Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses

6 August 2020

Version history

Version	Date	Specific updates
V1.0	13 May 2020	
V2.0	9 June 2020	Updated search with 35 new studies
V3.0	6 August 2020	Updated search with 28 new studies

Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses

Key points

- This evidence summary reviewed the immune response following infection with SARS-CoV-2 or other human coronaviruses.
- The original (13 May 2020) and updated (9 June 2020) evidence summaries of the immune response following coronavirus infections retrieved studies that focussed on six separate research questions (rate and timing of antibody detection after infection, the duration of the immune response, the re-detection rate in recovered patients, the infectiousness of re-detected patients, and the association between the immune response and the severity of initial disease).
- Due to the recent emergence of the virus and the rapidly evolving evidence base, research questions relating to the duration of immunity and the reinfection rate following SARS-CoV-2 infection were further updated. Twenty-nine additional studies were identified, resulting in a total of 131 studies.
- Thirty-four studies were identified that examined the duration of antibody responses (IgG and or neutralising antibodies) ≥28 days post-symptom onset. Maximum follow-up was 94 days (mean=49, SD=15.7).
- Of the studies that reported IgG seropositivity at the end of follow up, most studies (n=23/26) reported 100% IgG seropositivity. In the three studies reporting less than 100% seropositivity, the first reported 95-98% IgG detection, the second reported that 2-8.5% of participants never seroconverted at ≥2 weeks (but of those that did, all had detectable IgG) and the third reported 2/65 did not seroconvert (although samples from these patients were taken within eight days post-symptom onset). Maximum duration of IgG detection was 94 days.
- Across seven (out of eight) studies that reported individual patient-level neutralising antibody data, 261 out of 289 patients were seropositive at the end of follow-up (≥90% seropositivity rate).
- Twenty-six studies were retrieved that reported re-detection of SARS-CoV-2 following recovery. An agreed definition for reinfection (as opposed to re-detection) was not identified.

- Nearly all patients who were re-detected positive did not show new clinical symptoms or disease progression. However, two case series and one case study reported new-onset or worsening symptoms among re-detected cases. An additional case study reported new IgM seroconversion in an asymptomatic re-detected case, suggestive of re-infection. These four studies suggest that reinfection may be possible.

- Most re-detection cases are likely due to technical issues including intermittent false negatives from the inconsistent viral shedding in the later course of the disease, or the detection of dead viral remnants by RT-PCR when no viable virus is present. Re-detection of non-viable virus is supported by one study that attempted, unsuccessfully, to perform live virus isolation and whole genome sequencing on re-detected cases.

- No study was found that directly addressed whether individuals re-detected with SARS-CoV-2 or other human coronaviruses are infectious to others. Five case series were identified that examined onward transmission in individuals who retested positive for SARS-CoV-2 despite having two previous negative respiratory RT-PCR tests. None of the studies reported onward transmission to any of the close contacts of those who re-tested positive for SARS-CoV-2, though only one study explicitly conducted contact tracing or follow-up.

- The overall quality of evidence was low due to the inherent limitations associated with the study designs, and 45 out of 131 studies have not yet been peer reviewed.

- In conclusion, the adequacy or long-term duration of the immune response is not yet known. SARS-CoV-2-specific IgG was detected in nearly all individuals at the end of follow-up (up to 94 days) and over 90% developed a neutralising antibody response. Many studies have reported the re-detection of SARS-CoV-2 following recovery. While most patients were asymptomatic on re-detection, cases of new symptom onset and serology suggestive of reinfection have been reported, suggesting reinfection may be possible.

Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses

Introduction

The Health Information and Quality Authority (HIQA) has developed a series of 'Evidence Summaries' to assist the Clinical Expert Advisory Group (EAG) in supporting the National Public Health Emergency Team (NPHET) in their response to COVID-19. These summaries are based on specific research questions. This evidence summary was developed to address the following research question:

> **What is the rate of reinfection/duration of immunity in individuals who recover from a laboratory-confirmed coronavirus infection?**

The objective of this review was to summarise the evidence on the immune response following acute coronavirus infections, including SARS-CoV-2.

The following research questions were addressed:

1. What proportion of confirmed cases develop specific antibodies to SARS-CoV-2 (seroconversion rate)?
2. How quickly does one develop specific antibodies to SARS-CoV-2 (seroconversion timing)?
3. What is the duration of detection of serum antibodies and antibody titres over time associated with infection with SARS-CoV-2 or other coronaviruses?
4. What is the reinfection rate following recovery from acute SARS-CoV-2 infection?
5. Are individuals reinfected with SARS-CoV-2 or other human coronaviruses infectious?
6. Does the seroconversion rate and or timing, and duration of immunity, depend on the severity of the initial infection?

