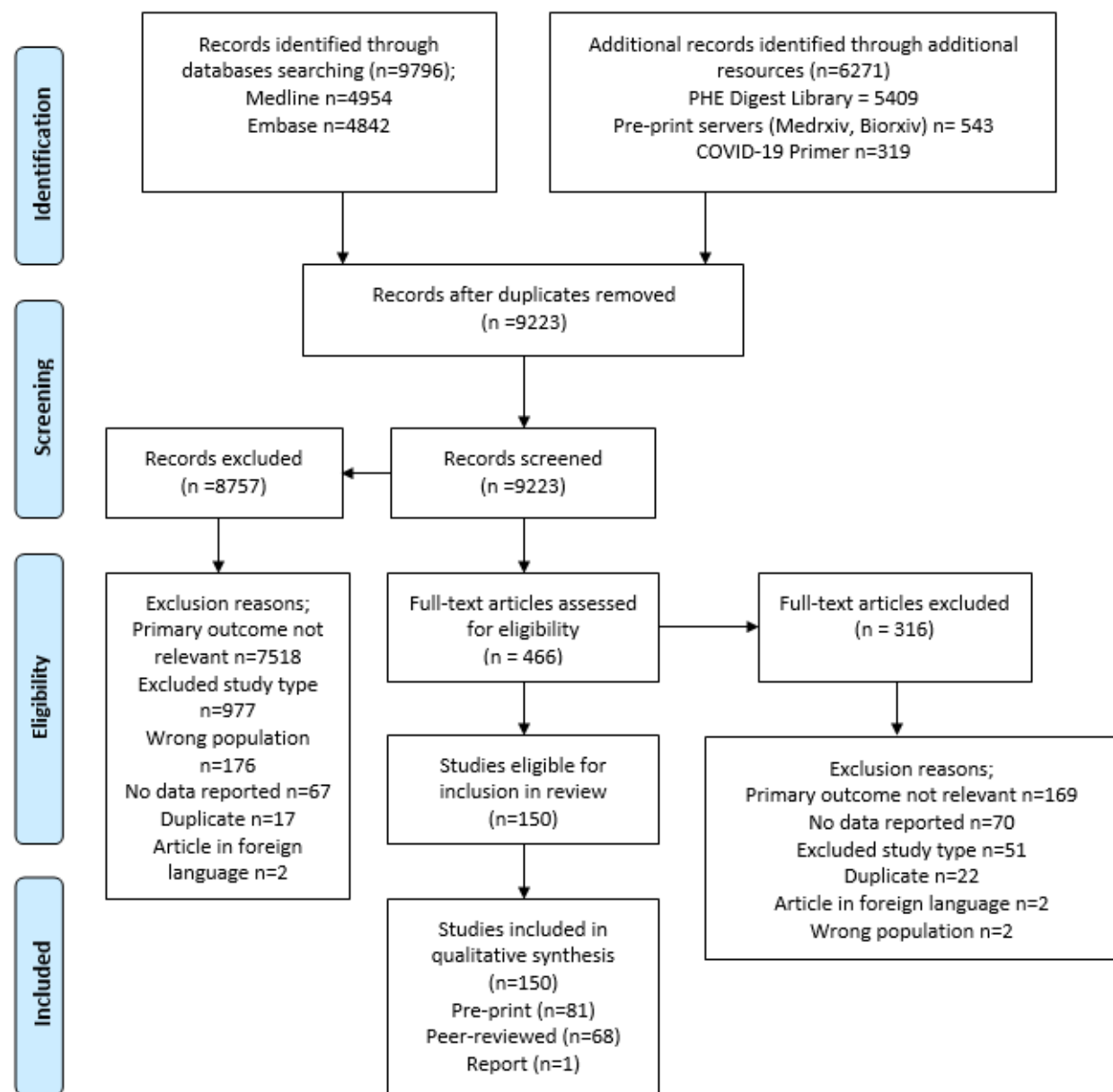


Figure 1. PRISMA flowchart describing the process of screening and selection of included studies.

	<i>Antibody response</i>	<i>Protective Immunity</i>
<i>Article type</i>		
Pre-print	57	43
Peer reviewed paper	51	26
Report	0	1
<i>Study designs</i>		
Cohort	58	18
Case control	20	14
Case series	15	8
Basic science	4	22
Narrative review	4	2
Systematic review with meta-analysis	5	2
Systematic review without meta-analysis	1	1
Non-randomised trial	1	2
<i>Subjects</i>		
Human	104	58
Animal	1	6
Both	3	6
<i>Country of origin</i>		
China	41	20
USA	15	14
Europe excl UK	29	9
UK	7	5
Other countries	5	4
Multiple populations	10	6
Lab or animal based*	1	12
<i>Study setting</i>		
Hospital patients	70	33
Mixed hospital and community	18	11
Community	13	5
Unclear	6	12
Animal only study	1	9
<i>Overall MetaQAT quality assessment</i>		
High	25	9
Moderate	74	51
Low	9	10

Table 1. Summary of characteristics of included studies.

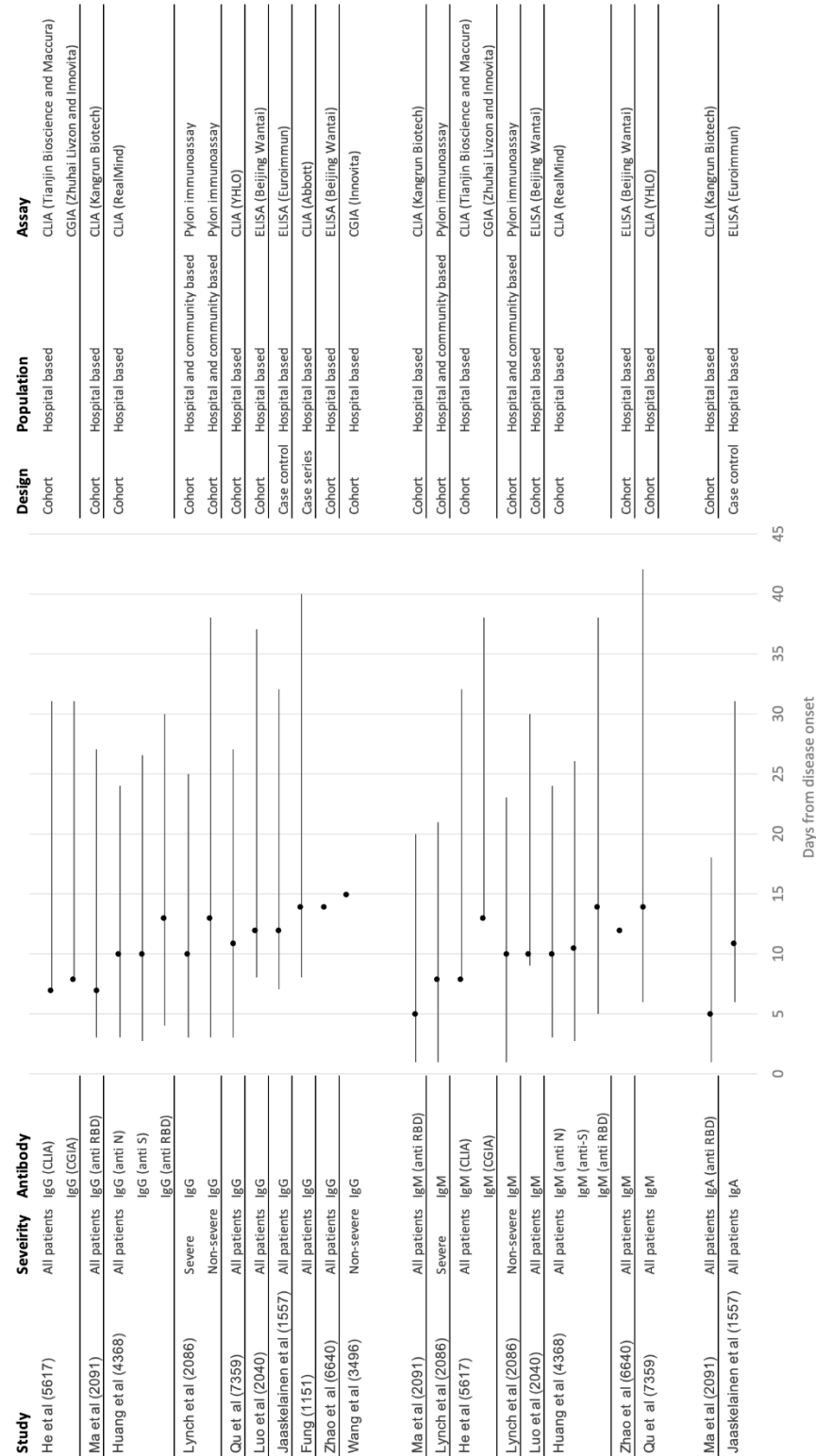


Figure 2. Forest plot showing median time to seroconversion by severity across included studies. Central points in the forest plot represent the median reported by each study overall; the range across participants in each individual study is represented by whiskers either side.

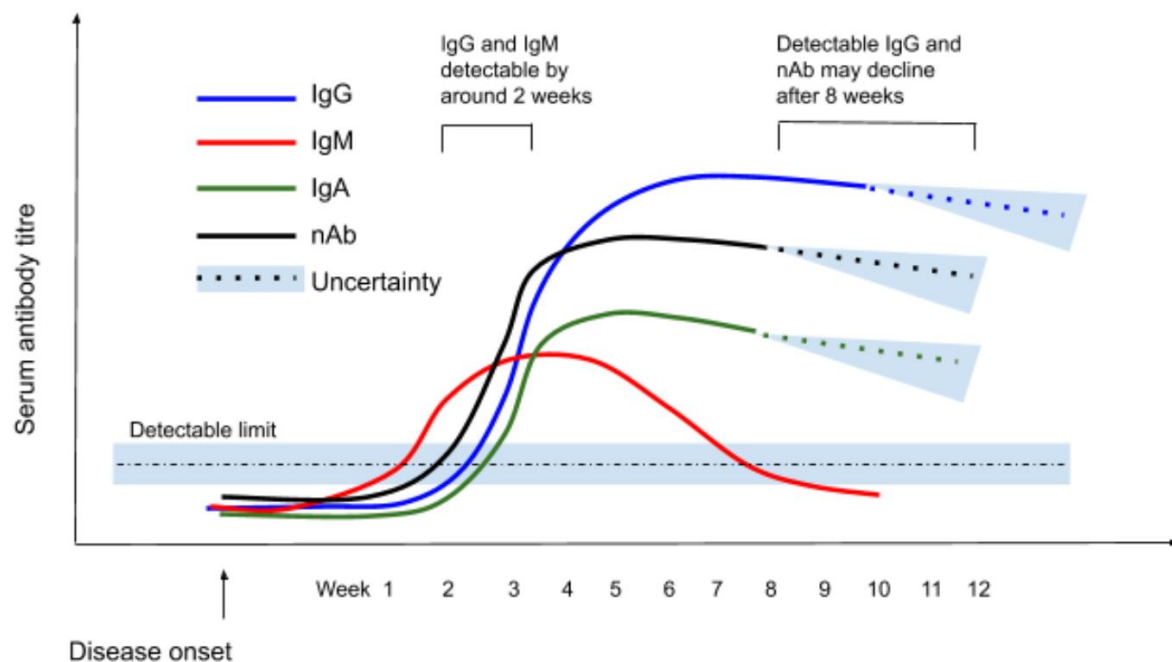


Figure 3. Schematic showing scale of IgG/IgM/IgA/Neutralising Ab response over time from disease onset (note that the y axis is illustrative – no scale is given).

Table 2. Evidence on correlates of antibody response

Category	Correlate	Dimension or sub-population	Findings
Clinical	Disease severity	Longitudinal trends in Ab production	- Most studies report no relationship between time to seroconversion for IgG or IgM and disease severity.^{22,35,53,56} - A number of studies report earlier antibody response to more severe disease^{134,135}, including specifically for IgG;⁷ a shorter time to peak antibody titre,^{19,26,136–138} including specifically for IgA,³⁰ and that IgG persists for longer in severe disease compared to milder cases.^{139,140} - Three studies report an earlier antibody response to milder disease,^{19,43} including specifically IgM¹⁴¹ and IgA,¹⁴⁰ shorter time to peak for IgG,¹⁴⁰ and IgG persists for longer compared to severe cases.¹⁴² - One study reports lower seroconversion rate amongst asymptomatic compared to symptomatic cases.¹⁴³ - Two other studies on this association were limited by low quality.^{144,145}
		Antibody titre	- Ten studies reported that more severe cases have higher IgG titres,^{23,34,39,42,75,146–150} three studies reported no difference between mild and severe cases,^{45,53,63} and two studies report severe cases have lower IgG titres.^{53,63} - Five studies reported severe cases have higher IgM titres,^{23,34,39,45,53} two studies reported no difference in between mild and severe cases,^{64,102} and three studies reported severe cases have lower IgM titres.^{150–152} - Three studies report severe cases have higher IgA titres,^{23,140,148} one study reports no difference between mild and severe cases.¹⁵¹
	Co-morbid disease		- Three studies report an association between co-morbidities and seroconversion or antibody positivity,^{64,153} with one finding immunocompromised individuals developed a lower response.¹⁵⁴ - One study reports antibody responses to be independent of co-morbidities, for both IgA and IgG.¹⁴⁸ - One study on this association was limited by low quality.¹⁵⁵
	Symptom profile		- Three studies report an association between COVID-19 symptoms and seropositivity,^{156–158} and with higher titres of IgG,^{29,159} IgA,¹⁵⁹ and anti-RBD and anti-S antibodies.¹⁶⁰ - Two study reported that asymptomatic healthcare workers did develop antibodies.^{161,162} - Fever appears to have a consistent relationship with seropositivity and antibody titres,^{29,158,160} although other symptoms such as ageusia have also been associated.^{156,158}
Demographic	Sex		- Four studies report no association between antibody titres (either IgG or IgM) and sex.^{21,148,163,164} - Two studies report a higher IgG titre in women,^{165,166} although one found this association in severe patients only.¹⁶⁶ - Two studies report a higher proportion of women tested positive for antibodies.^{156,164} - One study found higher anti-RBD and anti-S antibodies in male plasma donors.¹⁶⁰
	Age	Older adults	- Five studies found no association between antibody response and age, for both antibody positivity¹⁴⁷ or IgM/IgG titre.^{21,58,148,167} - One study found that 'older' patients were more likely to seroconvert,¹⁵³ and concentration of IgG was related to age.³⁴ - Three studies reported that older people had higher titres of IgA and IgG,²³ IgM,¹⁶³ and anti-S and anti-RBD IgG.¹⁶⁰
		Children	Two studies found children generally developed a detectable antibody response to SARS-CoV-2 infection^{86,168}

