


REVIEW

Immune response following infection with SARS-CoV-2 and other coronaviruses: A rapid review

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Summary

In this review, we systematically searched and summarized the evidence on the immune response and reinfection rate following SARS-CoV-2 infection. We also retrieved studies on SARS-CoV and MERS-CoV to assess the long-term duration of antibody responses. A protocol based on Cochrane rapid review methodology was adhered to and databases were searched from 1/1/2000 until 26/5/2020.

Of 4744 citations retrieved, 102 studies met our inclusion criteria. Seventy-four studies were retrieved on SARS-CoV-2. While the rate and timing of IgM and IgG seroconversion were inconsistent across studies, most seroconverted for IgG within 2 weeks and 100% (N = 62) within 4 weeks. IgG was still detected at the end of follow-up (49-65 days) in all patients (N = 24). Neutralizing antibodies were detected in 92%-100% of patients (up to 53 days). It is not clear if reinfection with SARS-CoV-2 is possible, with studies more suggestive of intermittent detection of residual RNA.

Twenty-five studies were retrieved on SARS-CoV. In general, SARS-CoV-specific IgG was maintained for 1-2 years post-infection and declined thereafter, although one study detected IgG up to 12 years post-infection. Neutralizing antibodies were detected up to 17 years in another study. Three studies on MERS-CoV reported that IgG may be detected up to 2 years.

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, Confidence Interval; Covid-19, Coronavirus disease 2019; HIQA, Health Information and Quality Authority; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; KCDC, Korea Centers for Disease Control and Prevention; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; N protein, Nucleocapsid protein; RNA, Ribonucleic Acid; RT-PCR, Reverse Transcriptase Polymerase Chain Reaction; S protein, Spike protein; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization.

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In conclusion, limited early data suggest that most patients seroconvert for SARS-CoV-2-specific IgG within 2 weeks. While the long-term duration of antibody responses is unknown, evidence from SARS-CoV studies suggest SARS-CoV-specific IgG is sustained for 1-2 years and declines thereafter.

KEYWORDS

COVID-19, MERS-CoV, SARS-CoV, SARS-CoV-2, seasonal coronaviruses

1 | INTRODUCTION

Following the emergence of a novel coronavirus (SARS-CoV-2) in China in December 2019 and declaration by WHO of a public health emergency of international concern on 30 January 2020, countries worldwide have experienced epidemics of Covid-19. While much is yet unknown about the immune response following infection with SARS-CoV-2, evidence is emerging at a fast pace. The Health Information and Quality Authority (HIQA) of Ireland has conducted a series of rapid reviews on various public health topics relating to SARS-CoV-2 infection. These reviews arose directly from questions posed by policy makers and expert clinicians supporting the National Public Health Emergency Team to inform the national response to the pandemic in Ireland.

The primary objective of this review was to summarize the evidence on the immune response following SARS-CoV-2 infection. Due to the recent emergence of SARS-CoV-2, studies were also retrieved on SARS-CoV and MERS-CoV to summarize the long-term duration of the immune response following coronavirus infections. The following specific research questions were addressed:

1. What proportion of symptomatic cases develop SARS-CoV-2-specific antibodies (seroconversion rate)?
2. How quickly are SARS-CoV-2 specific antibodies developed post-onset of symptoms (seroconversion timing)?
3. What is the long-term duration of immunity following infection with SARS-CoV-2, SARS-CoV and MERS-CoV?
4. Does the severity of initial infection with SARS-CoV-2 affect the immune response?
5. What is the reinfection rate following laboratory-confirmed SARS-CoV-2 recovery (≥ 2 consecutive negative reverse transcriptase polymerase chain reaction [RT-PCR] tests at least 24 hours apart along with clinical improvement in symptomatic cases)?
6. Are SARS-CoV-2 reinfected individuals infectious to others?

2 | METHODS

A standardized protocol was adhered to¹ based on Cochrane rapid review methodology guidance.²

Electronic databases (PubMed, EMBASE and EuropePMC) and pre-print servers (medRxiv, bioRxiv and Health Research Board

[HRB] Open) were searched for the period 1 January 2000 until 26 May 2020. All potentially eligible papers, including non-peer-reviewed pre-prints, were exported to Endnote X8.2 and screened for relevance.

For each included study, data on the study design, participant demographics and clinically relevant data (such as the severity of initial infection) were extracted by two reviewers. As no universally accepted quality appraisal tool exists for many study designs included in this review, including for case series, a de-novo quality appraisal tool was developed, adapted from existing tools (such as the Newcastle-Ottawa scale³ and the ROBINS-I tool⁴). Supplementary Material 1 in Data S1 provides the full search strategy, inclusion criteria for the selection of studies and details of the quality appraisal tool used. The findings of the research question were synthesized narratively due to the heterogeneity of study designs and outcome data.