The processes as outlined in HIQA's protocol (available on www.hiqa.ie) were followed. Relevant databases of published literature and pre-print servers were searched. The original search was carried out from 1 January 2000 until 1 May 2020 (n=67 studies), and updated on 26 May 2020 (n=35 new studies). The search was further updated on 6 July 2020 limited to new studies (n=29 new studies) that relate to the duration of SARS-CoV-2 antibody responses (research question 3) and reinfection (research questions 4 and 5).

Results

Across all updates, 131 studies were identified that met our inclusion criteria. These included 111 case series,[1-111] 10 case reports,[112-121] five cohort studies[122-126] and five cross-sectional studies.[127-131]

Eighty-five studies were conducted in China, eight in France, six in Italy, five in the US, four in Germany, three each in South Korea, Taiwan and the UK, two each in Hong Kong, Saudi Arabia, and Singapore, and one each in Belgium, Finland, Japan, the Netherlands, the Philippines, Reunion Island, Spain and Switzerland. SARS-CoV-2 was investigated in 103 studies, SARS-CoV in 25 and MERS-CoV in three.

Below is a summary of the updated evidence relating to research questions 3, 4 and 5 (search current to 6 July 2020). Appendices 1.1 to 1.3 present the evidence previously retrieved relating to questions 1, 2 and 6 (search current to 26 May 2020), respectively.

Research question 3: Duration of immune response following SARS-CoV-2 infection

Thirty-four studies were identified that examined the duration of antibody responses (IgG and or neutralising antibodies) in SARS-CoV-2 infection for ≥28 days (Table 2).[1, 18, 19, 23-27, 29, 31, 32, 42, 49, 52, 61, 63-65, 67, 70, 73, 76, 79, 82, 83, 86, 94, 101, 102, 111, 128, 130-132] Maximum follow-up was 94 days in one study[111] and mean maximum follow-up was 49 days across all studies (standard deviation=15.7). Thirteen studies were conducted in China, four in the US, three in France and the UK, two in Italy, and one each in Belgium, Germany, Hong Kong, Israel, Italy, Japan, the Netherlands, Reunion Island and Spain. All studies were case series or cross-sectional studies, and over half were published as pre-prints at the time of search (18/34). A wide variety of testing platforms were used, including both laboratory and rapid point-of-care tests, and a number of studies did not provide details of the serological test used (Table 2 provides details of serological tests used in included studies).

Twenty six of the 34 studies reported IgG seropositivity rate at the end of follow-up. Twenty three of these studies reported 100% IgG seropositivity, while three studies reported IgG seropositivity rates of 91% or more. The first study reported close to 100% sensitivity for IgG detection at 43 days post-diagnosis (anti-S1-IgG: 96%, anti-S-IgG: 98%, and anti-S-RBD-IgG: 95%).[128] The second study followed individuals for almost 60 days[79] and reported that 8.5% (15/177) did not seroconvert over the entire follow-up period. However, only four of the 15 non-seroconverters were followed beyond 20 days, suggesting that 2.3%-8.5% of patients may not develop IgG antibody responses ≥20 days post-infection. Of seroconverters, all had IgG detected at end of follow-up. The third study reported

that 2 out of 65 individuals (3.1%) did not generate detectable IgG.[111] However, samples were only available up until 2 and 8-days post-symptom onset for these two individuals. The mean time to seroconversion against at least one antigen was 12.6 days post-symptom onset for the rest of the study cohort, so it is possible that these two individuals would have seroconverted if tested at a later timepoint.

Nine studies reported detection rates for neutralising antibodies ≥28 days.[25, 27, 64, 69, 73, 76, 86, 111, 128] Across all studies that reported individual level data (n=7), 261 out of 289 patients were seropositive at the end of follow-up (90.3% seropositivity rate).