			- Two studies found children with pneumonia generally mounted lower IgG¹⁶⁹ and IgA responses¹⁷⁰ and one study reported no differences.¹⁶⁷ - Two studies reported most neonates born to COVID-19 positive mothers had raised IgM,^{171,172} and COVID-19 recovered donor breast milk was found to have reactive IgA in one study.¹⁷³
	Ethnicity		One study reported non-white ethnicity was associated with higher antibody levels than white ethnicity.¹⁵³

Table 3. Evidence on correlates of neutralising antibody response

Category	Correlate	Dimension or sub-population	Findings
Clinical	Disease severity	Longitudinal trends in Ab production	One study reported asymptomatic cases with neutralising antibodies were more likely to lose detectable neutralising antibodies in the convalescent phase.¹⁵⁹
		Antibody titre	- Ten studies reported a higher titre of neutralising antibodies in more clinically severe cases.^{7,43,49,66,85,87,95–98} - One study reported undetectable neutralising activity in plasma from a majority of asymptomatic cases.⁸⁵
Demographic	Sex	N/A	- Five studies reported neutralising antibody response was positively correlated with male sex,^{66,68,87,96} although it is unclear how this is related to disease severity.⁴⁹ - One study reported a positive correlation between neutralising antibody formation and female sex.⁸⁵
	Age	Older adults	- Two studies reported increasing neutralising antibody response with increasing age.^{20,94} - Two studies reported no association between neutralising antibodies and age.^{68,85}
		Children	Two studies reported children can develop a neutralising antibody response.^{48,86}
	Ethnicity	N/A	One study reported that individuals with Hispanic/Latino ethnicity were more likely to have detectable neutralising antibody responses (although this study was based on a convenience sample in an atypical cohort – US service personnel on a warship).⁶⁵

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY APPENDIX A: Sample search strategy

Database(s): Embase 1996 to 2020 Week 17

Search Strategy:

#	Searches	Results
1	exp coronavirus/	12437
2	exp Coronavirus Infections/	12279
3	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.	551
4	(coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).tw,kw. ("2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV-2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2").tw,kw.	15440
5		4488
6	((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*).tw,kw.	1738
7	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*).tw,kw.	91
8	("severe acute respiratory syndrome*" or SARS).tw,kw.	11647
9	or/1-8	31091
10	exp *serology/	16162
11	exp *antibody/	312568
12	exp *antibody response/	7205
13	exp *seroprevalence/	5135
14	exp *serum/	19113
15	exp *assay/	93624
16	exp *immunity/	306567
17	exp *diagnosis/	1200947
18	(sero* or antibod* or serum or sera or test or tests or testing or diagnostic or diagnosis or immunity or "immune response").tw,kw.	6175013
19	(assay* adj3 sero*).tw,kw.	6289
20	or/10-19	7090637
21	9 and 20	10106
22	limit 21 to english language	9349
23	limit 22 to dc=20200101-20200331	451
24	limit 22 to dc=20200401-20200428	688

Supplementary figure B1. Sample data extraction template as used in the review.

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SUPPLEMENTARY APPENDIX C: Approach to critical appraisal used in the review

There is a wide range of critical appraisal tools (CAT) available to support evidence assessment and synthesis work in public health and policy, but the applicability of these tools in the context of primary work in immunology is limited by (among other limitations):

- An overwhelming focus on interventional studies, rather than those concerned with exposures;
- A relative absence of tools for critical appraisal of laboratory studies, in particular experimental animal models;
- A relative absence of summative tools that enable critical appraisal of varied study types in a standardised way (rather than application of specific checklists for each study design).
- The time and resource-intensity, which limits scope for reproducible, meaningful, and robust appraisal of evidence in the context of a pandemic in which prodigious volumes of evidence are being generated.

These limitations make it very challenging to identify a coherent approach to critical appraisal that allows for evidence quality to be meaningfully compared across multiple study designs. Preliminary scoping work for this review suggested a tendency in the field of immunology to publication of narrative reviews (rather than conventional systematic reviews) without clear description of study selection criteria or critical appraisal methods. For the purposes of this review, we sought to identify a CAT that:

- Was closely related to an existing, validated tool so that it can be presented as a modification of that tool without the need for new and extended validation work;
- Was low burden and quick to use given required speed of turn-around;
- Facilitated high-level comparison of quality across diverse study designs for reporting purposes;
- Would be rapidly interpretable (ideally in the form of a traffic light system or similar) for time-pressed report readers.

Following a review of existing, generic CATs, we selected the Public Health Ontario MetaQAT 1.0 as our base tool¹⁴. This is a qualitative critical appraisal tool based around 4 dimensions (relevance, reliability, validity, applicability of research findings). We made two main modifications to this tool:

- Inclusion of additional domains for publication type (pre-print, peer-reviewed etc) and for assay type and validity.
- Introduction of a scoring and weighting system to translate findings from the tool into a traffic-light grading system for individual papers. This was not used to inform aggregate assessment of evidence strength against the review's over-arching research questions – these assessments were made narratively.

Supplementary figure C1 shows the tool developed from this process. Reliability assessment questions were given an overall weighting of 20%, and internal external validity assessment questions 40%. The aggregated score developed from this tool was out of 10; a score of over 8 was scored “high”; 5-8 scored “medium” and scores less than 5 were “low” quality.

Domain	Assessment	Additional comments (if any)	Notes/interpretation (example prompt questions)	Question score	Weight	Weighted domain total
Publication type			Self-explanatory	0	10%	0
Assessment of relevance: is the study relevant to the review questions?			Is the justification for the study clearly stated?	0	10%	0
			Does it consider a similar population to the UK?			
			Assessment of reliability (i.e. reproducibility)			
Is the study presented clearly?			Is the rationale clearly stated?	0	20%	0
			Is the conduct of the study clearly described?			
			Are all relevant results stated?			
Are the methodology and results clearly described?			Are inclusion/exclusion criteria clearly stated?	0		
			Was an appropriate statistical analysis approach applied?			
Are ethics procedures described?			Was appropriate consent sought and received?	0		
			Was the study REC approved?			
Assessment of internal/external validity						
Is the methodology appropriate for the scope of research and the research questions?			Is the design congruent with the research questions?	0	40%	0
			Were appropriate controls sought and included?			
Is the methodology free from bias?			Were there major sources of bias in the design, selection of participants/controls etc?*	0		
(Where relevant) what assay was used and was it validated?			For validated tests, did the study team deviate in important ways from the manufacturers' instructions?	0		
			Was a control used (e.g. for Ab measurement)?			
Are the conclusions explicit and transparent?			Do the conclusions logically follow-on from the results presented?	0		
Can I be confident about the findings?			Are there major methodological flaws limiting interpretation of findings?	0		
Assessment of applicability:						
How applicable are the study findings to the population(s) and public health questions to which the rapid review is addressed?			Can the results be meaningfully applied to the focus questions for the rapid review?	0	20%	0
			Can they be applied to the UK population (or groups of interest)?			
			TOTAL SCORE			0

Supplementary figure C1. Sample MetaQAT template including prompt questions, and weightings applied to each of the main question domains in the tool for the purpose of quality scoring.

SUPPLEMENTARY APPENDIX D: Assays used in studies on antibody response

A range of assays were used in included studies (**supplementary table 1**), although in the majority of cases it was not stated how the assay had been validated internally, or the nature of third party controls that were employed as part of the quality control process. In around half of studies, it was not stated whether commercial assays were performed according to the manufacturer's instructions. Included studies used a range of methods for quantification of neutralising ability, based either on plaque reduction neutralisation tests (PRNT) or microneutralisation tests (MN). In general, EC50 or IC50 were recorded using a range of end points such as cytopathic effect or luciferase activity.

Assays for neutralising antibodies were generally established in house rather than sourced from commercial suppliers and the detailed analysis of these methods was beyond the scope of this review. One study directly compared MN and PRNT neutralisation assays, finding PRNT more sensitive in a small cohort ⁷⁵. Both types of neutralising antibody assays have been employed using either authentic virus or pseudoviral particles in which SARS-CoV-2 S protein has been incorporated into a low pathogenicity, virus-like particle capable of only a single infection cycle. There was no clear predominance of use of either substrate. Two studies suggested that neutralisation sensitivity was lower with primary SARS-CoV-2 than pseudovirus ^{87,106}, although this finding was not reproduced in another study ⁷⁰.

<i>Assay</i>	<i>Number of studies in which assay type was used</i>	<i>Number in which validation status was reported</i>	<i>Number in which use as per manufacturer's instructions was reported</i>
ELISA	43	23	28
CLIA/CMIA	27	8	14
LFIA	11	8	7
CGIA	4	1	1
Multiplex	4	3	4
LIPS	3	3	3
EIA	3	2	2
IFA	3	2	2
Other	3	2	2
In house or commercial assay unable to characterise	5	4	3
Assay not described	8	n/a	n/a
Total	114	56	64

Supplementary Table 1. Summary of assays used for serology measurements in included studies by type, reporting of validation status and according to whether use was in accordance with manufacturer's instructions.

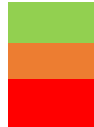
SUPPLEMENTARY APPENDIX E: FULL LIST OF INCLUDED STUDIES

Key – study quality assessment scoring system:

High quality:

Medium quality:

Low quality:



Paper	Country	Publication type	Study design	Population	Relevant Outcomes	Measurement	Findings	Quality Assessment
Adams, E et al ⁵⁸	UK	Pre-print	Case control	Mixed hospitalised and community participants 40 cases, 142 controls	IgM and IgG kinetics including titre	ELISA (anti S) (in house) and IgM, IgG and total Ab LFIA (9 commercial assays)	85% of 40 RT-PCR-confirmed positive patients had IgG detected by ELISA, including 100% patients tested ≥ 10 days after symptom onset. IgG antibody titres rising over the first 3 weeks from symptom onset, and fell during the second month after symptom onset. No temporal association between IgM titres and time since symptom onset. No evidence that SARS-2-CoV severity, need for hospital admission or patient age were associated with IgG or IgM titres in multivariable models.	Selection of participants not clearly described Validation of ELISA assay not described
Agarwal, V et al ²⁷	USA	Pre-print	Cohort	Hospitalised participants 81 cases	IgG kinetics	Not described	Mean upper bound of time to IgG seroconversion of 38.1 days Data suggests COVID-19 patients potentially continue to shed viral RNA while generating IgG antibodies	Selection of participants not clearly described Validation of ELISA assay not described
Anderson et al ¹²¹	Singapore	Peer reviewed paper	Case series	Hospitalised participants 7 cases (SARS-CoV-2) 12 cases (SARS-CoV)	Cross neutralisation ability (SARS-CoV)	ELISA (anti S) (in house) and IgM, IgG and total Ab LFIA (9 commercial assays)	SARS-CoV patient sera contains neutralising antibodies 9-17 years post infection SARS-CoV patient sera has very limited neutralisation ability against SARS-CoV-2	Selection of participants not clearly described Validation of ELISA assay not described

Bao et al ⁹¹	Lab or animal based	Pre-print	Basic Science	Animal study (rhesus macaques)	Specific antibody titre following challenge, neutralising antibody titre, protection against reinfection	ELISA (anti S) Neutralising antibody observed by cytopathic effect	SARS-CoV-2 antibody gradually increased to peak 21 days post disease onset 4/4 monkeys showed evidence of neutralising antibody No recurrence of COVID-19 in rechallenged monkeys following primary infection	Selection of participants not clearly described Validation of ELISA assay not described
Bao et al ¹⁵²	Multiple populations	Pre-print	Systematic review with meta-analysis	Mixed hospitalised and community participants 5,912 cases Mean age 54 52% male	IgA, IgM and IgG kinetics including titre T lymphocyte profile	Not described	Severe cases had lower levels of CD4 T cells and CD8 T cells Compared with the non-severe group, severe cases had lower IgM with no significant difference in other antibodies	Selection of participants not clearly described Validation of ELISA assay not described
Benotmane et al ⁵⁶	France	Pre-print	Cohort	Hospitalised participants (kidney transplant recipients) 40 cases Median age 63 75% male	IgM and IgG kinetics including titre	ELISA (anti N and anti S IgM and IgG) (DIA.PRO Diagnostic)	All cases developed antibodies by the second week after symptom onset that persisted for two months. A stable titer of IgG antibodies was maintained until day 59, suggesting persistence for at least until two months IgM and IgG antibody level and delays in seroconversion were not correlated with COVID-19 severity	Selection of participants not clearly described Validation of ELISA assay not described
Borremans et al ²²	Multiple populations	Pre-print	Systematic review with meta-analysis	Mixed hospitalised and community participants 516 participants	IgM and IgG kinetics Neutralising antibody detection	ELISA, MCLIA and LFIA PRNT80	Mean IgG seroconversion time is 13.3 days post symptom onset with ELISA-NP and 12.6 days for IgM using ELISA- S with similar values when using MCLIA, and wide variation between participants. Disease severity does not significantly affect seroconversion time for IgM or for IgG Maximum probability of IgG detection increases to days 25-27 up to at least 60 days (end of follow up in included studies). Maximum detection probability of IgM peak near 90% around day 25 then decreases. Detection probability for nAb rapidly rises to near 100%, where it remains up to the last time available in the dataset (29 days), and detection probability does not differ significantly with severity	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Brocato et al ¹¹⁸	Lab or animal based	Pre-print	Basic Science	Animal study (syrian hamsters) 30 hamsters	Neutralising antibody titre, protection against reinfection	PRNT80	Non-immunocompromised hamsters developed a robust neutralizing antibody response compared to immunocompromised hamsters. Previously infected hamsters who tested positive for neutralising antibodies were re-challenged and none exhibited clinical signs of COVID-19 infection Hamsters treated with mAbs targeting the S protein of	Selection of participants not clearly described Validation of ELISA assay not described