3 | RESULTS

The database search retrieved 4744 citations. Following removal of duplicates, 4119 unique citations were screened for relevance. Overall, 102 studies were identified that met our inclusion criteria, encompassing 6792 cases diagnosed by respiratory RT-PCR testing (SARS-CoV-2, SARS-CoV or MERS-CoV). These included 92 case series/cohort studies,⁵⁻⁹⁶ eight case reports⁹⁷⁻¹⁰⁴ and two cross-sectional studies.^{105,106}

Seventy-four studies were conducted in China, five in France, four in Italy, three each in Germany, South Korea, and Taiwan, two each in Saudi Arabia, Singapore and the US, and one each in Finland, the Philippines, Switzerland and the UK. SARS-CoV-2 was investigated in 74 studies, SARS-CoV in 25 and MERS-CoV in three. A diverse range of serological tests was used, including chemiluminescent immunoassay, enzyme-linked immunosorbent assay, enzyme immunoassay, gold immunochromatographic assay, immunofluorescence assays, immunochromatography strip assay, lateral flow immunoassay, magnetic chemiluminescence enzyme immunoassay, modified cytopathogenic assay, rapid point-of-care test kits and proteomic microarrays. Supplementary Material 2 in Data S2 provides details of included studies, including demographic details, testing platforms used and primary outcome data.

3.1 | Seroconversion rate and timing for SARS-CoV-2

In total, 43 studies were identified that assessed the rate and/or timing of seroconversion for IgM or IgG following acute SARS-CoV-2 infection.^{7,9-11,18,21,23,25,26,30-32,34,37,39,40,43,44,46,49,60-62,67,68,71,73,82,86,87,90,92,94,97,98,101,104-107} Up to 338 patients were enrolled in any single study³⁷ and the largest number of samples taken was 535.⁹⁰ The median age ranged from 37¹⁰⁶ to 68 years,⁵⁵ and a similar number of males and females were followed across studies.

The seroconversion rate for SARS-CoV-2-specific antibodies varied across studies and stage of disease. One case series reported daily serial antibody samples to identify the exact day of seroconversion post-symptom onset in 22 patients using four commercial immunochromatographic tests.²¹ On day 15, 82%-100% were seropositive for IgM and 100% were seropositive for IgG in all four tests.

Where there was an absence of serial daily samples to identify the exact timing of seroconversion, under the assumption that all individuals were negative for SARS-CoV-2-specific antibodies prior to December 2019, the first positive test was taken as a proxy for seroconversion timing. Eight studies investigated the IgM and IgG detection rate at three different stages of the disease (N = 492 patients included across studies and eight different antibody tests used, Supplementary Material 2 in Data S2).^{30,62,64,68,82,86,92,106} The detection rate for IgM ranged between 11% and 71% in the early stage of infection (1-7 days after symptom onset), between 36% and 87% in the intermediate stage (8-14 days), and between 56% and 97% after 14 days. The detection rate for IgG ranged between 4% and 57% in the early stage, between 54% and 88% in the intermediate stage, and between 91% and 100% after 14 days. Figures 1 and 2 illustrate these findings. The remaining studies reported seroconversion rates of 74%-100% for IgM and 65%-100% for IgG; however, the timing of samples varied widely (from one to 51 days post symptom onset).

The median time to antibody detection following symptom onset ranged from five days³² to 17 days³⁹ for IgM and from 6 days³⁹ to 14 days³² for IgG. Only one study simultaneously measured antibody titres (by immunofluorescence), viral load (by RT-PCR) and infectivity (by live virus isolation on Vero E6 cells) in nine patients.⁷³ Whereas virus was readily isolated during the first week of symptoms from a considerable proportion of samples (16.7% in nasopharyngeal swabs, 83.3% in sputum samples), no isolates were obtained from samples taken after day eight despite persistent high viral loads ($\geq 2 \times 10^5$ RNA copies in each sample). Antibody detection (IgM and or IgG) in 50% of patients occurred by day seven, and in all by day 14. This study supported the hypothesis that an appropriate antibody response is associated with clearance of infectious virus. Additionally, cross-reactivity or cross-stimulation against four endemic human coronaviruses was found in several patients using recombinant immunofluorescence assays.

3.2 | Duration of immune response

As SARS-CoV-2 was first identified in December 2019, there is a lack of evidence on the long-term duration of antibody responses following infection. Therefore, studies were also retrieved that investigated the long-term duration of immune responses to SARS-CoV and MERS-CoV.