One study measured the potency of antibody responses over time in sequential samples from 65 individuals up to 94 days post-symptom onset.[111] All individuals sampled after eight days post-symptom onset developed an IgG and neutralising antibody response. The IgG optical density (as measured at 1:50 dilution) remained high in the majority of individuals, even up to 94 days. Potency of neutralisation was measured by using HIV-1 based virus particles, pseudotyped with SARS-CoV-2 S in a HeLa cell line stably expressing the ACE2 receptor. This technique found that neutralising antibodies waned with time; comparison of the ID_{50} (infectious dose 50; serum dilution that inhibits 50% infection) at peak neutralisation and ID_{50} at the final time point collected showed a decrease in almost all cases. For serum samples collected after 65 days post-symptom onset, the percentage of donors with potent neutralising antibodies (ID_{50}>2000) had reduced to 16.7%. Additionally, some seropositive individuals who were asymptomatic were able to generate neutralising antibody titres ID_{50}>1000. The magnitude of the response was associated with disease severity, although waning occurred in both severe and non-severe patients.

Table 1: Summary of studies of SARS-CoV-2-specific IgG and neutralising antibodies ≥28 days (or maximal follow-up)

Immunoglobulin G (IgG)	
Adams 2020[1]	50-60+ days post-symptom onset: N=9/9 seropositive; including N=2/2 positive at ≥60 days.*
De Vriese 2020[18]	29-35 days post-symptom onset: 100% seropositive (N=7 patients on haemodialysis, number sampled at end of follow-up N/R)
Dellière 2020[19]	≥28 days post-symptom onset: N=19/19 seropositive (by either Abbott or Orient gene test)
Dobi 2020[24]	28-64 days post-symptom onset: N=4/4 seropositive
Dobano 2020[23]	Higher sensitivities were obtained when specificities were set to 99%, reaching 100% for samples ≥28 days since symptom onset. Number tested at end of follow-up N/R
Dong 2020[25]	25–33 days post-admission to hospital: N=6/6 seropositive
Du 2020[26]	49-56 days post-symptom onset: N=10/10 seropositive, but titres declining
Fu 2020[29]	53-55 days post-symptom onset: N=5/5 seropositive
Fujigaki 2020[31]	35 days post-symptom onset: N=1/1 seropositive in 3/3 platforms
Gallais 2020[32]	47-69 days post-symptom onset: N=9/9 seropositive by Abbott and Euroimmun ELISA; N=7/9 seropositive by Biosynex lateral flow assay
Hu 2020[42]	46-51 days post-symptom onset: N=11/11 seropositive
Jin 2020a[48]	Serum IgG persisted at a high level up to 56 days (total sample N=89 patients, number tested at end of follow-up N/R)
Jin 2020b[49]	31-55 days post-symptom onset: N=8/8 seropositive
Klein 2020[128]	Sensitivity for IgG at 43 days post-diagnosis (IQR 38-48 days): S1-IgG: 96%, S-IgG: 98%, and S-RBD-IgG: 95%. Raw counts N/R
Kreer 2020[52]	69 days post-diagnosis: N=1/1 seropositive
Liu 2020d[61]	N=5/32 patients followed for 28 days post-diagnosis; N=5/5 seropositive
Liu 2020e[63]	Day 61-65 post-symptom: Mild: 2/2 seropositive for total antibodies (IgA/IgG/IgM) Severe: 14/14 seropositive for total antibodies (IgA/IgG/IgM) (at 61-65 days, it is presumed IgG is the prevailing antibody detected)
Ma 2020[65]	31-41 days post-symptom onset: N=23/23 seropositive
Munitz 2020[67]	IgG anti RBD and IgG anti NP detectable up to 50 days after symptom onset; seroconversion rate in individuals sampled ≥28 days not reported
Robbiani 2020[76]	N=91/91 cases had IgG detected at 28-63 days post-symptom onset
Padoan 2020b[70]	At 26-30 days post-fever onset: Mean and standard error AU/mL values>60 (above cut off) (number sampled at end of follow-up N/R)
Perera 2020[73]	29-42 days post-symptom onset: N=12/12 seropositive
Seow 2020[111]	100% (63/63) seropositive after 8 days post-symptom onset, including 1 patient at 94 days post-symptom onset