							SARS CoV2 did not exhibit clinical signs of COVID-19 infection	
Brochot et al ¹⁸⁵	France	Pre-print	Cohort	Hospitalised participants 30 cases Median age 77 66% male	Ab kinetics Neutralising antibody titre	ELISA (anti N, anti RBD, anti S1 and anti S2) (in house) Commercial neutralisation assay	Antibodies targeting the N protein and the RBD were the earliest detected, detectable in all cases after 13 days and anti S2 by 15 days, anti S1 were detected last and not detected in all cases Significant differences observed between mild and severe disease patients for anti-S1, anti-S2 and anti-N antibody levels, after eight days. Slight difference in anti-N antibody levels according to sex from 14 days. Significant difference in anti-S1 and anti-S2 antibodies according to age between 8 and 14 days NAb kinetics correlate with production of antibodies targeting the S1, S2 and RBD. NAbS detected in all hospitalised cases by 15 days. NAb titres increased from 1 week and plateau 1 week later, although titres were variable between cases. NAb titre dropped to low or undetectable level in most samples beyond 40 days. Significantly higher NAb titres observed in severe cases and in females.	Selection of participants not clearly described Validation of ELISA assay not described
Brotons et al ¹⁵⁶	Spain	Pre-print	Cohort	Community participants 311 asymptomatic cases Mean age 44 55% female 634 symptomatic cases Mean age 47 58% female	IgG and IgM seroprevalence	LFIA (IgG and IgM)	Reports seroprevalence in sample Logistic regression concludes seropositive individuals more likely to have symptoms	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Brouwer et al ⁷⁰	Lab or animal based	Peer reviewed paper	Basic Science	3 participants	Detection of neutralising antibodies and neutralising ability	ELISA (anti S) Pseudovirus and live virus neutralisation assays (not detailed)	Strong and specific B cell responses detected including memory and antibody producing B cells in response to infection. Strongest response in individual with most severe clinical disease. NAbS isolated which targeted a diverse range of S protein antigenic sites, including both RBD and non-RBD epitopes and NAbS targeting multiple sites. Potent neutralisers of live virus identified. Extensive affinity maturation not required for potent neutralisation.	Selection of participants not clearly described Validation of ELISA assay not described

Bryan et al ¹¹⁶	USA	Pre-print	Cohort	Hospitalised participants 245 cases 60% male	Correlates of IgG detection	ELISA (anti N) (Abbott Architect)	IgG inversely correlated with viral load 33% of participants seroconverted prior to admission Seroconversion on admission trended towards lower mortality, although not significant	Selection of participants not clearly described Validation of ELISA assay not described
Buntinx et al ²¹	Belgium	Pre-print	Cohort	Community participants 201 cases	IgG and IgM seroprevalence	LFIA (IgG and IgM)	No association was found between either IgM or IgG and gender or age, or presence of symptoms. Of 42 participants positive with PCR, 19 (45%) also had antibodies (IgM/IgG +). Of 134 PCR participants who were negative with PCR, 15 (11%) had antibodies (IgM/IgG +). Of 9 participants tested for antibodies between day 11 and 14 after the positive PCR test, positive IgM results were detected on day 12 and 13 after the positive PCR test, positive IgG results on day 11, 12, 13 and 14	Selection of participants not clearly described Validation of ELISA assay not described
Burbelo et al ¹⁵⁴	USA	Peer reviewed paper	Cohort	Hospitalised participants 35 cases, 32 controls Median age 44 87% male	Ab kinetics	LIPS (anti N and anti S) (Sure Screen Diagnostic)	Antibodies against the N and S proteins appeared day 8 and day 14 after the onset of symptoms for a group of 10 cases Antibody profiles in 3 immunocompromised patients showed more blunted responses	Selection of participants not clearly described Validation of ELISA assay not described
Bwire et al ¹⁷²	Multiple populations	Pre-print	Systematic review with meta-analysis	Infants born to CVOVID-19 positive mothers 2 studies included in quantitative synthesis	IgG and IgM kinetics including titre	Not fully described	Median antibody levels in infants born to COVID-19 positive mothers was 75.49AU/mL and 3.79AU/mL for anti-SARS-CoV-2 IgG and IgM, respectively, suggesting passive immunity	Selection of participants not clearly described Validation of ELISA assay not described
Candel et al ¹³⁹	Spain	Peer reviewed paper	Cohort	Hospitalised participants 35 cases, 5 controls Mean age 57 56% female	IgM and IgG kinetics	LFIA (IgG and IgM) (Autobio Diagnostics Co)	All SARS-CoV-2 positive cases showed corresponding IgG positivity (controls negative) after an average of 28 days from symptom onset. 74% of cases also presented with positive IgM. IgG appeared around day 20 in mild cases and slightly later in severe cases. IgM lasted longer in severe cases compared to moderate cases but was not observed beyond day 25 in mild moderate cases.	Selection of participants not clearly described Validation of ELISA assay not described
Cao et al ¹⁰⁴	China	Peer reviewed paper	Basic Science	Hospitalised participants 60 cases Average age and sex not described	Detection of neutralising antibodies and neutralising ability	PRNT and CPE neutralisation assays	14 potent neutralizing mAbs were identified the most potent of which exhibited an IC50 of 1.2 and 15 ng/mL against pseudotyped and authentic SARS-CoV-2 Prophylactic efficacy demonstrated in mice	Selection of participants not clearly described Validation of ELISA assay not described

Carsetti et al ¹⁴⁰	Italy	Pre-print	Cohort	Mixed hospitalised and community participants 64 cases and contacts Among cases mean age 65 (severe) 55 (mild) Among cases 60% male	IgG and IgA kinetics	ELISA (anti S1 IgG and IgA) (Euroimmun)	Higher levels and persistent levels of IgA and IgG, produced relatively late in infection, associated with severe disease High levels of S1-specific IgA early after diagnosis, rapidly declining and becoming undetectable after 5-7 weeks in asymptomatic cases. Cases with mild disease have IgG and IgA increasing later and remaining relatively low	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Cervia et al ¹⁴⁸	Switzerland	Pre-print	Cohort	Mixed hospitalised and community participants 56 cases Median age 61 55% male 109 exposed contacts Median age 36 77% female	IgG and IgA kinetics including titres	ELISA (anti S1 IgG and IgA) (Euroimmun)	In mild cases, SARS-CoV-2 IgA became positive 8 days after symptom onset and was often transient, IgG levels remained negative or reached positive values 9–10 days after symptom onset. IgA increased slightly as a function of disease duration and IgG increased moderately. In severe cases, higher IgA and IgG correlated with disease duration. Very high IgA correlated with severe acute respiratory distress syndrome (ARDS). 15–20% of S protein-seronegative individuals had detectable S protein-specific IgA antibodies at several mucosal sites. IgA levels inversely correlated with patient age, suggesting increased mucosal antibody responses in younger SARS-CoV-2-exposed individuals. Severe cases had higher serum titers of IgA and IgG. No overall association between antibody response and age.	Selection of participants not clearly described Validation of ELISA assay not described
Chandrashekar et al ⁸⁹	Lab or animal based	Peer reviewed paper	Basic Science	Animal study (rhesus macaques)	Neutralising antibody titre, protection against reinfection	ELISA (anti S IgG) (in house) Pseudovirus and live virus luciferase neutralization assays	All 9 macaques developed binding antibody responses to the SARS-CoV-2 S protein and NAb responses using both a pseudovirus neutralization assay and a live virus neutralization assay. NAb titers of approximately 100 were observed in all animals on day 35. Antibody responses of multiple subclasses were observed against RBD, S and N. After rechallenge very limited viral RNA was observed in BAL on day 1 following rechallenge in 3 animals, with no viral RNA detected at subsequent timepoints. High levels of viral RNA were observed in concurrently challenged naïve animals. Little or no clinical disease was observed in the animals following rechallenge. NAb titers were markedly higher on day 14 following rechallenge compared with day 14 following primary challenge	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

Chen et al ¹⁶⁷	China	Peer reviewed paper	Case series	Hospitalised participants Children 20 adult controls Median age 14.5 6 cases male	IgG and IgM titres	Not described	No significant difference between levels of antibodies between children and adults: children 1.22 +/-0.39 g/L IgM, 10.86 +/-1.44 g/L IgG Children had higher total T cell, CD8+T cell and B cell than adults	Selection of participants not clearly described Validation of ELISA assay not described
Chen et al ¹⁰⁵	China	Peer reviewed paper	Basic Science	Hospitalised participants 26 cases	IgG titres	ELISA (anti S1 and anti RBD)	23 of 26 cases produces high titers of S1-specific IgG antibodies, 3 mounted relatively lower anti-S1 IgG responses, only 3 patients showed effective blockade of SARS-CoV-2 RBD binding to hACE2. SARS Cov-2 RBD-specific IgG antibodies were present in sera of all patients by ELISA	Selection of participants not clearly described Validation of ELISA assay not described
Chen et al ⁸³	China	Peer reviewed paper	Cohort	Community participants 105 healthcare worker contacts of cases Median age 30 79% female	IgG and IgM seroprevalence and neutralising ability	EIA (anti N and anti RBD IgG and IgM) (in house)	19 serum samples showed various degree of neutralization capability, in which from 42% to 99% of SARS-CoV-2 pseudovirus was neutralized. The percentage of neutralization was correlated with anti-NP IgG and anti-RBD IgG 8 out of 19 serum samples showed neutralization percentage of over 50%.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Chi et al ⁷³	China	Peer reviewed paper	Basic Science	Hospitalised participants 10 cases Age range 23 - 53	Detection of neutralising antibodies and neutralising ability	ELISA (anti S and anti N) Pseudovirus and authentic virus luciferase neutralisation assays	Of 35 identified mAbs, only 3 neutralised authentic SARS-CoV-2. Neutralizing ability of plasma against authentic and pseudovirus were correlated although some mAbs neutralised pseudovirus but not authentic virus. On mAb had high neutralising potency but did not bind to RBD.	Selection of participants not clearly described Validation of ELISA assay not described
Choe et al ⁷⁶	South Korea	Peer reviewed paper	Case control	Hospitalised participants 7 asymptomatic cases Median age 25 72% male 17 symptomatic cases 7 subtle (43%M, median age 53y), 4 apparent but mild (75%M, median age 59y), 6 apparent and severe(83%M, median age 75y)	IgG titre (by optical density) Detection of neutralising antibodies and neutralising ability	ELISA (anti S1 IgG) (Euroimmun)	71% of asymptomatic cases seropositive. Higher optical density value in patients with pneumonia; titers correlated with disease severity. All patients showed neutralizing antibody response. Geometric mean titer 78 in asymptomatic patients (n = 7), 256 in patients with subtle pneumonia (n = 4), and 3,158 in patients with apparent pneumonia (n = 8; 4 mild and 4 severe cases).	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings

Cohen et al ¹⁶⁸	France	Pre-print	Case control	Community participants 605 cases (children) Mean age 4.9 53% asymptomatic, 47% paucisymptomatic	IgG and IgM seroprevalence	LFIA (IgG and IgM) (Biosynex)	Only 3/605 children were RT-PCR-positive without any antibody response. The frequency of positivity on RT-PCR for SARS-CoV-2 was significantly higher in children with positive serology than those with negative serology	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Dahlke et al ¹³⁷	Germany	Pre-print	Case series	Hospitalised participants 4 cases and 1 control	SARS-CoV-2 proteome, host B cell immunophenotyping and IgG, IgM and IgA serum antibody interactions	Peptide microarrays	Mild cases displayed stronger IgA response day 3-4 that decreased during the course of disease 7 – 14 days later. IgG response similar but less pronounced trend and appears more persistent. The number of reactive IgG peptides lower in the early acute phase in comparison to IgA. Data showed generally more IgA than IgG or IgM epitopes, with most epitopes located in the S and N protein. Seroconversion occurred at day 7 post onset of symptoms in 50% of infected individuals.	Selection of participants not clearly described Validation of ELISA assay not described
Danh et al ⁸⁸	Multiple populations	Pre-print	Basic Science	37 convalescent plasma samples	Neutralising antibody detection	In house neutralisation assay	NAb detectable at 10 days after onset of symptoms and continue to rise, plateauing after 18 days. S1 proteins showed stronger NAb signals.	Selection of participants not clearly described Validation of ELISA assay not described
De Vriese et al ⁵⁷	Belgium	Peer reviewed paper	Case series	Hospitalised participants 7 cases	IgG kinetics	ELISA (anti N IgG) (NovaLisa)	Overall IgG seroconversion rate was 100% and by the second week after symptom onset. Antibody titer plateaued during the third week. Anti-SARS-CoV-2 IgG antibodies coexisted with virus suggesting these antibodies are not neutralizing	Selection of participants not clearly described Validation of ELISA assay not described

Deeks et al ¹³⁰	Multiple populations	Peer reviewed paper	Systematic review with meta-analysis	Mixed hospitalised and community participants 8,526 cases from 54 studies	Sensitivity and specificity of antibody assays	ELISA (anti N IgG) (NovaLisa)	Pooled results for IgG, IgM, IgA, total antibodies and IgG/IgM all showed low sensitivity during the first week since onset of symptoms (all less than 30.1%), rising in the second week and reaching their highest values in the third week. The combination of IgG/IgM had a sensitivity of 30.1% for 1 to 7 days, 72.2% for 8 to 14 days, 91.4% for 15 to 21 days. Estimates of accuracy beyond three weeks are based on smaller sample sizes and fewer studies. For 21 to 35 days, pooled sensitivities for IgG/IgM were 96.0%. There are insufficient studies to estimate sensitivity of tests beyond 35 days post-symptom onset. Summary specificities (provided in 35 studies) exceeded 98% for all target antibodies with confidence intervals no more than 2 percentage points wide. False-positive results were more common where COVID-19 had been suspected and ruled out, but numbers were small and the difference was within the range expected by chance.	Selection of participants not clearly described Validation of ELISA assay not described
den Hartog et al ¹⁹	Netherlands	Pre-print	Cohort	Mixed hospitalised and community participants 115 cases, 334 controls	IgG kinetics including titre	Multiplex assay (anti S1, anti RBD and anti N)	Hospitalised cases developed higher IgG concentrations and the rate of IgG production increased faster compared to non-hospitalised cases. Hospitalised cases seroconverted around day 10 of disease onset and reached a plateau after two weeks (25 days for non-hospitalised cases)	Selection of participants not clearly described Validation of ELISA assay not described
Dingens et al ⁸⁶	USA	Pre-print	Case series	Mixed hospitalised and community participants 10 cases of 1,076 total participants Children 50% female	Antibody kinetics Neutralising antibody detection and neutralising ability	ELISA (anti S and anti RBD IgG) Pseudovirus neutralisation assay	Demographic and clinical data had no detected associations with seropositivity Eight of 10 seropositive children neutralized virus at a >1:25 dilution with neutralization correlating with RBD and spike binding as measured in the ELISAs. Two children had very high neutralizing activity, including one with a potency that exceeded the limit of our assay (>1:18,000 dilution). The two children without neutralizing activity had not experienced symptoms	Selection of participants not clearly described Validation of ELISA assay not described
Dobi et al ¹⁴⁴	Reunion	Pre-print	Cohort	Hospitalised participants 20 cases	IgG and IgM kinetics	ELISA and IFA (IgG and IgM)	IgM and IgG detected early during the course of the disease (5-7 days post-first symptoms), significant decrease of IgG levels in severe cases - for these cases seroconversion for IgG and IgM occurred simultaneously and antibody titers plateaued within 6 days after seroconversion. In mild cases a steady rise in specific IgG was observed. Both responses (IgM and IgG) were initially against N and spreading to other S1 and S2	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings

Du et al ⁴⁷	China	Peer reviewed paper	Case series	Hospitalised participants 60 cases	IgG and IgM kinetics including titres	Not described	All cases tested positive for IgG while 13 tested negative for immunoglobulin M (IgM), with the immunoglobulin G (IgG) titer being greater than the IgM titer. IgM and IgG titers in 10 cases were tested twice (1 week apart, i.e. 7-8 weeks since symptom onset); both titres showed a decrease, with the IgG titer still remaining greater than the IgM titer.	Selection of participants not clearly described Validation of ELISA assay not described
Du et al ¹⁷⁴	China	Peer reviewed paper	Cohort	Hospitalised participants 182 cases (children) Median age 6 66% male	IgG and IgE titre	Not described	IgG significantly lower in those with pneumonia than in those without Serum total IgE level of allergic children was higher than that of non-allergic individuals, and allergic children had greater percentage of increased IgE	Selection of participants not clearly described Validation of ELISA assay not described
Duan et al ¹⁴⁵	China	Pre-print	Case control	Hospitalised participants 616 cases Median age 64 57.5% female	Correlates of antibody detection	Not described	Compared with confirmed cases (antibody positive), antibody negative probable cases were younger, had higher lymphocytes and similar symptom and comorbidity profile	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Edouard et al ²⁰	France	Pre-print	Cohort	Hospitalised participants 888 cases Median age 45 54% female	IgG and IgM kinetics including titre	IFA (in house)	Seroprevalence 47% after 15 days after disease onset. Seroconversions of specific IgM and IgG antibodies were observed as early as day four after the onset of symptoms Severe cases developed a serological response in most cases (and all patients who died) that was characterised by high levels of IgG Significant higher IgG titre in cases with a poor clinical outcome compared to cases with good outcome	Selection of participants not clearly described Validation of ELISA assay not described
Ejemel et al ¹¹³	Lab or animal based	Pre-Print	Basic Science	36 serum samples	Detection of neutralising antibodies and neutralising ability	ELISA (anti S) neutralising assay not described	IgA mAb neutralizes via competing S protein binding to hACE2 receptors. IgG weakly neutralizes SARS-CoV-2 while its IgA1 isotype variant and its dimeric form showed significantly enhanced neutralization potency	Selection of participants not clearly described Validation of ELISA assay not described

Espejo et al ⁹³	Multiple populations	Peer reviewed paper	Systematic review without meta-analysis	55 studies included	Sensitivity and specificity of antibody assays	ELISA, CLIA and LFIA	Total antibody or combined IgG/IgM detection offered the highest sensitivity of detection Conflicting evidence regarding whether antibody titres correlated with clinical severity Preliminary investigations indicated some immunoassays may be a surrogate for the prediction of neutralizing antibody titers and the selection of recovered patients for convalescent serum donation	Selection of participants not clearly described Validation of ELISA assay not described
Fafi-Kremer et al ⁶⁶	France	Pre-Print	Cohort	Community participants 160 cases Median age 32 69% female	Antibody kinetics Neutralising antibody detection	Anti RBD rapid test (Biosynex) and anti S flow cytometry	Antibodies against SARS-CoV-2 were detected in virtually all hospital staffs sampled from 13 days after the onset of COVID-19 symptoms. The neutralizing activity of the antibodies increased over time. Neutralizing ID50$\geq$100 were found in 91% of the individuals, reaching 97% four weeks after the onset of symptoms. Individuals with factors associated with more severe disease (e.g., male sex, high body mass index and high blood pressure), were more likely to have high titers of neutralizing antibodies compared to others.	Selection of participants not clearly described Validation of ELISA assay not described
Farrera et al ¹¹⁴	Switzerland	Pre-print	Basic Science	Hospitalised participants 12 cases, 6 controls	Antibody epitope mapping	ELISA (anti S1 IgG) (Euroimmun) Peptide array	3 linear epitopes most abundantly detected (SARS-CoV-2 S protein) were: 655-672, 787-822, and 1147-1158. None of these epitopes was singularly detected in all the positive samples tested, but each is detected in >40% of positive cases. Antibodies binding to protease cleavage sites were identified from COVID-19 patients, raising the possibility that other mechanisms than blocking the RBD-ACE2 interaction could be harnessed for neutralization. Blocking proteolytic cleavage could be important to reduce antibody-dependent enhancement of viral entry, a key feature for vaccine development	Selection of participants not clearly described Validation of ELISA assay not described
Favara et al ¹⁵⁷	UK	Pre-print	Cohort	Community participants (healthcare workers) 70 cases Median age 41 87% female	IgG seroprevalence and correlates	LFIA (anti N and anti S IgG and IgM) (Abbexa) Multiplex assay (anti S and anti N IgG)	IgG positive cases had a 3.6 times higher odds of having previously had symptoms 13% of cases who reported no prior symptoms were IgG positive, 28.6% amongst those asymptomatic who were exposed to a suspected case in their household 12.5% of participants with chronic underlying health conditions had positive antibodies in contrast to 24.1% of those without.	Selection of participants not clearly described Validation of ELISA assay not described

Fox et al ¹⁷³	USA	Pre-print	Case series	Hospitalised participants 15 cases	IgG, IgM and IgA titres (in breast milk)	ELISA	Most milk (80%) obtained post-COVID-19-recovery exhibits IgA reactivity to RBD Mean OD values of undiluted milk in COVID-19-recovered group were significantly greater for IgA, secretory-type Abs, and IgG, but not for IgM No correlation between the reactivities of Ab subclasses, with the exception of IgM v IgG, which were found to correlate	Selection of participants not clearly described Validation of ELISA assay not described
Fung et al ²⁸	USA	Peer reviewed paper	Case series	Mixed hospitalised and community participants 10 cases (solid organ transplant recipients) Median age 57 60% male	IgG kinetics	CLIA (anti N IgG) (Abbott)	100% of hospitalised cases had positive SARS-CoV-2 IgG, 6 observed to seroconvert between day 6 and day 28 after symptom onset	Selection of participants not clearly described Validation of ELISA assay not described
Galson et al ¹¹⁵	UK	Pre-print	Basic Science	Hospitalised participants 19 cases Mean age 50 68% male	B cell receptor heavy chain sequencing	BCR sequencing	Stereotypical naïve immune response to SARS-CoV-2 which is consistent across patients and maybe a positive indicator of disease outcome. SARS-CoV-2 infection stimulates both naïve and memory responses - Clonal expansion of the B cell memory response is also observed and may be the result of memory bystander effects. Sequence convergence can be used to identify putative SARS-CoV-2 specific antibodies. BCR clonotype sequence convergence signatures are shared between different COVID-19 studies in different locations and from different anatomical sites: the BCR repertoires of the COVID-19 patients were significantly more diverse than the BCR repertoires of the healthy controls; this increase in diversity was positively correlated with an increased proportion of unmutated sequences	Selection of participants not clearly described Validation of ELISA assay not described
Garcia-Basteiro et al ¹⁶³	Spain	Pre-print	Case control	Community participants 578 healthcare workers	IgG, IgM and IgA kinetics	Multiplex assay	Among seropositive cases no statistically significant associations of antibody levels with sex. IgM levels positively correlated with age. IgA levels higher in participants reporting COVID-19-compatible symptoms in the previous month than in those asymptomatic. Duration of symptoms greater than 10 days associated with higher IgM levels Antibodies detected in individuals with 6 or more days between symptoms onset and recruitment for IgA and later for IgM and IgG with no seropositive results	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

							detected among individuals with symptoms onset less than 6 days prior to recruitment. Antibody levels increased and peaked between day 20 and 25 for IgM and IgG, and a few days earlier for IgA	
Giagulli et al ¹⁶⁵	Multiple populations	Peer Reviewed paper	Narrative Review	Details of included studies not provided	IgG seroprevalence and correlates	Not described	In a study with n=331, delayed peak of antibody response with a lower generation of effective IgG was found in men compared to women	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Gniffke et al ²⁹	USA	Pre-print	Case control	Hospitalised participants 24 cases Median age 42 Female 71% 30 controls Median age 37 Female 60%	IgG kinetics Neutralising ability	Flow Cytometry (anti S and anti RBD IgG)	Anti S IgG and anti RBD IgG in cases detected at median of 36days following documented SARS-CoV-2 RNA secretions COVID-19 case samples significantly inhibited binding compared to no plasma and pre-covid plasma. Case samples produced greater inhibition than pre-COVID for both trimer and RBD Fever associated with increased anti-trimer IgG and inhibition	Selection of participants not clearly described Validation of ELISA assay not described
Grzelak et al ¹⁸	France	Pre-print	Case control	Mixed hospitalised and community participants 260 cases, 491 controls	Antibody titres Neutralising antibody titres	ELISA (anti N and anti S) and LIPS (anti N and anti S) (in house) Pseudovirus neutralisation assay	High antibody titers associated with neutralisation activity In hospitalized patients, seroconversion and neutralisation occurred on 5-14 days post symptom onset Seropositivity was detected in 29% of pauci-symptomatic individuals within 15 days post-symptoms and 3 % of blood of healthy donors collected in the area of a cluster of COVID cases	Selection of participants not clearly described Validation of ELISA assay not described

Hansen et al ¹¹⁰	Lab or animal based	Peer reviewed paper	Basic Science	3 human cases and animal model (mice)	Detection of neutralising antibodies and neutralising ability	ELISA VZV-based psuedoparticle assay	All of the detected neutralizing mAbs bound to the RBD of SARS-CoV-2 spike and blocked its ability to interact with ACE2 with double-digit pM IC50s supporting ACE2 blockade as the primary mechanism for neutralization The antibodies bound specifically and with high affinity to monomeric SARS-COV-2 RBD (KD = 0.56 to 45.2nM) and dimeric SARS-COV-2 RBD (KD = 5.7 to 42.8 pM). While recombinant ACE2 was able to mediate neutralization of the VSV-spike pseudoparticles as previously reported, it was more than 1000-fold less potent than the best neutralizing mAbs. The IC50s of all Fabs were shifted compared to their parental IgG, indicating that biva-lent binding, cross-linking and steric hindrance might all augment neutralization. A small subset of antibodies showed significantly higher neutralising potential against non-replicating pVSV-SARS-CoV-2-S- mNeon and replicating VSV-SARS-CoV-2-S virus, with mAbs combinations appearing to have neutralising impact at lower concentrations	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
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Hartman et al ⁴¹	Lab or animal based	Pre-print	Basic Science	Animal study (African green monkeys)	IgG and IgM kinetics Neutralising antibody detection	ELISA PRNT80	All animals seroconverted with IgM and IgG in the second week post exposure and those that were exposed via the mucosal route had higher overall titers than those that received the virus via the aerosol route Neutralising antibodies detected in samples taken 7-11 days post infection. There were no differences in kinetics or activity between the two exposure routes demonstrating that higher dose received during multi-route mucosal infection neither affected the onset nor strength of the humoral immune response.	Selection of participants not clearly described Validation of ELISA assay not described
Harvala et al ⁶⁷	UK	Pre-Print	Case series	Hospitalised participants 52 cases 100% male	Detection of neutralising antibodies and neutralising ability	ELISA (anti S1 IgG) (Euroimmun and Fortress) Pseudovirus and live virus microneutralisation assay	Neutralising antibodies detected in 43 of 52 samples using a cut-off titre of 1:20. The highest detectable titre was 1:4096. Correlation observed between neutralizing antibody titres and reactivity IgG ELISA and between neutralizing antibody titres and IC50 values in pseudotype assay	Selection of participants not clearly described Validation of ELISA assay not described
He et al ¹⁵⁰	China	Peer reviewed paper	Case control	Hospitalised participants 204 cases	IgG, IgM, IgA and IgE titres	Not described	Higher IgG in severe cases, with lower IgM. IgM and IgA significantly lower in patients with comorbidities	Selection of participants not clearly described Validation of ELISA assay not described
He et al ⁵⁰	China	Peer reviewed paper	Cohort	Hospitalised participants 169 cases Median age 55 54% male	IgG and IgM kinetics	CGIA (Tangshan) and CLIA (IgG and IgM) (Maccura and Tanjin)	Cumulative positive IgM conversion rate was close to 100% after 3 weeks by both assay methods After 23 days the cumulative positive conversion rate of IgG reached more than 95%. Regardless of assay, no downward trend in positive rate of IgG detection during the observation period (35 days) The positive conversion time of IgG is 2 days later than IgM by chemiluminescence method on average, and it is 3 to 5 days later by colloidal gold method.	Selection of participants not clearly described Validation of ELISA assay not described
Herroelen et al ³⁶	Belgium	Pre-print	Cohort	Mixed hospitalised and community participants 135 cases and suspected cases	IgG, IgM and IgA kinetics	Multiple ELISAs and LFIAs (Wantai, Orient Gene, Elecsys, Euroimmun, Innovita, Liaison)	Lack of seroconversion by any test was seen in 1.4% of hospitalized and 4.7% of paucisymptomatic infections All tests except Wantai SARS-COV-2 Ab ELISA showed a significantly higher positivity rate between 10 and 20 days post onset as compared to less than 10 days. No significant differences in positivity rates between 10 and 20 and more than 20 days	Selection of participants not clearly described Validation of ELISA assay not described