3.3 | Duration of immune response: SARS-CoV-2

Eleven studies were identified that examined the duration of the immune response in SARS-CoV-2 infection beyond 4 weeks.^{5,24,25,28,32,39,45,60,86,106,108} Maximum follow-up was between 60 and 65 days.⁵ Eight studies (range: 5-11 patients) reported on the duration of IgG antibody responses following infection, with the longest follow-up 60-65 days post-symptom onset.^{5,24,25,28,39,45,86,106} All patients tested positive for IgG at the end of follow up, including 24 patients that were followed for more than 7 weeks in three studies.^{5,25,28} Additionally, four case series (range: 3-48 patients) reported neutralizing antibody serology data beyond 4 weeks, with the longest follow-up 41-53 days post-symptom onset.^{24,26,60,72} Two case series used live SARS-CoV-2 virus neutralization^{60,72} and two used pseudo-virus neutralization assays (Supplementary Material 2 in Data S2).^{24,26} By the end of follow-up, 92%-100% of patients had detectable neutralizing antibody levels.

3.4 | Duration of immune response: SARS-CoV

The duration of the immune response to SARS-CoV was investigated in 25 studies.^{8,12-16,33,36,38,42,50,51,53,56,58,59,63,66,69,74,78,80,95,96,109} Sample sizes ranged from two⁵³ to 311²⁷ participants and the maximum follow-up was 17 years.⁸ Studies found that SARS-CoV-specific IgM antibodies generally begin to decline 2-3 weeks after the onset of symptoms^{15,36,38,42,110} and had disappeared by 3 to 12 months after infection.^{15,38,50} In general, the SARS-CoV-specific IgG response is sustained for 1-2 years and declines thereafter.^{12,15,33,36,42,50,56,58,66,69,74,96} A meta-analysis of SARS-CoV IgG seropositivity rates across studies over the first 3 years is given in Figure 3 (with individual study data presented in Supplementary Material 3 in Data S3).

Three studies on SARS-CoV had greater than 10 years follow up and assessed the long-term duration of IgG,³³ neutralizing antibodies⁸ and T-cells⁵⁹ among SARS-CoV survivors. SARS-CoV specific IgG antibodies against the whole virus were detected for at least 12 years in one study.³³ In general, the proportion IgG positive peaked at 100% (32/32) in 2004 (1-2 years after the outbreak), declined quickly from 2004 to 2006, and subsequently continued to decline at a slower rate, decreasing to 69% (18/26) in 2015 (approximately 12 years after infection). Authors also reported that patients treated with corticosteroids at the time of

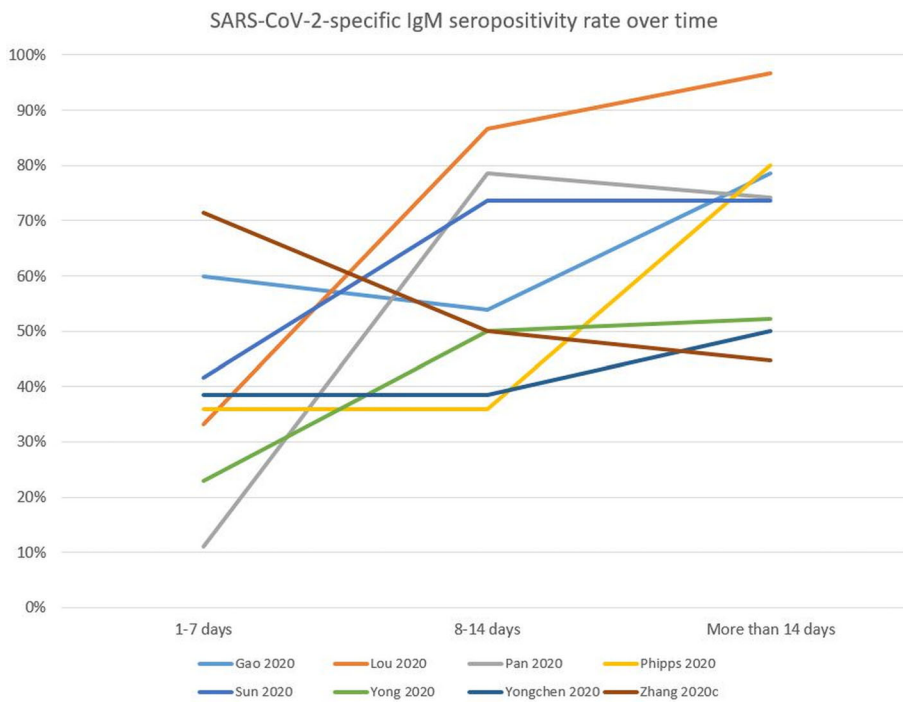


FIGURE 1 SARS-CoV-2-specific IgM seropositivity rate at three time points is displayed (1-7 days, 8-14 days and ≥ 14 days). Note: Zhang 2020c collected data at following time points: <10 days, 10-20 days and 20-30 days

