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 22.3 million confirmed cases and 782,456 deaths reported to the WHO. 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. 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; treatment options such as infusion of convalescent plasma or derived immunoglobulin; sero-surveillance to monitor progression of the epidemic in the population; 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. 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.

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. 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. 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. Furthermore, understanding of the mechanistic correlates of protective immunity in humans remains limited, including the antibody titre and specificity required to confer protection.

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. 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 library 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; 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. 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),\textsuperscript{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,\textsuperscript{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.\textsuperscript{15,27–33} For IgM, mean or median time to seroconversion ranged from 4-14 days post symptom onset,\textsuperscript{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,\textsuperscript{23,35,36} with some outliers, including two reports of 24 days to first detection.\textsuperscript{37,38}

\textit{Sequential antibody response}

In line with the expected sequential appearance of antibody isotypes, the majority of studies reported detection of IgM followed by IgG.\textsuperscript{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.\textsuperscript{23} One study detected IgG seroconversion in advance of IgM,\textsuperscript{26} and a study involving African green monkeys reported simultaneous IgM and IgG responses.\textsuperscript{41} These disparities may reflect the use of differing antibody assays across a range of species and without standardisation.

\textit{Antibody dynamics over time}

IgG dynamics appeared to follow a pattern of peak, plateau, and persistence at lower levels (\textbf{figure 3}). After appearance, IgG titres rose to a peak between three and seven weeks post symptom onset,\textsuperscript{7,23,30,42–48} with studies recording the presence of IgG in and beyond weeks four,\textsuperscript{40,49} five,\textsuperscript{50} six,\textsuperscript{23,51} seven,\textsuperscript{52,53} and eight\textsuperscript{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.\textsuperscript{32,57–59} A decrease in antibody levels was reported in the eighth week post symptom onset by two studies,\textsuperscript{17,38} while another reported a decline from the second month after symptom onset.\textsuperscript{58} Evidence from a cohort of 40 UK patients suggests a decline in titres after eight weeks,\textsuperscript{58} although persistence of virus-specific IgG has been described at varying levels up to 12 weeks post symptom onset,\textsuperscript{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\textsuperscript{7,26,30,34,43,46,53,60,61} then decline over time to below the detection limit.\textsuperscript{38,43,62} Beyond the peak, IgM is consistently reported to decrease from as early as two to three weeks,\textsuperscript{53,61} to as late as eight weeks\textsuperscript{55} post symptom onset, with the majority of studies reporting this decline to occur at between three to five weeks.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{7,18,22,29,65–88} and animal\textsuperscript{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.\textsuperscript{83} Another high-quality cohort study also found most patients (91%, n=22) developed a neutralising antibody response by 21 days after disease onset.\textsuperscript{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.\textsuperscript{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.\textsuperscript{87}

Neutralising antibodies were generally detectable between 7 - 15 days following disease onset,\textsuperscript{7,18,75,84,85,88,93,94} increasing over days 14 - 22 before plateauing\textsuperscript{22,68,69,88,93,94} and declining over a period of six weeks.\textsuperscript{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.\textsuperscript{51} A second medium quality preprint found neutralising antibodies became undetectable in four of 11 previously detectable cases.\textsuperscript{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.\textsuperscript{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.\textsuperscript{29,49,67,74,87,99–101} Specifically, high quality studies found that neutralisation ability correlated positively with anti-S IgG\textsuperscript{49,72,87,99} or anti-RBD IgG.\textsuperscript{72,74,87,102} There was more limited evidence for correlation with anti-RBD IgM, including one high quality study.\textsuperscript{51,84} and IgA.\textsuperscript{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.\textsuperscript{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.\textsuperscript{104,105} RBD-specific antibodies were also shown to have potent neutralising activity in a range of other small studies,\textsuperscript{70,104,106–112} including one using an IgA isotype.\textsuperscript{113} Neutralising ability correlated in particular with competition for the angiotensin converting enzyme - 2 (ACE2) receptor.\textsuperscript{70,72,106} Two studies demonstrated a lack of association with affinity,\textsuperscript{73,106} although a moderate correlation with binding affinity was reported in one study.\textsuperscript{107} Potently neutralising N specific antibodies were isolated in other studies,\textsuperscript{73,109} and the potential for antibodies binding to protease cleavage sites as alternatives to RBD isolated from convalescent plasma has also been identified,\textsuperscript{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.\textsuperscript{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.\textsuperscript{87}

**Correlation of antibodies with viral load**

Several studies investigated the relationship between SARS-CoV-2-specific IgG and viral load\textsuperscript{116,117} or the co-existence of antibodies and viral RNA.\textsuperscript{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).\textsuperscript{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.\textsuperscript{117} Another high-quality cohort study had similar findings but did not quantify viral load.\textsuperscript{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.\textsuperscript{25} Other studies were mixed, with one finding higher levels of specific antibodies correlated with viral clearance within 22 days,\textsuperscript{38} and another finding weaker IgG response correlated with viral clearance within seven days after antibodies become detectable,\textsuperscript{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.