Hou et al ⁵³	China	Peer Reviewed paper	Cohort	Hospitalised participants 338 cases Mean age 62 50% male	IgG and IgM kinetics	CLIA (IgM and IgG) (YHLO)	The median number of days from symptom onset to antibody detection was not significantly different across the mild, severe and critical groups (20.95 +/- 9.226 days, 21.9 +/- 8.724 days and 20.86 +/- 8.126 days, respectively) . Severe and critical cases had higher IgM levels than mild cases, whereas IgG in critical cases was lower than those in both mild and severe cases. IgM levels slightly higher in deceased patients than recovered patients, but IgG levels in these groups did not significantly differ. A longitudinal detection of antibodies revealed that IgM levels decreased rapidly in recovered patients whilst IgG was detectable for longer. IgM level reached its peak after 2 weeks and then decreased rapidly by 3 weeks. IgG was maintained at a high concentration even after 7 weeks. In deceased cases, either IgM levels remained high or both IgM and IgG were undetectable during the disease course.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Houlihan et al ¹⁶¹	UK	Pre-Print	Cohort	Community participants (healthcare workers) 200 participants Median age 34 61% female	Seroprevalence amongst healthcare workers	ELISA	All but one HCW with PCR evidence of infection developed antibodies. Antibodies to the spike protein of SARS-CoV-2 remained detectable over the one month of follow up. There was no evidence of reinfection in those with antibodies at baseline over one month follow up.	Selection of participants not clearly described Validation of ELISA assay not described

Hu et al ⁶⁴	China	Pre-print	Cohort	Hospitalised participants 211 cases Median age 47 40% female	IgG and IgM kinetics including titres	MCLIA (IgG and IgM) (Chongqing Bioscience)	Peak of both antibodies on day 19-21, after which IgM gradually decreased while IgG remained at a high level, with a median concentration of 17·38 and 5·59 (IQR 0·73 , 13·65), respectively. IgG significantly higher in the severe group than in the mild group; IgM level in the two groups not significantly different Of 74 recovered patients 39 (52·7%) presented with re-detectable positive virus nucleic acid during this period. These patients had significantly lower IgG concentration within 7 days after discharge but the difference in IgM concentration was not significant. The decrease of SARS-CoV-2 IgG and IgM antibodies in 40 recovered patients between two tests within 14 days after discharge with a 7-day interval was not statistically significant but the decrease of IgG and IgM each reached 21·2% This study found no correlation between IgG and IgM concentration and viral shedding, course and outcome of the disease through a retrospective analysis without the knowledge of SARS-CoV-2 viral load.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Hu et al ⁷¹	China	Pre-print	Basic Science	Hospitalised participants 41 convalescent plasma samples	Detection of neutralising antibodies and neutralising ability	Pseudovirus luciferase neutralisation assay	Among the 41 tested sera, 38 showed neutralizing activities against one or both pseudovirus. Sera from 3 cases high neutralizing activity against one pseudovirus with ID50 ranging from 894 to 1337, but decreased titres against an alternative pseudovirus (alternative pseudoviruses related to identified S-D614 to S-G614). These data indicated that D614G mutation changed the antigenicity of S protein, thereby decreasing neutralization sensitivity to individual convalescent sera.	Selection of participants not clearly described Validation of ELISA assay not described

Huang et al ³⁸	China	Pre-print	Cohort	Hospitalised participants 33 cases Median age 47 52% male	IgG and IgM kinetics	MCLIA (IgG and IgM) (Chonqing Bioscience)	8 weeks from symptom onset, IgM negative in many of the previously positive patients, and IgG levels remained less than 50% of the peak levels in more than 20% of the patients. In about 40% of the patients, anti-RBD IgG levels increased 4-times higher in convalescence than in acute phase. The median seroconversion time of anti-S IgM, anti-RBD IgM, and anti-N IgM was 10.5 days, 14 days, and 10 days, respectively. The median seroconversion time of anti-S IgG, anti-RBD IgG, and anti-N IgG was 10 days, 13 days, and 10 days, respectively. SARS-CoV-2 RNA coexisted with antibodies for more than 50 days. Anti-RBD IgM and IgG levels, including anti-RBD IgM levels at presentation and peak time, were significantly higher in viral RNA short persistence patients than in long persistence cases.	Selection of participants not clearly described Validation of ELISA assay not described
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Huang et al ⁷	Multiple populations	Pre-print	Systematic review with meta-analysis	Multiple populations 40 studies in quantitative synthesis	IgG and IgM kinetics and correlates	Multiple assays including ELISA, IFA, Western blot, HAI and complement fixation, and neutralisation assays	The median time to antibody 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 - Antibody kinetics varied across the severity gradient with longer durations of detectable antibody associated with more severe symptoms. 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) While IgM antibodies appear at the same time in severe and non-severe cases, IgG appears sooner in severe cases. On the other hand, neutralizing antibody titers were higher in severe cases. 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)	Selection of participants not clearly described Validation of ELISA assay not described
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Hurlburt et al ¹¹¹	Lab or animal based	Pre-print	Basic Science	1 convalescent plasma sample	Structural mechanism of RBD/ACE2 receptor blocking	Neutralisation assay	CV30 binds almost exclusively to the concave ACE2 binding epitope (also known as the receptor binding motif (RBM)) of the RBD using all six CDR loops with a total buried surface area of ~1004 Å², ~750 Å² from the heavy chain and ~254 Å² from the kappa chain The structure reveals that the CV30 epitope overlaps almost completely with the ACE2 epitope. A total of 26 residues of the SARS-CoV-2 RBD interact with hACE2, CV30 binds to 19 of these residues 3) Additionally, the minimal affinity maturation observed 21 days after infection in the VH gene of CV30 showed ~100-500-fold increase in affinity and neutralization potency, indicating that further affinity maturation may increase potency and potential cross-reactivity. Of the interacting residues from the SARS-CoV-2 RBD, only 16 are conserved in the SARS-CoV S protein RBD, which could explain the lack of cross-reactivity of CV30 to SARS-CoV S1547. Thus, minimal affinity maturation of CV30 significantly impacted the ability of this mAb to neutralize SARS-CoV-2.	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
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Imai et al ⁹²	Lab or animal based	Peer reviewed paper	Non-randomised controlled trial	Animal study (syrian hamsters) 8 hamsters	Neutralising antibody titre, protection against reinfection	ELISA Neutralising assay	SARS-CoV-2–infected hamsters mounted neutralizing antibody responses and were protected against subsequent rechallenge with SARS-CoV-2 Passive transfer of convalescent serum to naïve hamsters efficiently suppressed the replication of the virus in the lungs even when the serum was administered 2 d postinfection of the serum-treated hamsters Virus titers in the nasal turbinates and lungs of the animals that received postinfection serum on day 1 postinfection were statistically significantly lower than the virus titers in those organs of animals that received normal serum at the corresponding time point postinfectio. No statistically significant differences in the virus titres in the respiratory organs were found between the animals that received postinfection serum and those that received normal serum on day 2 postinfection	Selection of participants not clearly described Validation of ELISA assay not described
Jaaskelainen et al ³⁵	Finland	Peer Reviewed paper	Case control	Hospitalised participants 40 cases median age 56 65% male 37 controls median age 53 60% female	IgG and IgA kinetics	ELISA (anti S1 IgG and IgA) (Euroimmun)	IgA and IgG detected in 13/39 confirmed COVID-19 cases, IgA detected alone in 11/39. Total positive = 24/39 The median time after onset of symptoms was 12 days for detection of IgGs, and 11 days for detection of IgAs Amongst probable cases, 1/13 positive for IgA and IgG, 1/13 positive for IgG alone and 1/13 for IgA alone Did not see any clear patterns between the IgG or IgA results and disease severity	Selection of participants not clearly described Validation of ELISA assay not described
Jin et al ⁴⁶	China	Peer reviewed paper	Case control	Hospitalised participants 43 cases and 33 controls median age 47	IgG and IgM titres	CLIA (IgG and IgM)	The IgM-positive rate increased slightly initially then decreased over time; in contrast, the IgG-positive rate increased to 100% and was higher than IgM at all times. Both IgM and IgG levels were not high in the first 5 days following symptom onset. In the COVID-19 group. Median IgM and IgG titers among cases were 12.1AU/ml and 132.2AU/ml, respectively. IgM-positive rate and titer were not significantly different before and after conversion to virus-negative. The IgG-positive rate was up to 90% and also not significantly different before and after conversion to virus-negative. However, the median IgG titer after testing virus-negative was double that before, and the difference was statistically significant.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

Jin et al ⁵⁵	China	Peer reviewed paper	Cohort	Hospitalised participants 89 cases Median age 62 55% female	IgG and IgM kinetics including titres	CLIA (IgG and IgM)	Pooled serum IgM was significantly higher in the prolonged shedding groups at weeks 4 and 5 compared with the non-prolonged shedding group Serum IgM was similar between two groups from week 6 to week 8 after symptom onset. At week 8, serum IgM in both groups declined almost to the reference level Serum IgM to SARS-CoV-2 persisted at a high level during the acute phase of illness up to week 8. In individuals with prolonged viral RNA shedding, serum IgM was found to be positive at week 6 after symptom onset, which was also consistent with the median time to viral RNA shedding (44 days). Serum IgG persisted at a high level up to 8 weeks in both groups	Selection of participants not clearly described Validation of ELISA assay not described
Ju et al ¹⁰⁶	China	Peer Reviewed paper	Basic Science	Hospitalised participants 8 cases, 1 control age range 10-66	Detection of neutralising antibodies and neutralising ability	ELISA	206 RBD-specific monoclonal antibodies isolated. Antibodies were identified with potent anti-SARS-CoV-2 neutralization activity that correlates with their competitive capacity with ACE2 for RBD binding. Many antibodies with high Kd values minimally competed with ACE2, suggesting binding affinity does not predict ACE2 competing capacity No single or group of antibody families stood out across various patients, suggesting different patients had immunologically distinct responses. Plasma samples from severe demonstrated relatively higher anti-SARS-CoV-2 binding activities than those from mild cases Neither the anti-SARS-CoV-2 antibodies nor the infected plasma cross-reacted with SARS-CoV or MERS-CoV RBDs, although substantial plasma cross-reactivity to their trimeric Spike proteins was found.	Selection of participants not clearly described Validation of ELISA assay not described
Jungbauer et al ⁹⁶	Austria	pre-print	Case series	100 convalescent plasma samples	Neutralising antibody titres	ELISA (anti S and anti RBD) Microneutralisation assay	Correlation between neutralising antibody titre and ELISA was highly significant although quantitatively limited Severe cases had mean NT50 antibody titer of 1:696, milder cases of 1:208 While increased age and male sex were significantly correlated with neutralising antibody titres, the differences may not be clinically meaningful.	Selection of participants not clearly described Validation of ELISA assay not described

Juno et al ⁷²	Australia	Pre-Print	Case control	Community participants 41 cases, 27 controls median age 59 57% male	IgG, IgM and IgA titres Neutralising ability	ELISA (anti S and anti RBD IgG and IgM and IgA) Microneutralisation	Antibody responses against S and RBD consistently elicited in SARS-CoV-2 infected individuals, the endpoints titres of which correlate significantly with neutralising activity and ACE2 binding inhibition High plasma neutralisation activity was associated with increased spike-specific antibody, but notably also with the relative distribution of spike-specific cTFH subsets. Expanded populations of spike-specific memory B cells and circulating T follicular helper cells (cTFH) were detected within convalescent donors, while responses to the receptor binding domain (RBD) constitute a minor fraction Overall, SARS-CoV-2 infection efficiently elicits both S- and RBD-specific B cells in most subjects after recovery, which constitute a 'significant' proportion of the memory B cell pool, which are mostly IgG+ and of a resting memory phenotype The majority of spike+RBD- class-switched B cells were IgG+ with smaller proportions displaying IgM+ and IgA+	Selection of participants not clearly described Validation of ELISA assay not described
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Kellam and Barclay ⁹	Multiple populations	Peer Reviewed paper	narrative Review	Multiple populations Inclusion of studies not described	Antibody kinetics	Assays not described in detail	Seroconversion appears to occur in majority of cases before 21 days post symptom onset, and amongst those who do seroconvert, mostly between 10-15 days , with those affected by severe disease appearing to seroconvert earlier and have higher proportions of neutralizing antibodies. A range of titres being described between patients Early studies suggest that the immune response to SARS-CoV-2 is similar to that for SARS-CoV and MERS-CoV. SARS-CoV-2 seroconversion occurs on a time course that is consistent with other epidemic CoVs and antibodies to spike RBD were the most reliable for case counting in this study. At 2weeks post-symptom onset, antibody titres were statistically higher in critical compared to non-critical patients. One study exposed Rhesus Macaques with detectable to SARS anti-spike antibodies 28 days from primary infection and neither became infected.	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Klimstra et al ⁷⁷	USA	pre-print	Basic Science	3 convalescent plasma samples	Neutralising antibody titres	IFA PRNT80	For all patients the first serum sample (ranging from 4-9 days after first reported symptoms) failed to neutralize SARS-CoV-2, however seroconversion occurred in all patients the subsequent day and all samples neutralized Mean PRNT 80 appears to increase over time	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings

Kohmer et al ¹⁶	Germany	Peer Reviewed paper	Case series	Hospitalised participants 33 cases	IgG kinetics	FLA (FaStep) ELISA (Euroimmun IgG, Vircell IgG) IFA PRNT	Between 5-9 days post symptom onset between 58.8% and 76.5% patients had positive assays, variable by assay. Between 10-18 days, between 93.8% and 100% of patients had positive assays (variable by assay) All but one participant demonstrated neutralizing ability	Selection of participants not clearly described Validation of ELISA assay not described
Kreer et al ¹⁰⁷	Germany	pre-print	Cohort	Mixed hospitalised and community participants 12 cases, 48 controls	IgG and IgM kinetics and B cell response	ELISA (IgG) (Euroimmun) Neutralisation assay	A polyclonal B cell response against the SARS-CoV-2 S protein was initiated in all 7 studied cases. A SARS-CoV-2-reactive IgG+ B cell response readily develops after infection with the same B cell clones detectable over time and a preference for facilitating the VH gene segment 3-30. A positive correlation between neutralization and binding could be detected 27 out of 28 neutralizing antibodies found displayed binding to the RBD, but only 31% of the non- neutralizing antibodies. 4 of 28 showed signs of autoreactivity. The development of a neutralizing antibody response is followed by limited additional somatic mutation. All 48 naive repertoires included at least one κ and one λ chain precursors, with 3 potent neutralising antibodies identified.	Selection of participants not clearly described Validation of ELISA assay not described
Laing et al ¹⁰²	UK	Pre-Print	Cohort	Hospitalised participants 63 cases, 55 controls median age 61 (cases) 36 (controls)	IgG and IgM kinetics	ELISA and LIPS	Most cases produced SARS-CoV-2-specific antibodies, whose host-protective potentials were inferred from strong correlations of RBD-specific IgG. There was no clear correlation of disease severity with either SARS-Cov-2-specific IgM or IgG	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Lee et al ³¹	China	Peer reviewed paper	Case series	Hospitalised participants 14 cases, 28 controls	IgM and IgG kinetics	LFIA (IgG and IgM) (Alltest)	All symptomatic COVID-19 patients were positive for IgG (n=6/6) and less for IgM (n=4/6). Earliest IgM and IgG detected on day 5. IgG antibodies were absent in 3 cases in the asymp/mild group with positive RT-PCR. IgM was negative in all asymptomatic/mild group with RT-PCR confirmed diagnosis.	Selection of participants not clearly described Validation of ELISA assay not described