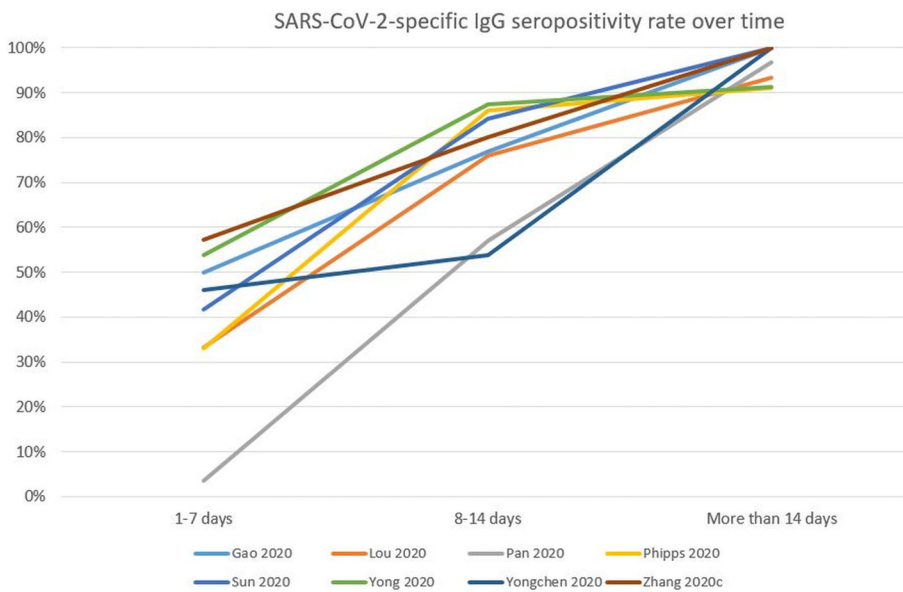


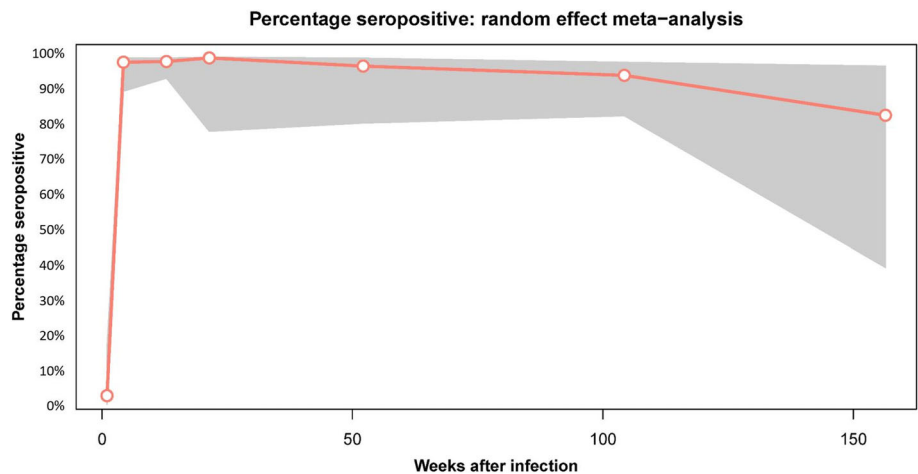
FIGURE 2 SARS-CoV-2-specific IgG seropositivity rate at three time points is displayed (1-7 days, 8-14 days and ≥ 14 days). Note: Zhang 2020c collected data at following time points: <10 days, 10-20 days and 20-30 days

infection, such as prednisone and methylprednisolone, had lower IgG titres than those without. The second study screened for the presence of SARS-CoV-specific T cells in a cohort of three recovered individuals at nine and 11 years post-infection.⁵⁹ Memory T cell responses targeted SARS-CoV structural proteins (membrane and nucleocapsid proteins). Responses were found to persist up to 11 years post-infection. Additionally, authors reported that SARS-specific T cells were not activated by MERS-CoV peptides. The third study found significant levels of anti-SARS CoV neutralizing antibodies in 12 recovered patients, including five patients followed nine to 17 years after infection.⁸ Cross-neutralization of SARS-CoV sera against SARS-CoV-2 was not found, however.

3.5 | Duration of immune response: MERS-CoV

Three studies were identified that investigated the immune response associated with MERS-CoV infection, with the longest follow-up 24 months. One study (n = 9) reported a rigorous antibody response in all survivors who had severe disease, but not in survivors of mild disease.⁶ Similar findings were reported in another study of 11 patients (five with severe disease and six with mild disease) who were followed up for 1 year.¹⁹ The third study included 21 patients (14 had samples taken at 6 months, seven at 24 months), and found that antibody responses were present at 24 months in all patients, including those with mild and subclinical illness.⁸⁹

FIGURE 3 Solid line gives mean estimate of SARS-CoV-specific IgG seropositivity rate and shaded area gives 95% CI at each time point (1 week, 1 month, 3 months, 4-6 months, 1 year, 2 years and 3 years post-infection) by random effects meta-analysis (N = 614 participants; studies included: Cao 2007, Chang 2005, He 2004, Huang 2005, Li 2003, Liu 2006, Mo 2006, Shi 2004, Tang 2011, Wu 2007a, Wu 2007b, Yang 2009)