\textit{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\textsuperscript{89–91,118} and re-exposure following passive transfer of neutralising antibodies.\textsuperscript{92,103}

Following primary infection, timing of re-challenge varied between 20-43 days post inoculation. All studies but one\textsuperscript{90} 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.\textsuperscript{89} Similar findings were reported in a hamster model.\textsuperscript{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.\textsuperscript{90}

Two studies examined protection from SARS-CoV-2 infection following the passive transfer of neutralising antibodies in Syrian hamster models.\textsuperscript{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.\textsuperscript{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. 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. Whilst seasonal HCoVs are more common in the population, only 10% of sera exposed to HCoVs demonstrated cross-reactivity again with very little neutralisation activity. 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. 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-CoV1 and MERS-CoV. 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.\textsuperscript{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,\textsuperscript{124} and is consistent with data emerging from vaccine development studies showing that protective antibodies can be induced.\textsuperscript{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.\textsuperscript{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.

\textit{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.\textsuperscript{130} However, in the UK, nationally validated assays have been evaluated with convalescent samples from community participants and a number of large-scale serosurveys now use these.\textsuperscript{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.

\textit{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).\textsuperscript{125} However, longitudinal studies of those already infected with SARS-CoV-2 is required to examine the degree of protection arising from prior infection.

\textit{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
JM – validation, writing – review and editing
AMS – validation, writing – review and editing
GA – conceptualisation, supervision, validation, writing – review and editing
SJP – conceptualisation, supervision, validation, writing – review and editing
SAI – conceptualisation, investigation, methodology, project administration, writing – original draft, writing – review and editing

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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.
| Article type                  | Antibody response | Protective Immunity |
|------------------------------|-------------------|---------------------|
| Pre-print                    | 57                | 43                  |
| Peer reviewed paper          | 51                | 26                  |
| Report                       | 0                 | 1                   |

| Study designs                | Antibody response | Protective Immunity |
|------------------------------|-------------------|---------------------|
| 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                   |

| Subjects                     | Antibody response | Protective Immunity |
|------------------------------|-------------------|---------------------|
| Human                       | 104               | 58                  |
| Animal                      | 1                 | 6                   |
| Both                        | 3                 | 6                   |

| Country of origin            | Antibody response | Protective Immunity |
|------------------------------|-------------------|---------------------|
| 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                  |

| Study setting                | Antibody response | Protective Immunity |
|------------------------------|-------------------|---------------------|
| Hospital patients            | 70                | 33                  |
| Mixed hospital and community | 18                | 11                  |
| Community                    | 13                | 5                   |
| Unclear                      | 6                 | 12                  |
| Animal only study            | 1                 | 9                   |

| Overall MetaQAT quality assessment | Antibody response | Protective Immunity |
|------------------------------------|-------------------|---------------------|
| 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 whisks 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 disease134,135, 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.54  
• 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 infection86,168 |
Two studies found children with pneumonia generally mounted lower IgG\textsuperscript{169} and IgA responses\textsuperscript{170} and one study reported no differences.\textsuperscript{167} Two studies reported most neonates born to COVID-19 positive mothers had raised IgM,\textsuperscript{171,172} and COVID-19 recovered donor breast milk was found to have reactive IgA in one study.\textsuperscript{173}

| Ethnicity                  | One study reported non-white ethnicity was associated with higher antibody levels than white ethnicity.\textsuperscript{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.\textsuperscript{159}                                      |
|            | Antibody titre       | N/A                        | • Ten studies reported a higher titre of neutralising antibodies in more clinically severe cases \textsuperscript{7,43,49,66,85,87,95–98}                                                                                          |
|            |                      |                            | • One study reported undetectable neutralising activity in plasma from a majority of asymptomatic cases.\textsuperscript{85}                                                                                                                                 |
| Demographic| Sex                  | N/A                        | • Five studies reported neutralising antibody response was positively correlated with male sex,\textsuperscript{66,68,87,96} although it is unclear how this is related to disease severity.\textsuperscript{49} |
|            |                      |                            | • One study reported a positive correlation between neutralising antibody formation and female sex.\textsuperscript{85}                                                                                     |
| Age        | Older adults         | N/A                        | • Two studies reported increasing neutralising antibody response with increasing age.\textsuperscript{20,94}                                                                                             |
|            |                      |                            | • Two studies reported no association between neutralising antibodies and age.\textsuperscript{68,85}                                                                                                  |
| 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).\textsuperscript{65} |

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