Li et al. ¹⁷⁰	China	Peer reviewed paper	Cohort	Hospitalised participants 127 cases (all children)	Lymphocyte subsets, immunoglobulin titres, cytokine and inflammatory factor levels	Immunofixation electrophoresis (BNII, Siemens)	12.6% low IgA, 8.4% low IgG and 5.9% low IgM No controls Low IgA associated with pneumonia OR=4.00 95%CI = 1.13-14.18 (p=0.03) (IgG and IgM not significant)	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Li et al. ⁴³	China	Pre-print	Cohort	Hospitalised participants 1,850 confirmed adult patients	Total antibodies and S-, RBD-, and nucleoprotein (N)-specific IgM and IgG levels over time	CLIA (anti S, anti N, anti RBD IgG and IgM) (Shenzhen YHLO Biotech Co.)	Total IgM low in 1st week POS, peaked in 5th week, then decreased to initial levels. Total IgG peaked in 7th week POS then remained high until end of observation at week 12. Mild/moderate patient groups have earlier S-, RBD-, and N-specific IgM and IgG response and severe/critical patient groups have later higher response (statistically significant) Older patients have higher S-, RBD-, and N-specific IgG response, (statistically significant)	Selection of participants not clearly described Validation of ELISA assay not described
Liu et al. ⁷⁸	China	Peer reviewed paper	Case series	Hospitalised participants 9 children	Neutralising antibody titres over time and correlates with viral shedding	Not stated	3/8 cases induced NAb in the acute phase, 8/9 cases produced medium to high NAb titre in convalescent phase of infection. Viral shedding persisted after NAb production. Median NAb titre IC50 = 1,483.9 (307.2–5,925.4)	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Liu et al. ¹³⁶	China	Peer reviewed paper	Cohort	Hospitalised participants 192 cases	RBD specific IgM or total IgM/IgA/IgG levels over time and associated	MCLIA (anti RBD IgM and total Ab) (Wantai)	Both total antibody and RBD specific IgM higher in severe than mild cases after day 6 POS (statistically significant) Mean IgM titre peaked at day 21 in severe cases, and positive rate at days 7 to 12 higher in severe cases. No documented peak in IgM for mild cases.	Selection of participants not clearly described Validation of ELISA assay not described

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Long et al. ¹⁵⁹	China	Peer reviewed paper	Case control	Hospitalised participants 37 cases (symptomatic), 37 controls (asymptomatic cases)	IgG and IgM titre	MCLIA (IgG and IgM) (Chongqing Bioscience)	IgG levels in the asymptomatic group were significantly lower ($P=0.005$) relative to the symptomatic group in the acute phase. Change in neutralising Ab response also noted into the early convalescent phase: Median percentage of decrease in NAb titers was 8.3% in the asymptomatic group and 11.7% in the symptomatic group.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Lou et al. ¹⁵	China	Peer reviewed paper	Cohort	Hospitalised participants 80 cases, 300 controls	Levels of total Ab, IgG and IgM positivity over time and comparison with disease severity	ELISA and LFIA (IgG, IgM and total Ab) (Beijing Wantai Biological Pharmacy Enterprise) CLIA (Xiamen InnoDx Biotech)	Seroconversion rates for total Ab, IgM and IgG were 98.8%, 93.8% and 93.8%, respectively Seroconversion sequentially for total Ab (9 days), IgM (10 days) and IgG (12 days) Seroconversion rate for total Ab and IgM reached 100% and IgG reached 97.1% on days 16, 21 and 29 post symptom onset, respectively	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Lou et al. ⁷⁹	China	Pre-print	Basic Science	Hospitalised participants 18 cases, 3 controls	Anti-RBD IgG response in convalescent plasma	ELISA (anti RBD IgG)	Plasma from 17 of 18 included convalescent cases demonstrated a high degree of (IgG) binding affinity to SARS-CoV-2 RBD compared to controls	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings

Lu et al. ⁸⁰	China	Pre-print	Case control	Hospitalised participants 87 cases, 150 controls	Neutralising antibody titres	Microneutralization assay	For samples collected median 37 days (range 23-47 days) post illness onset (n=59) (98.3%) cases developed NAbs with a titre >4, ranging from 4 to >102	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Luchsinger et al. ⁶⁸	USA	Pre-print	Case control	370 cases, 10 controls Median age 41 55% female	Neutralising activity of convalescent plasma (NT50 titre)	LFA and ELISA (in house) Neutralisation assay	83.1% and 92.7% of the CP donor samples had detectable neutralization activity using HIV-S and VSV-S assays, respectively CP donors 2-3 weeks POS had a statistically significant increase in NT50 values compared to CP donors >3 week POS NT50 values of male CP donor samples were ~1.7-fold higher than those from female CP donors with a strong correlation between antibody titre and neutralising response	Selection of participants not clearly described Validation of ELISA assay not described
Lv et al. ¹¹⁹	China	Peer reviewed paper	Case control	Hospitalised participants 15 cases, 8 controls age range 37-73 50% female	Plasma binding to SARS-CoV-2 spike, RBD and S2 (OD450 titre) Neutralising activity of convalescent plasma (neutralising titre)	ELISA (anti RBD, anti S2) (in house) microneutralisation assay	Cross-reactive antibody-binding responses to both SARS-CoV-2 and SARS-CoV S proteins appear to be common but only 1 of 15 patients were able to generate a cross-neutralising response to SARS-CoV-2 and SARS-CoV and this response was weak.	Selection of participants not clearly described Validation of ELISA assay not described
Lynch et al. ³⁹	USA	Pre-print	Cohort	Mixed hospitalised and community cases 94 cases median age 49, 68% male	Longitudinal IgG and IgM Ab titres	Pylon automated immunoassay (IgG and IgM)	44/52 (84.6%) and 42/52 (80.8%) had observed IgM and IgG seroconversion at a median of 8 and 10 days, respectively. Peak measurements were significantly higher for patients admitted to the intensive care unit for all time intervals between 6 and 20 days for IgM, and all intervals after 5 days for IgG.	Selection of participants not clearly described Validation of ELISA assay not described

Ma et al. ²³	China	Peer Reviewed paper	Cohort	Hospitalised participants 87 cases median age 48	IgA, IgG and IgM response	CLIA (IgG, IgM and IgA) (Kaeser 1000)	RBD-specific IgA peaked before IgG and both remained high at day 41 Serum IgM and IgG levels in moderate and severe COVID-19 patients were significantly higher than mild cases, no significant difference was observed between severe and moderate patients. IgA levels in severe cases were significantly higher than those mild or moderate cases.	Selection of participants not clearly described Validation of ELISA assay not described
Madariaga et al. ¹⁶⁰	USA	Pre-print	Non-randomised controlled trial	Hospitalised participants 103 cases	Antibody titres and correlates	ELISA (anti RBD, anti S)	Higher anti-RBD and anti-spike antibody titers were associated with plasma donors who were older, male, had higher BMI, had fever and had been hospitalized (p<0.05).	Selection of participants not clearly described Validation of ELISA assay not described
Marcos-Jimenez et al. ¹⁴²	Spain	Pre-print	Cohort	Hospitalised participants 276 cases, 19 controls	Differential T cell and Ig levels over time and by severity	Immunonephelometry (Immage800)	At admission, IgA and IgM are similar in cases and controls IgG decreased in cases compared to controls (correlated with number of plasma cells) (statistically significant) 10 days after admission IgG decreased further in severe cases (n=37) (statistically significant)	Selection of participants not clearly described Validation of ELISA assay not described
Minervina et al. ⁵²	Russia	Pre-print	Basic Science	Community participants 2 cases 50% female	Presence of RBD antibody over time, fraction of reactive CD4 and CD8 T cells over time	ELISA (anti RBD) (National Research Centre for Hematology)	Both donors developed IgG response by day 30 and remained positive to end of follow up (day 45)	Selection of participants not clearly described Validation of ELISA assay not described
Mueller et al. ⁸¹	Germany	Pre-print	Cohort	Community participants 42 contacts of a confirmed case	Neutralising antibody titres and detection of IgG	ELISA (Euroimmun, Roche, Abbott and DiaSorin) Neutralisation assay	PCR confirmed cases had neutralising antibody titres higher than asymptomatic individuals (p<0.01). Controls had no neutralising antibodies (PCR confirmed and symptomatic) (p<0.001) NAb titre range 1:40 - 1:10240 for PCR The neutralisation titre correlated strongly with all S Ab tests	Selection of participants not clearly described Validation of ELISA assay not described

Ng et al. ⁶⁹	USA	Pre-print	Cohort	Mixed hospital and community participants 387 cases, 1000 controls	Seroconversion detection rate (IgG and IgM) and neutralising antibody titre	ELISA (IgG and IgM) (Abbott Architect) Neutralisation assay	Neutralising antibody increased concomitantly with IgG and IgM NAb titre mean rose to 1:2048 day 22	Selection of participants not clearly described Validation of ELISA assay not described
Ng et al. ¹²⁰	UK	Pre-print	Case control	Hospitalised participants 170 cases, 95 controls	Antibody characteristics of patients with different combinations of HCoV, COV-2 and no prior COV infection Neutralising activity of antibodies from these patient groups	ELISA	Approximately 10% of participants with recent HCoV infections display IgG cross-reactivity towards the Sars-CoV-2 S protein, which also display neutralising potential against SARS-CoV-2 pseudovirus. HCoV patient sera also variably reacted with SARS-CoV-2 S and nucleocapsid (N), but not with the S1 subunit or the receptor binding domain (RBD) of standard enzyme immunoassays.	Selection of participants not clearly described Validation of ELISA assay not described
Ni et al. ¹⁰⁰	China	Peer reviewed paper	Case control	Hospitalised participants 14 cases, 6 controls median age 36 57% female	Longitudinal IgG and IgM titres associated with time since discharge Neutralising antibody titres	ELISA (IgG and IgM) (MABTECH AB, Sweden)	Patients mounted IgG and IgM responses to SARS-CoV-2 NP and S-RBD proteins, and maintained IgG levels for at least 2 weeks post discharge. Significant correlation between neutralizing antibody titers and anti-S-RBD IgG, but not of anti-NP IgG.	Selection of participants not clearly described Validation of ELISA assay not described
Okba et al. ¹³⁵	France and Germany	Peer reviewed paper	Cohort	Hospitalised participants 12 cases	Presence/absence of SARS-CoV-2 neutralizing, spike protein-specific, and nucleocapsid-specific antibodies	ELISA (Euroimmun)	After infection, all 3 patients seroconverted between days 13 and 21 after onset of disease. 2 mild and 1 severe case - all seroconverted, earlier seroconversion for severe case compared to mild cases	Selection of participants not clearly described Validation of ELISA assay not described

Ou et al. ³⁴	China	Pre-print	Cohort	Hospitalised participants 192 cases: median age 52 (IQR, 36-62 years) years and 64% female 130 controls: median age 49 62% female	IgM and IgG and correlates	ELISA (IgG and IgM) (MAGLUMI) and CLIA	Average time of IgM seroconversion was 5-10 days POS, levels peaked 2-3 weeks POS. IgG peak was around 3-4 weeks POS on average. IgM levels returned to below threshold in around 8 weeks. IgG decline was slower and >90% of patients in this study maintained positive IgG levels at 8 weeks POS. Concentration of IgM in COVID-19 patients was related to gender and disease severity (P <0.01), and the concentration of IgG was related to age and disease severity (P <0.001)	Selection of participants not clearly described Validation of ELISA assay not described
Ozturk et al ¹³⁸	UK	Pre-print	Cohort	Hospitalised participants 32 cases	IgG levels	ELISA (IgG)	IgG levels were very elevated within days of symptoms for hospitalised patients. Milder forms of COVID-19 reached similar IgG levels at 28 days post symptom onset.	Selection of participants not clearly described Validation of ELISA assay not described
Padoan et al ⁶¹	Italy	Peer reviewed paper	Cohort	Hospitalised participants 70 cases	IgM, IgA and IgG levels, over time	CLIA (MAGLUMI) ELISA (Euroimmun)	Average levels of IgM and IgA antibodies increased for 6–8 days from the onset of COVID-19. Compared to IgM-Ab, IgA-Ab showed persistently higher levels for the whole observation period, with a peak level at 20–22 days. IgM-Ab levels peaked at 10–12 days and significantly declined after 18 days.	Selection of participants not clearly described Validation of ELISA assay not described
Payne et al ⁶⁵	USA	Report	Cohort	Community participants 382 cases Median age 30 75% male	Seroprevalence Detection of neutralising antibodies	ELISA (anti S) (CDC developed) Microneutralisation assay	60% participants had a positive ELISA result, and among those 60% also had a positive microneutralization result Hispanic/Latino participants more likely to have positive microneutralization results non-Hispanic/Latino or unspecified ethnicity participants Among symptomatic participants with positive ELISA results and positive microneutralization test results a median of 22 days had elapsed since symptom onset at the time of specimen collection Among 12 participants with positive ELISA results >40 days after symptom onset, eight maintained positive microneutralization test results, including two participants who were tested >3 months after symptom onset.	Selection of participants not clearly described Validation of ELISA assay not described