3.6 | Immune response and severity of initial disease in SARS-CoV-2 infection

Seventeen studies with 2588 participants described the impact of the severity of initial infection with SARS-CoV-2 and the immune response.^{5,18,20,22,28,32,35,41,49,60,64,65,68,83,93,105,106} Studies investigated a range of associations, including the link between severity of initial infection and seroconversion timing, immunoglobulin titres, RNA re-detection rate and lymphocyte counts. As the virus has only recently been identified, none described how initial severity impacted the long-term duration of immunity. Overall, eight studies reported a significantly stronger antibody response (higher antibody titres) in severe compared with mild cases,^{28,32,49,60,65,83,93,105} while six reported no relationship or an inverse relationship.^{5,20,35,64,68,106} The association between lymphocyte counts (CD4 + and CD8 + subsets) and the severity of infection was investigated in two studies (N = 243 patients).^{35,57} In both, authors reported that CD4 + T cell and CD8 + T cell counts were significantly inversely associated with disease severity; the more serious the disease was, the lower were the T cell, CD4 + T cell and CD8 + T cell counts on admission. One study also measured the CD4 +/CD8 + ratio; all analyses indicated that the ratio was not significantly different between different conditions and outcomes.⁵⁷ The association between re-detection positive and severity of initial disease was investigated in two studies (N = 679 patients).^{7,41} Both studies found that mild or moderate cases were significantly more likely to re-present with detectable RNA by RT-PCR post-discharge compared with severe cases.

3.7 | Reinfection rate following SARS-CoV-2 infection

No agreed definition for what constitutes “reinfection” was identified, however 19 studies (N = 1312 patients) were retrieved that relate to re-detection of viral RNA following two consecutive negative RT-PCR samples.^{7,17,22,29,41,47,48,71,75,76,79,81,84,85,88,99,100,102,111} The sample sizes ranged from one¹⁰² to 414 patients.⁴¹ The age of included patients ranged from 12 months⁸⁴ to 92 years,⁷⁵ while the median age of patient cohorts

ranged from 37⁸¹ to 62 years.⁹⁴ All studies report hospitalized cases in whom SARS-CoV-2 RNA was re-detected following recovery, although there was no consistent definition of clinical recovery and all studies were referring to recovery by the failure to detect RNA by RT-PCR testing. The testing methodology, location of specimen, timing of testing (both recovery and re-detection times) and criteria for discharge from hospital all varied across studies. For studies conducted in China, patients were discharged in accordance with the Chinese Clinical Guidance for Covid-19 Pneumonia Diagnosis and Treatment which included two consecutive negative “RNA not detected” RT-PCR tests 24 hours apart.¹¹²

Eleven studies provided a rate of re-detection via RT-PCR of respiratory samples in a cohort of recovered patients (defined as at least two RNA not detected samples for SARS-CoV-2 collected at ≥ 24 -hour intervals).^{17,22,33,41,71,75,76,79,81,84} In these studies, the re-detection rate ranged from 3% (2/62 cases)⁷⁹ to 31% (4/13 cases),¹¹¹ with the largest cohort reporting a re-detection rate of 17% (95% CI: 13%-20%; n = 69/414 cases).⁴¹

Patients in whom SARS-CoV-2 RNA was re-detected were asymptomatic at the time of the positive re-detection test in all but two of the 19 studies.^{17,41} The first study reported that the majority of those in whom RNA was re-detected still had respiratory symptoms, including cough and increased sputum production on readmission.⁴¹ However, while symptomatic, only two of the 69 re-detected cases were febrile with typical clinical manifestations that satisfied the first admission criteria. The majority of cases had detectable RNA within 5-25 days after the first negative test. The second study reported that while most of the 11 re-detected patients were symptomatic on re-admission, compared with the first admission, hospital stay was shorter, clinical symptoms were milder, laboratory outcomes were improved, and radiological manifestations were ameliorated.¹⁷

3.8 | Infectiousness of SARS-CoV-2 re-detected cases

Four studies (N = 452 participants) investigated onward transmission from individuals in whom SARS-CoV-2 RNA was re-detected

following two previous RNA not detected RT-PCR results. None of the four included studies reported onward transmission to any close contacts of those who re-tested positive for SARS-CoV-2. However, there was very limited information on how contact tracing was conducted or how testing was performed. Only one of the four studies explicitly reported conducting contact tracing, but provided limited details.⁷ The other three studies simply stated that there were no reports of onward transmission, without providing any information on how this was established.^{22,48,71}

3.9 | Methodological quality

Figure 4 provides details of the quality appraisal of all included studies, across nine critical domains. The overall quality of evidence is low due to the inherent biases in included study designs. Overall, 21% of studies (n = 21/102) had not yet been peer-reviewed at the time of writing. However, we deemed the inclusion of pre-prints necessary in reviews of SARS-CoV-2 at these early stages of the pandemic due to the recent emergence of the virus.

4 | DISCUSSION

In this review, the evidence on the immune response following SARS-CoV-2 was synthesized. Due to the recent emergence of this virus, evidence on SARS-CoV and MERS-CoV was also retrieved to assess the long-term duration of immune responses to coronaviruses, which

may be of interest due to the genetic and epidemiological similarities with SARS-CoV-2.

For SARS-CoV-2 infection, while the rate and timing of IgM and IgG seroconversion were inconsistent across studies, most seroconverted for SARS-CoV-2-specific IgG antibodies within 2 weeks post-symptom onset. By 4 weeks, all patients in all studies had seroconverted for IgG, suggesting that the standard for assessment of antibodies should be at least 3-4 weeks post-infection based on the current evidence. Additionally, over 90% of individuals seroconverted for neutralizing antibodies after 4 weeks. These results are based on studies with small sample sizes. In studies that measured serial titres in patients from the time of diagnosis, IgM was often the first antibody to rise, followed by IgG; IgM titres then waned over time while IgG titres were sustained. Unlike the immune response to most other viruses, however, IgM and IgG seroconversion times were not significantly different. One hypothesis for this finding is that if memory cells to any of the seasonal coronaviruses exist, the IgG response may rise more quickly.

Studies on the duration of the immune response to SARS-CoV-2 were limited to 60-65 days follow-up post-symptom onset. While IgG and neutralizing antibody titres appear to be maintained in most patients over this time period, further studies will be needed to determine if these levels are maintained for longer periods of time. Unlike studies that looked at the immune response early in the course of disease, less variability was observed after 4 weeks, whereby IgG was detected in all samples at the end of the follow up period. However, these findings were based on studies with very small sample sizes (median = 9, range = 3-48 participants for studies with ≥ 4 weeks follow up).

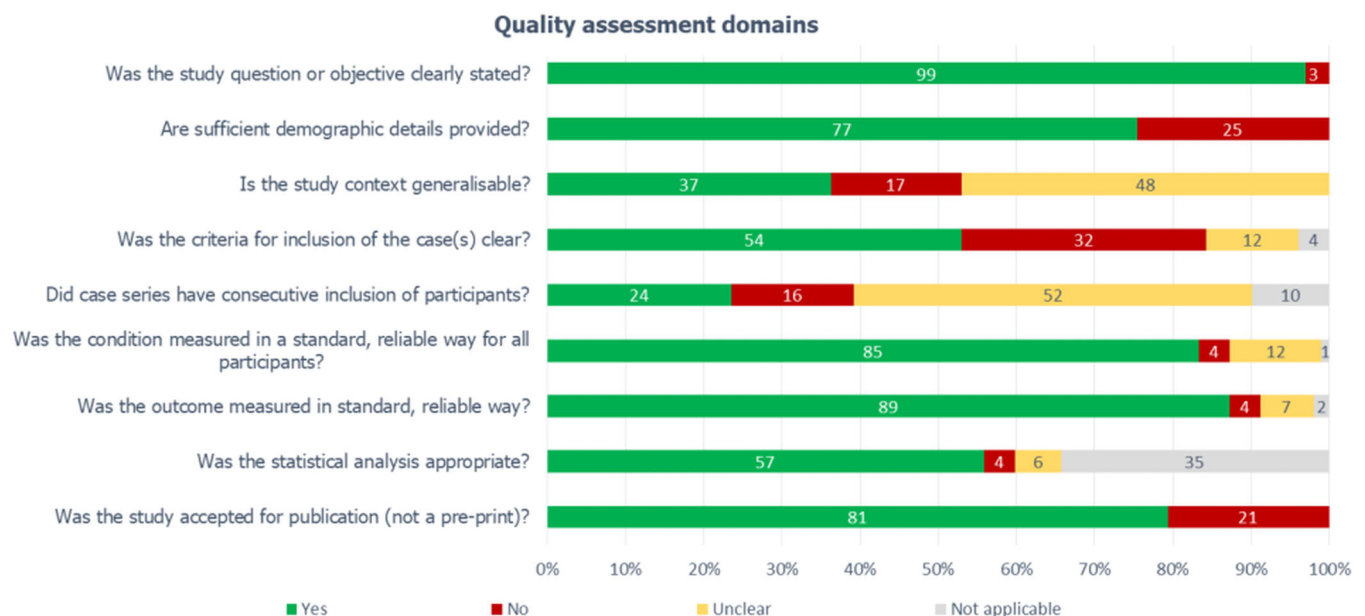


FIGURE 4 Quality assessment for all included studies presented (n = 102); numbers on bars indicate number of studies that were answered yes/no/unclear/not applicable for each domain. The same risk of bias tool was used across all designs due to the lack of clarity in some studies regarding the distinction between cohorts and case series. For the purposes of this assessment, all were considered as case reports/case series. The generalizability of studies was often unclear due to the testing platforms used that are not widely available and healthcare systems and practices that are country-specific