Percivalle et al. ⁹⁷	Italy	Peer reviewed paper	Cohort	Mixed hospitalised and community participants 390 blood donors, 38 convalescent cases age range 19-70	Neutralization titers of convalescent patients vs blood donors	Microneutralisation assay	The majority of blood donors had lower neutralising titers than convalescent patients suggesting that neutralizing titers are related to severity of disease. No statistical analysis.	Selection of participants not clearly described Validation of ELISA assay not described
Perera et al. ⁷⁵	China	Peer reviewed paper	Cohort	Hospitalised and community participants 24 cases, 200 controls, 19 cases of other CoV	Antibody response and disease severity	ELISA (Chondrex Inc, Redmon, US) Microneutralisation assay	Neutralisation titres and ELISA IgM OD (point biserial correlation coefficient=0.08; p value=0.69) were not correlated with disease severity but severe/critical cases had higher serum ELISA IgG OD than the mild/moderate cases (point biserial correlation coefficient = 0.37; p-value =0.049).	Selection of participants not clearly described Validation of ELISA assay not described
Premkumar et al. ⁸⁴	USA	Peer reviewed paper	Cohort	Mixed hospitalised and community participants 50 cases	Relationship between RBD binding activity and neutralisation antibody response	ELISA (in house) Neutralisation assay	Total RBD binding IgG correlated with the levels of neutralising antibodies $p < 0.0001$. Those with highest IgM had highest neutralising titers in early convalescence (<6 weeks POS) ($p < 0.00001$). Neutralising antibody kinetics mirrored kinetics of RBD antibody development. No patients had detectable neutralising antibodies within first 8 days.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Prevost et al. ⁵¹	Canada	Pre-print	Case control	98 cases median age 56 56% female	Cross reactivity with other HCoV and virus neutralisation	ELISA Neutralisation assay	Cross reactivity with sarbecovirus and betacoronavirus but not alphacoronavirus. 75% elicited antibody response within 2 weeks and all convalescent cases were seropositive Neutralisation capacity decreases significantly after 6 weeks of symptom onset	Selection of participants not clearly described Validation of ELISA assay not described
Qin et al. ¹⁵¹	China	Peer reviewed paper	Case control	Hospitalised participants 452 cases median age 58 52% male	Antibody response according to severity		There were no significant differences in the levels of IgA, IgG, between the mild and severe groups, while IgM was slightly decreased in severe cases.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

Qu et al. ²⁶	China	Peer reviewed paper	Cohort	Hospitalised participants 41 cases: median age 62 66% female 38 controls: median age 34	IgM and IgG levels, over time	CLIA (YHLO)	Seroconversion time of IgG antibody was earlier than that of IgM antibody (12.45±4.36 vs. 13.75±4.60 days, p=0.0019). 97.6% of patients (40/41) were positive with IgG and 87.8% of patients (36/41) were positive with IgM IgG response of the critical group was significantly stronger than that of non-critical groups within 4 weeks POS (p=0.0001). For IgM, the fitting curve of the critical group rose above the cut-off value on day 10, peaked on day 23, then began to decline.	Selection of participants not clearly described Validation of ELISA assay not described
Reifer et al. ¹⁴⁹	USA	Pre-print	Cohort	Community participants 240 cases	IgG response by disease severity	Anti S1, anti S2 IgG (Liaison)	SARS-CoV-2 IgG antibody levels are positively correlated with symptom severity (p-value < 0.01). This trend is true regardless of whether the patient was male or female.	Selection of participants not clearly described Validation of ELISA assay not described
Rijkers et al. ¹⁴⁶	Netherlands	Pre-print	Cohort	Mixed hospitalised and community participants 63 cases	Antibody response by severity of disease	ELISA (Wantai and Euroimmun) Neutralisation assay	Most patients responded for Ig and IgA between day 10 and 15. 100% had detectable antibodies. Patients admitted to ITU had similar antibody response to patients in general wards i.e. no statistical difference between the two. In week 1 43% of hospitalised cohort had detectable neutralising antibodies (VNT50). At 21-28 days all patients had detectable neutralising antibodies with a median titer of 226. In non-hospitalised cohort 87% developed antibodies by day 21-28 with a significantly lower titer than severe hospitalised patients (p<0.0001). 33% of the mild patients remained negative for the presence of virus neutralizing antibodies.	Selection of participants not clearly described Validation of ELISA assay not described
Robbiani et al. ⁸⁷	USA	Peer reviewed paper	Case control	Mixed hospitalised and community participants 157 cases, 8 controls	Neutralising antibodies	ELISA (in house) Neutralisation assay	Most convalescent plasmas do not contain high levels of neutralising activity, but there are some RBD specific antibodies have very potent neutralising activity. 78% tested positive for anti-RBD and 70% anti-S IgG that were at least 2 SD above the control. Level of neutralising activity were generally low with 33% less than 50 and 79% below 1000 (NT50) Anti-RBD and -S IgG correlated strongly with neutralisation activity, as did age duration of symptoms and disease severity. Significant difference in neutralisation titers between males and females - higher anti-RBD and -S in males.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

Rogers et al. ¹⁷⁵	USA	Peer reviewed paper	Basic Science	Animal study (syrian hamsters) 6 hamsters 17 human cases	Mining potent neutralising antibodies and their passive transfer in an animal model	Neutralisation assay	Passive transfer of nAbs provides protection against disease in high-dose SARS-CoV-2 challenge. Most potent NAb were those aimed at the RBD-A epitope. Used nAbs aimed at RBD-A and S-B epitope to transfer to Syrian Hamsters. Those that received a high dose passive nAb (against RBD-A) had no evidence of weight loss when challenged with SARS-CoV-2.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Rogers et al. ¹⁰³	USA	Pre-print	Basic Science	Animal study (Syrian hamsters) 6 hamsters 17 human cases	Description of potent nAbs and passive transfer in an animal model	Neutralisation assay	Passive transfer of nAbs provides protection against disease in high-dose SARS-CoV-2 challenge. Most potent NAb were those aimed at the RBD-A epitope. Used nAbs aimed at RBD-A and S-B epitope to transfer to Syrian Hamsters. Those that received a high dose passive nAb (against RBD-A) had no evidence of weight loss when challenged with SARS-CoV-2.	Selection of participants not clearly described Validation of ELISA assay not described
Rudberg et al. ¹⁵⁸	Sweden	Pre-print	Case series	Community participants 2149 hospital employees	Seroprevalence amongst healthcare workers	Multiplex (in house)	Seroprevalence 19.1% (n=410) amongst healthcare workers Symptoms with the strongest association to seroprevalence were anosmia (OR 28.43; p=2.02*10 ⁻¹²⁰), ageusia (OR 19.21; p=1.67*10 ⁻⁹⁹) and fever (OR 6.27; p=4.24*10 ⁻⁸).	Selection of participants not clearly described Validation of ELISA assay not described
Ryan et al. ⁹⁰	UK	Pre-print	Trial - non randomised	Animal study (ferrets) 6 ferrets	Neutralising antibody activity Re-challenge day 28 post infection	PRNT	NAb titres for ferrets in high and medium dose groups generally increased longitudinally following challenge. Re-challenged ferrets cleared virus in 5 days post exposure and reduced viral shedding was seen in re-challenged ferrets Immune response to virus 'higher' in re-challenged animal compared to naive animals	Selection of participants not clearly described Validation of ELISA assay not described
Sandri, et al. ¹⁶⁴	Italy	Pre-print	Cohort	Community participants 3985 cases and controls	IgG response and correlates with age and sex	CLIA (anti S1, anti S2 IgG) (Liaison)	Higher proportion of IgG positivity in females (p=0.03) but magnitude of antibody response similar in males and females When assessing a difference of IgG plasma levels across age ranges, males between 41 and 50 y/o had significantly higher plasma levels of IgG than younger individuals (21-30 or 31-40).	Selection of participants not clearly described Validation of ELISA assay not described
Sarina Yang et al. ⁵⁹	USA	Peer reviewed paper	Case control	Mixed hospitalised and community participants 42 cases, 144 convalescent plasma samples	IgM and IgG levels in emergency department patients and convalescent patients	Pylon automated immunoassay (IgG and IgM)	IgM reached peak levels between days 10 and 20 POS and then declined IgG and total antibody reached a peak in a similar time frame to IgM but then plateaued Antibody levels in convalescent sera varied widely.	Selection of participants not clearly described Validation of ELISA assay not described

Schmidt et al ¹⁶²	Germany	Peer reviewed paper	Case series	Community participants (healthcare workers) 406 cases and contacts	Seroprevalence amongst healthcare workers	ELISA (Euroimmun)	Prevalence amongst staff was 2.9% Comparisons of seronegative and seropositive groups showed there was no difference in medical conditions between groups.	Selection of participants not clearly described Validation of ELISA assay not described
Selva et al ¹²²	Australia	Pre-print	Basic Science	Mixed hospitalised and community participants 19 cases, 155 adult and 89 child controls	Cross reactivity in children and elderly between SARS-CoV-2, SARS-CoV-1, MERS-CoV and HCoV spike and nucleoprotein (NP)	ELISA (anti RBD) (ThermoFisher)	Observed distinct cross-reactive coronavirus serological signatures in healthy children compared to elderly. Children had elevated CoV-specific IgM signatures, whereas elderly had more mature, class-switched CoV-specific IgA and IgG Children induced elevated IgM, while elderly had higher RBD-specific IgA1 responses while no differences in IgG were observed.	Selection of participants not clearly described Validation of ELISA assay not described
Shen et al ¹⁴¹	China	Peer reviewed paper	Case control	Hospitalised participants 58 cases	IgM response and its correlates with disease severity	CGIA (IgM) (ShanghaiOutdo Biotech Co.)	Significant differences can be observed ($p < 0.01$) in IgM between mild and severe patient groups. The positive rate in the mild group was 38% (13/34), compared to 0% (0/7) in the severe group at ≤ 3 days after symptom onset. At 4–7 days POS, the positive rate of the mild group was 64% (16/25), compared to 16.7% (1/6) in the severe group. At 15–21 days after symptom onset, the positive rate of the mild group was 100% (15/15), compared to 75% (6/8) in the severe group.	Selection of participants not clearly described Validation of ELISA assay not described
Siracusano et al ⁸²	Multiple populations	Peer reviewed paper	Narrative review	Multiple populations Inclusion of studies not described	Narrative review of Ab and nAb response to COVID-19	N/A	Estimate of development of nAb at day 6 for severe disease and day 8 for mild disease with a sharp accession day 1 and subsequent plateau	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings

Solbach et al ³⁷	Germany	Pre-print	Cohort	Community participants 110 cases 55% female	Antibody kinetics (onset, duration) in a low incidence population	ELISA (IgG and IgA) (Euroimmun)	Within a period of 50 days after the infection, 84/110 (76 %) and 78/110 patients (71 %) of the patients developed antibodies for IgA and IgG, respectively In around 30 % of the patients with mild to moderate symptoms, no significant antibodies could be detected in two consecutive analyses No correlation between symptoms and antibody profile or with gender.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Solodky et al ¹⁵⁵	France	Peer reviewed paper	Case series	Community participants 329 cases	Presence of antibody	LFIA (Toda Coronadiag)	30% of cancer patients with positive RT PCR had positive Ab at 15 days post symptom onset, 71% for healthcare workers Rate of seroconversion significantly lower in cancer patients compared to healthcare workers (30% vs 71%, p=0.04)	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Staines et al ¹⁵³	UK	Pre-print	Cohort	Mixed hospitalised and community cases 177 cases median age 64 57% male	Seroconversion timing and correlates	ELISA (Omega Diagnostics)	8.5% (95%CI 5.2% -13.5%; 15/177) did not seroconvert during the entire follow up period, 7.3% (95%CI 4.3% - 12.1%; 13/177) seroconverted after enrolment and 84% (95%CI 78% - 89%; 149/177) had already seroconverted at the time of the first serological test. 2-8.5% of patients may not develop detectable IgG antibody responses to SARS-CoV-2 for weeks following infection. Seroconversion peaks around d20 then plateaus	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Sun et al ¹⁴⁴	China	Peer reviewed paper	Cohort	Hospitalised participants 38 cases	Neutralising Ab titres	ELISA (anti N and anti S IgM and IgG)	N-IgM and S-IgM in some non-ICU patients reached a peak in the second week, while N-IgG and S-IgG continued to increase in the third week. S-IgG was significantly higher in non-ICU patients than in ICU patients in the third week. In contrast, N-IgG was significantly higher in ICU patients than in non-ICU patients	Selection of participants not clearly described Validation of ELISA assay not described
Suthar et al ⁷⁴	USA	Pre-print	Case series	Hospitalised participants age range 33-87 59% male	Antibody kinetics and Neutralising Ab titres	Multiple assays (in house)	IgG subclass analysis showed that the COVID-19 patients exclusively made RBD-specific IgG1 and IgG3, with no detectable IgG2 or IgG4. Taken together, these findings illustrate that antibody class-switching to IgG occurs early during acute infection. Antibody responses against the RBD as well as SARS-CoV-2 neutralisation titres can be detected in a majority of patients around day 8 POS. When the number of days after PCR confirmation is used to assess the duration of infection, both RBD-binding titers and viral neutralization titers can be detected in many patients already between days 2-6. Both RBD-specific and neutralizing antibody responses occur rapidly after SARS-CoV-2 infection.	Selection of participants not clearly described Validation of ELISA assay not described

Tan et al ⁴²	China	Pre-print	Cohort	Hospitalised participants 66 cases (3 children) median age 49 52% male	IgM and IgG antibody titres	ELISA (IgG and IgM) (Livzon Diagnostics)	The anti-nucleocapsid-protein IgM started on day 7 and the positive rate peaked on day 28, while that of IgG was on day 10 and day 49 POS. In severe patients, IgM and IgG appear earlier, and their titers are significantly higher than non-severe patients ($p<0.05$) The positive rate for IgM increased to 28 days (57.1%) then decreased to 33.3 % at 42 days. The positive rate for IgG increased to 74.3 % at 28 days and increased to 86.7% at 42 days, and persisted	Selection of participants not clearly described Validation of ELISA assay not described
Thompson et al ¹⁰¹	UK	Pre-print	Cohort	Community participants 1000 unknown COVID-19 status blood donors, 100 controls	Neutralising antibody titres	ELISA (in house) Neutralisation assay	In 6 positive control samples (samples taken from control population during pandemic ie not pre-pandemic controls) neutralising antibody IC50 range 83.18- 323.59; R2 range: 0.79-0.96. In 5 blood donor samples IC50 range 78.42-3434.90; R2 range: 0.64-0.95 Presence of neutralising antibodies correlates with presence of IgG/M on ELISA - ELISA OD correlates with IC50 on pMN R2 = 0.49, $p=0.036$	Selection of participants not clearly described Validation of ELISA assay not described
To et al ¹¹⁷	France	Peer reviewed paper	Cohort	Hospitalised participants 23 cases median age 62 57% male	IgG and IgM titres	EIA (in house)	Serum antibody levels did not correlate with clinical severity More patients had earlier seropositivity for anti-RBD than anti-NP for both IgG (43% RBD earlier vs 9% NP earlier) and IgM (26% RBD earlier vs 17% NP earlier). More patients had earlier seroconversion for IgG than IgM for anti-NP (IgG earlier 26% vs IgM earlier 4%) and anti-RBD (IgG earlier 57% vs IgM earlier 4%). Seropositivity for anti-NP IgG 94% (n=16) by 14 days, anti-NP IgM 88% (n=14), anti-RBD IgG 100% (n=16), 94% anti-RBD IgM (n=15)	Selection of participants not clearly described Validation of ELISA assay not described
Vabret et al ¹⁷	Multiple populations	Peer reviewed paper	Narrative review	Multiple populations Inclusion of studies not described	Narrative review on immunity to COVID-19	N/A	Robust B cell response of virus-specific IgM, IgG and IgA, and nAbs in the days following infection. IgG specific to SARS-CoV-2 trimeric spike protein was detectable in serum up to 60 days after symptom onset, but IgG titers began decreasing by 8 weeks post symptom onset The SARS-CoV-1 humoral response is relatively short lived, and memory B cells may disappear altogether, suggesting that immunity with SARS-CoV-2 may wane 1–2 years after primary infection.	Selection of participants not clearly described Validation of ELISA assay not described