SARS-CoV and MERS-CoV share some similar clinical, genetic and epidemiological features with SARS-CoV-2,^{113,114} and the process of generating SARS-CoV-specific and MERS-CoV-specific antibodies may be similar to that of SARS-CoV-2-specific antibody production. Thus, the duration of detection of these antibodies may be of interest. In general, SARS-CoV-specific IgG antibodies were maintained for 1-2 years post-infection in included studies and declined thereafter. There was uncertainty regarding the duration of the immune response beyond 3 years, although one study detected SARS-CoV-specific IgG up to 12 years and another detected neutralizing antibodies up to 17 years post-infection. Differences in the positivity rate reported by studies may be attributable to IgG antibody levels falling below the limit of detection of the tests at follow-up, or cross reactivity with other common human respiratory pathogens. Moreover, in the absence of data on reinfection, the levels of IgG associated with effective SARS-CoV immunity are unknown.

Based on data from SARS-CoV, it is possible that a specific immune response can be maintained for at least 2 years post-infection in most patients. However, even if an immune response is maintained over this period, it is not known if it is sufficient to ensure full protection against reinfection by the same virus. It is possible that the antibody response would result in a less severe, or asymptomatic infection, which raises the possibility of an associated risk of transmission to others.

While we did not search a priori for studies that examined cross-protection between coronaviruses, two SARS-CoV studies reported no cross-protection against MERS-CoV or SARS-CoV-2 and one SARS-CoV-2 study reported some cross-protection against endemic (or seasonal) coronaviruses. In the first study, specific T cells in SARS-CoV survivors were not activated by MERS-CoV peptides, suggesting that T cell immunity is unlikely to provide cross-protection.⁵⁹ However, it must be noted that the sample size was small (N = 3). The second study tested cross-neutralization of SARS-CoV sera against SARS-CoV-2 by neutralizing antibodies, and failed to demonstrate a response (N = 12 recovered individuals).⁸ However, the strong cross-reactivity of N-directed antibodies proves the close relatedness of the two viruses, which should be taken into consideration when developing serological tests and vaccine candidates. The third study found cross-reactivity or cross-stimulation against four endemic (or seasonal) human coronaviruses in several SARS-CoV-2 patients, suggesting some degree of cross-protection.⁷³

Two studies that were published after our search date support the findings of cross-protection between seasonal human coronaviruses and SARS-CoV-2.^{115,116} The first study, published as a pre-print, demonstrated pre-existing humoral immunity (mostly IgG) to SARS-CoV-2 spike (S) glycoprotein in uninfected and unexposed individuals.¹¹⁵ In contrast, SARS-CoV-2 infection induced higher titres of SARS-CoV-2 S-reactive IgG antibodies as well as concomitant IgM and IgA antibodies. The second study investigated SARS-CoV-2-reactive CD4 + T cells in SARS-CoV-2-infected as well as unexposed individuals.¹¹⁶ Reactive CD4 + T cells were detected in 40%-60% of unexposed donors (serum samples provided between 2015 and 2018), suggesting cross-reactive T cell recognition between seasonal human coronaviruses and SARS-CoV-2.

An agreed definition for reinfection (as opposed to re-detection) with SARS-CoV-2 was not identified, possibly due to the limited number of

such events described in the literature. The evidence to date suggests the intermittent detection of residual RNA following recovery as opposed to reinfection. Of the 1312 re-detected cases identified in this review, only two cases (out of 69 in one study⁴¹) were febrile on readmission and fulfilled the initial admission criteria. Additionally, no evidence of onward transmission from re-detected cases was found in this review.

There are many explanations for these re-detected cases. None of the included studies sequenced and compared the genomes of the first and second infections, or attempted culture of viable virus in addition to RT-PCR testing. Therefore re-detection could reflect detection of non-viable viral material (which is being inconsistently shed) rather than viable virus.

It is also possible that the confirmation of virus clearance in the initial infection was based on a false negative test result, for a number of reasons. Firstly, there is a potential for pre-analytical errors including issues such as insufficient sampling, contamination of specimens, and inappropriate storage and transport conditions. Secondly, the analytical process can affect results with the use of different sample preparations, the presence of PCR inhibitors, or operator errors.¹¹⁷ Thirdly, the viral dynamics of SARS-CoV-2 across the time course of the infection are still not fully understood. Hence, false negative test results may occur if samples are tested during the late convalescent phase, when virus levels may be fluctuating.¹¹⁸ Molecular diagnostic tests (such as RT-PCR) detect viral RNA, but do not confirm presence of live virus. Intermittently positive test results may therefore reflect inconsistent shedding of non-viable virus, later in the course of an infection.