Varnaite et al. ⁹⁹	Sweden	Pre-print	Case control	Hospitalised participants 20 cases, 7 controls	Antibody kinetics, neutralising antibody kinetics, T-cell response	ELISA (anti S1 IgG) (Euroimmun) IFA Microneutralisation assay	IgA, IgG and IgM antibody levels positively correlated with neutralizing antibody titers Total and spike S1-specific SARS-CoV-2 IgG antibody level positively correlated with the number of days since symptom onset ($r_s = 0.577$, $P = 0.01$ and $r_s = 0.603$, $P = 0.005$ respectively) Total SARS-CoV-2-specific IgG antibody levels positively correlated with neutralizing antibody titers ($r_s = 0.865$, $P < 0.001$)	Selection of participants not clearly described Validation of ELISA assay not described
Vogelzang et al. ⁵⁴	Netherlands	Pre-print	Case control	Mixed hospitalised and community participants 284 cases median age 31	Antibody response in non-hospitalised and hospitalised patients	Multiple in-house assays	Antibodies detected in both hospitalised and non-hospitalised groups Non-significant trend in declining IgM and IgA levels as time progresses in both hospitalised and non-hospitalised Non hospitalised patients have a slower rise in IgG and has a weaker response than hospitalised patients In the group highly suspected of having COVID-19 9 of 14 patients seroconverted for IgG within 15 days POS and 3 seroconverted after	Selection of participants not clearly described Validation of ELISA assay not described
Wang et al. ¹¹²	China	Pre-print	Case series	Animal study (rabbits) 10 human cases	Neutralising antibody kinetics	Neutralisation assay	Potential neutralising epitopes (involved in RBD) identified in 2 cases (IgG) and 1 case (IgM) Cross reactivity of SARS-CoV-1 Ab to SARS-CoV-2 in rabbits	Very small sample and selection not clearly described Unclear if or how assay validated Lack of detail in reporting limits interpretation of findings
Wang et al. ²⁵	China	Peer reviewed paper	Cohort	Hospitalised participants 26 cases age range 5-72	Antibody kinetics	CGIA (Innovita)	IgM and IgG detected from day 7 POS. All 25/26 developed IgG but 11/26 cases did not develop IgM. One case had not developed antibodies by day 66 post onset (5 year old female) All other cases maintained IgG until the end of their follow up (range 16-39 days)	Selection of participants not clearly described Validation of ELISA assay not described

Wang et al. ⁹⁵	China	Peer reviewed paper	Cohort	Hospitalised participants 70 cases mean age 45 59% female	Neutralising Ab titres	In house assay	The mean titre of neutralizing antibodies (average: 1:271.2) was the highest at 31-40 days since onset and antibody titers at 31-40 days were significantly higher than 10-20 days POS. The antibody levels according to different time course since onset were significantly different (P=0.0012). The effect of gender was not statistically significant. A significant neutralizing antibody response was observed in older patients with a geometric mean titer of 1:220.1 (95% CI, 71.8 to 674.8) compared to patients at age of 16-30 (1:71.0, 95% CI, 27.7 to 181.8) and at age of 31-60 (1:200.6, 95% CI, 150.4 to 267.6) (P=0.0140).	Selection of participants not clearly described Validation of ELISA assay not described
Wang et al. ⁹⁸	USA	Pre-print	Case control	Hospitalised participants 35 cases 50% female	Neutrallisation activity in severe vs non severe patients.	In-house neutralisation assay	Titers of antibodies binding to the viral nucleocapsid and spike proteins were significantly higher in patients with severe disease Mean plasma titer was 8 fold higher in severe group (p=0.036) for NP directed antibodies and for S directed antibodies (p=0.016) Antibody neutralisation titers against the pseudovirus and live virus were higher in the sicker patients	Selection of participants not clearly described Validation of ELISA assay not described
Wang et al. ⁴⁵	China	Pre-print	Case control	Hospitalised participants 116 cases		CLIA (IgG and IgM) (YHLO)	IgM levels peaked in 4th week after onset of COVID-19 pneumonia, while serum IgG levels increased over 8 weeks. Serum IgM was higher in deceased patients than mild-moderate patients (p=0.019), but not IgG. Serum IgM levels were positively correlated with IgG levels (r=0.279, p=0.031), and negatively correlated with clinical outcome (r= 0.337, p= 0.008) No significant correlations between IgM levels and sex, comorbidities or duration between onset and antibody detection in patients with COVID-19 pneumonia - unmatched and when matched on age	Selection of participants not clearly described Validation of ELISA assay not described
Wec et al. ¹⁰⁹	Animal study	Pre-print	Basic Science	Animal study	Neutralising activity of cross reacting SARS-CoV-1 Ab to SARS-CoV-2	In house assay	0.14 % of class-switched MBCs were SARS-CoV-2 S-reactive (3 fold higher than control) 9 out of 200 antibodies displayed neutralizing activity at the 100 nM concentration tested, 8 of which targeted RBD and 1 targeted NTD IC50s of the RBD-directed nAbs ranged from 0.05-1.4µg/ml against SARS-CoV-2	Selection of participants not clearly described Validation of ELISA assay not described

Wu et al ⁹⁴	China	Pre-print	Cohort	Hospitalised participants 175 cases median age 50 53% female	Neutralising activity of SARS-CoV-2	ELISA (in house) Neutralisation assay	Some cross-binding Ab to SARS-CoV-1 but not cross-neutralising Ab NAb's titers moderately correlated with spike binding antibodies targeting RBD ($r=0.51$, $p<0.0001$), S1 ($r=0.42$, $p<0.0001$), and S2 ($r=0.435$, $p<0.0001$) - $n=175$ 30% of recovered patients had low NAb titres (ID<500). NAb titers of elderly and middle-age recovered patients were significantly higher than those of young recovered patients $p<0.0001$.	Selection of participants not clearly described Validation of ELISA assay not described
Wu et al ¹⁰⁸	Lab based	Peer reviewed paper	Basic Science	1 case	Neutralising activity of SARS-CoV-2	In house assay	Details of specific neutralising antibodies identified from single donor - 4 Ab identified, median IC50 values ranging from 0.177 to 1.375 mg/ml	Selection of participants not clearly described Validation of ELISA assay not described
Xiang et al ³²	China	Peer reviewed paper	Cohort	Hospitalised participants 109 cases	IgG and IgM titers	ELISA (IgG and IgM) (Livzon)	IgM cumulative seroconversion increased quickly from the 9th day and IgG from the 11th day POS. Both antibodies were seropositive in nearly all the patients for more than 30 days IgG and IgM detected as early as day 4. The seropositive rate of IgG was observed decreased around the 28th POS	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Xiao et al ⁴⁰	China	Peer reviewed paper	Case series	Hospitalised participants 34 cases	IgG and IgM titers	CLIA (IgG and IgM) (Shenzhen)	Profile of specific antibodies to SARS-CoV-2 is similar to SARS-CoV. Detectable and continuous high level IgM indicated acute phase of infection. IgG responded later and persisted. IgG detected in all patients ($n=6$) tested at 7 weeks after onset	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Xie et al ⁶³	China	Peer reviewed paper	Cohort	Hospitalised participants 56 cases	Antibody and cellular response, clinical characteristics of patients	CLIA (IgG and IgM) (YHLO)	IgG maintains high levels with severe and non-severe disease IgM increased in 1 week and then started to decline week 4-5	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Yongchen et al ¹³⁴	China	Peer reviewed paper	Cohort	Hospitalised cases 21 cases	IgG and IgM titers	CGIA (Innovita)	All symptomatic patients developed antibody response; an earlier antibody response was seen in patients with severe disease. IgM was not detected for 6/11 non-severe pts but all (5/5) severe patients were IgM and IgG positive All of 17 symptomatic patients (100%) were seropositive at the time point of discharge or during follow-up period Only 1 of 5 asymptomatic cases generated an antibody response at week 3	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

Zeng et al. ¹⁶⁶	China	Peer reviewed paper	Cohort	Hospitalised participants 331 cases 67% female median age 42 (F) 45 (M)	IgG concentration by sex and disease severity	CLIA (IgG) (YHLO)	Concentration of IgG antibody in mild, general, and recovering patients showed no difference between male and female patients In severe status, compared with male patients, there were more female patients having a relatively high concentration of IgG antibody Generation of IgG antibody in female patients was stronger than male patients in disease early phase	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Zeng et al. ¹⁷¹	China	Peer reviewed paper	Case series	Hospitalised participants 6 infants born to 6 cases	IgG, IgM, IL-6 levels	CLIA (IgG and IgM) (YHLO)	All 6 babies had antibodies detected in serum and were asymptomatic Two infants and their mothers had IgG and IgM concentrations higher than the normal level (<10 AU/mL) Three infants had elevated IgG levels (75.49, 73.19, 51.38 AU/mL) but normal IgM levels; all 3 mothers had elevated IgG and 2 also had elevated IgM levels. Inflammatory cytokine IL-6 was significantly increased in all infants.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Zhang et al. ³⁰	China	Pre-print	Cohort	Hospitalised participants 222 cases median age 62 52% female	IgG, IgM, IL-6 levels	CLIA (IgG and IgM) (Shenzhen)	IgG was first detected on day 4 of illness, and its peak levels occurred in the 4th week, whereas IgM was first detected on day 3 of illness, and its peak levels occurred in the 2nd week Severe cases more commonly found in those with high IgG levels in comparison to the low level group (51.8% vs 32.3%, p=0.008). Severe cases occurred more frequently in those with lower IgM levels (<34.1 AU/ml) than those with high IgM levels (>3.04AU/ml) (81.3% vs 40%; p=0.024) Severe patients had higher IL-2, IL-6 and IL-10 than non-severe patients. Severe patients also had higher proinflammatory cytokines levels including IL-2, IL-6 and IL-10, and decreased CD4+ T cell count (p<0.05).	Selection of participants not clearly described Validation of ELISA assay not described
Zhang et al. ⁶²	China	Peer reviewed paper	Cohort	Hospitalised participants 122 cases median age 38 71% female	IgG and IgM titres	EIA (IgG and IgM) (Yahuilong Biotechnology)	Fifty-eight (51.79%) were positive for both IgM and IgG, 7 (6.25%) were negative for both antibodies, 1 (0.89%) was positive for only IgM, and 46 (41.07%) were positive for only IgG. IgM antibody appeared within a week post-disease onset, lasted for 1 month, and gradually decreased, whereas IgG antibody was produced 10 days after infection and lasted for a longer time.	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Zhang et al. ³³	China	Peer reviewed paper	Cohort	Hospitalised participants 6 cases age range 30-50	IgG and IgM titres	ELISA (IgG and IgM) (Livzon)	5/6 had weakly reactive IgM and 5/6 had high IgG titres Paper focused on the use of convalescent plasma	Selection of participants not clearly described Validation of ELISA assay not described

Zhang et al ⁴⁸	China	Peer reviewed paper		Hospitalised participants 6 children age range 7-131 months	Total Ab, IgG and IgM positivity only (no measured titres)	CLIA (total, anti S and anti RBD IgG) (Kehua Bio-Engineering)	Relative quantitative analysis showed that total or IgG antibody for nucleocapsid and spike-RBD protein production were significantly increasing over the days after illness onset The percentage of CD3+, CD4+, and CD8+ T cells between infected and uninfected cases were comparable.	Selection of participants not clearly described Validation of ELISA assay not described
Zhang et al ¹⁴³	China	Pre-print	Cohort	Hospitalised participants	Total antibodies (Ab), IgG, IgA and IgM titres	CMIA	The total sero-positive conversion rate for Ab, IgG, and IgA of asymptomatic patients was 90.9% (20/22), 95.5% (21/22) and 90.9% (20/22), respectively All symptomatic patients experienced sero-positive conversion of total Ab, IgG and IgA. The total seropositive conversion rate of IgM reached 45.5% (10/22), 62.5% (20/32), and 63.2% (12/19) for asymptomatic, pre-symptomatic, and symptomatic patients, respectively.	Selection of participants not clearly described Validation of ELISA assay not described
Zhang and Qu. ⁴⁹	China	Pre-print	Cohort	67 cases	Ab neutralisation	ELISA	51 sera showed cross-neutralization with SARS-CoV-1, 12 (17.91%, 7.46% plus 10.45%) with MERS-CoV, and 7 (10.45%) with both. Compared to non-severe group, severe group exhibited higher titers of anti-S1 (p=0.012) and anti-S2 antibodies (p=0.011) and higher neutralization titers (p=0.001), but no difference for binding avidity nAb response was correlated with the severity of disease, though older age (p<0.001), longer course of disease (p=0.007), more comorbidities (p=0.044), and underlying diseases (p<0.001) were higher in severe group	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation
Zhao et al ²⁴	China	Peer reviewed paper	Cohort	Hospitalised participants 137 cases	IgG and IgM titres	ELISA (Wantai)	The seroconversion rate for Ab, IgM and IgG was 93.1% (161/173), 82.7% (143/173) and 64.7% (112/173) respectively Critical patients showed significantly higher seroconversion Ab values than non-critical cases in about 2-week after onset (p=0.02) No significant difference on the average seroconversion value of Ab tests between critical and non-critical patients before day 12 2 weeks after onset, critical patients showed significantly higher Ab S/CO values than non-critical cases (p=0.02) and this association was not significant in either IgM or IgG tests	Well conducted review with a large sample, although lack of clarity in individual study settings and assay validation

SUPPLEMENTARY APPENDIX F: PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Suppl. Appendix B
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7 (no meta-analysis performed)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, figure 1 (flow diagram)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Suppl. Appendix E
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl appendix E
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Suppl appendix E
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A (narrative synthesis)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-15 (narrative synthesis)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18