A final potential explanation of these re-detected cases is the possible reactivation of a latent virus in some individuals. While other coronaviruses are not known to result in latent infection, this hypothesis should be investigated.

These re-detected cases are unlikely to be clinically or epidemiologically important, due to the asymptomatic nature of most cases and the current lack of evidence that these re-detected cases are themselves infectious to others. Our results are supported by the recent findings from the Korea Centers for Disease Control and Prevention (KCDC) in South Korea, who conducted an epidemiological investigation that included contact tracing for 285 (63.8%) of the total 447 re-detected positive cases reported up to 15 May 2020, and found that no contacts became infected.¹¹⁹

4.1 | Quality of evidence

The overall quality of evidence was low due to the inherent bias associated with study designs. Concerns exist regarding the small sample size in many studies and the methodological quality of preprint studies that have not undergone a formal peer review process.

4.2 | Limitations of included studies

While studies consistently demonstrated anti-SARS-CoV-2 IgG and neutralizing antibody detection beyond 2 weeks, limitations of this

review included the variability in the accuracy of tests used across studies, the use of tests that have not yet been validated, poor reporting on the levels of detection employed, small sample sizes (both number of participants and number of samples taken), and limited duration of follow-up.

An international reference serum standard for SARS-CoV-2 antibody testing has recently been developed by the National Institute for Biological Standards and Control (NIBSC).¹²⁰ Reference standards are used to calibrate antibody testing systems against an international reference protocol.¹²¹ Without a reference standard, validation of tests is difficult and comparison of assays cannot be accurately performed. Studies in this review preceded the development of a reference standard and were not externally validated. Additionally, a wide variety of testing platforms were used, and test accuracy differs significantly depending on the type of test used. Earlier tests typically had lower sensitivity and specificity.^{122,123}

The levels of detection for SARS-CoV-2-specific antibodies were not uniform across studies, and frequently not reported. Differences in test accuracy, levels of detection, and the use of non-validated tests may partly explain differences observed in the early post-infection period, particularly for IgM and IgA. For IgG, however, studies in this review consistently identified most patients 2 weeks post-symptom onset, with 100% testing positive at the longest follow-up (8 weeks) in three studies. The same was true for neutralizing antibodies. Interim guidelines by the CDC has not identified an advantage of antibody tests whether they test for IgG, IgM and IgA, or total antibody.¹²⁴ Provided IgM or IgA are not the sole basis for detection of an immune response, and samples are taken a minimum of 3-4 weeks post-symptom onset, the testing platform used may not be of major concern.

This review was also limited by small sample size in a number of studies, although more recent studies typically included a larger number of participants with longer follow-up periods. Differences in the rate and timing of seroconversion, in particular, may become more consistent when studies that use validated tests on larger sample sizes are conducted. The evidence available to answer these research questions is evolving. While studies consistently found that all patients tested positive for IgG (and nearly all tested positive for neutralizing antibodies) beyond 4 weeks post-symptom onset, larger studies are necessary to validate these findings.

4.3 | Conclusion

While the role or duration of the antibody response following SARS-CoV-2 infection is unknown, all patients in reviewed studies maintained an IgG response at the longest follow-up (8 weeks post-infection). We hypothesize that this response may last much longer, as evidence from studies of SARS-CoV has shown that SARS-CoV-specific IgG is sustained for one to 2 years post-infection, with detection up to 12 years post-infection in one study. It is unclear if reinfection can occur following recovery from SARS-CoV-2, and the limited data to date are more suggestive of intermittent detection of

inconsistently shed residual viral RNA. Limited evidence suggests that these individuals are not infectious to others. In the coming months, as the pandemic progresses, more evidence will emerge on the duration of immunity, pre-existing immunity due to cross-protection from seasonal coronaviruses, potential for re-infection and recurrent infectivity.

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CONFLICT OF INTEREST

The authors have no competing interest.

AUTHOR CONTRIBUTIONS

Eamon O Murchu: Investigation, Formal analysis, Writing - Original Draft. **Paula Byrne:** Investigation, Writing - Original Draft. **Kieran A. Walsh:** Investigation, Writing - Original Draft. **Paul G. Carty:** Investigation, Formal analysis. **Máire Connolly:** Writing- Reviewing and Editing. **Cillian De Gascun:** Writing- Reviewing and Editing. **Karen Jordan:** Investigation, Writing - Original Draft. **Mary Keogh:** Writing- Reviewing and Editing. **Kirsty K O'Brien:** Investigation, Writing - Original Draft. **Michelle O'Neill:** Supervision, Writing- Reviewing and Editing. **Susan M. Smith:** Writing- Reviewing and Editing. **Conor Teljeur:** Formal analysis. **Máirín Ryan:** Supervision, Writing- Reviewing and Editing. **Patricia Harrington:** Supervision, Writing- Reviewing and Editing. All authors attest they meet the ICMJE criteria for authorship.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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