Staines 2020[79]	In seroconverters, antibodies did not decline up to 60 days post-diagnosis (number sampled at end of follow-up N/R)
Vogelzang 2020[82]	60 days post-symptom onset: Substantial amounts of anti-RBD detected (number sampled at end of follow-up N/R)
Yang 2020a[94]	≥32 days post-symptom onset: N=1 seropositive
Yang 2020b[130]	Of N=55 patients: N=1 at 76 days post-discharge seropositive N=8 at 60-75 days post-discharge seropositive N=10 at 50-60 days post-discharge seropositive N=55 ≥28 days post-discharge seropositive
Yongchen 2020[131]	44-50 days post-symptom onset: N=5/5 seropositive
Zeng 2020[101]	39 days post-symptom onset: N=17/17 seropositive
Zhang 2020[102]	40-50 days post-symptom onset: N=8/8 seropositive
Neutralising antibodies (NAbs)	
Dong 2020[25]	25-33 days post-admission to hospital: N=11/12 seropositive
Fafi-Kremer 2020[27]	28-41 days post-symptom onset: N=47/48 seropositive
Klein 2020[128]	43 days post-diagnosis (IQR 38-48 days): N=101/126 seropositive
Lu 2020[64]	Median of 35 days post- symptom onset: N=58/59 samples seropositive
Okba 2020[69]	20-30 days post-symptom onset: N=3/3 seropositive
Perera 2020[73]	29-42 days post-symptom onset: N=12/12 seropositive
Robbiani 2020[76]	Most convalescent plasmas obtained from individuals did not contain high levels of neutralising activity Rare but recurring RBD-specific antibodies with potent antiviral activity were found in all individuals tested
Seow 2020[111]	100% (63/63) seropositive after 8 days post-symptom onset, although significant reduction in neutralising antibody potency over time
Wang 2020e[86]	41-53 days post-symptom onset: N=29/29 seropositive

Note – duration denotes longest follow-up in included studies. Duration of immune response inconsistently reported as either duration from symptom onset, post-PCR diagnosis, post-admission or post-discharge.
*Data derived from graph (Figure 1 in Adams 2020)
N/R – not reported

Research question 4: Reinfection rate

No agreed definition for what constitutes 'reinfection' was identified in the literature; however, 26 studies were retrieved that relate to re-detection of viral RNA following a negative RT-PCR sample.[3, 13, 14, 21, 30, 44, 51, 53, 57, 64, 84, 85, 89, 90, 93, 96, 99, 100, 104, 108, 112, 113, 116, 117, 119, 127]

All studies report cases of re-detected SARS-CoV-2 following recovery, however the testing methodology, location of specimen, timing of testing (both recovery and re-detection times) and criteria for discharge from hospital varied across studies (Table 3). In addition to respiratory RT-PCR tests, five studies reported re-detected positive anal or faecal samples.[21, 64, 84, 104, 127] For studies conducted in China, patients were discharged in accordance with the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment: (1) normal temperature for three days or more, (2) significant improvement in respiratory symptoms, (3) chest radiology findings show substantial improvement of acute exudative lesions, (4) two consecutive negative nucleic acid tests using respiratory tract samples (taken at least 24 hours apart).[133] The largest sample size across studies was 619 patients.[64] The age of included patients ranged from 12 months[99] to 92 years,[89] while the median age of patient cohorts ranged from 37[96] to 62 years.[124] Ten studies have as yet only been published as pre-prints.

In terms of estimating the rate of re-detected positive specimens, individual case studies and case series that only enrolled re-detected positive cases do not provide meaningful data. Of the studies that followed a cohort of recovered patients (defined as at least two upper respiratory tract samples negative for SARS-CoV-2 collected at ≥ 24-hour intervals), 12 studies provided a rate of re-detection via RT-PCR of respiratory samples.[13, 14, 21, 44, 64, 84, 89, 90, 93, 96, 99, 134] In these studies, the re-detection rate ranged from 3% (2/62 cases)[13] to 30.7% (4/13 cases).[57] The largest cohort reported a re-detection rate of 14% (N=87/619 cases).[64]

Only one study reported results of live virus isolation and whole genome sequencing of re-detected cases.[64] Live virus isolation was attempted on 36 RT-PCR re-detected positive samples including 14 nasopharyngeal swabs, three throat swabs and 19 anal swabs by inoculation into Vero-E6 cell lines. No live viruses could be cultured. Virus whole genome sequencing was then attempted; no full-length SARS-CoV-2 genome could be obtained by sequencing 94 samples from 54 patients (the sequencing coverage ranged from 0.00–75.48%).

Across studies, almost all re-detected positive patients were asymptomatic at the time of the positive re-detection test. All re-detected positive anal or faecal samples were in asymptomatic patients.[21, 64, 84, 104, 127]However, two case series[44, 85] and two case studies[112, 113] reported results inconsistent with this trend.

The first case series reported that those who were re-detected positive had respiratory symptoms, including cough and increased sputum production on readmission.[44] However, while symptomatic, only two of the 69 re-detected cases were febrile with typical clinical manifestations that satisfied the first admission criteria. The second case series found that one re-detected positive patient (out of 17) presented with recurrent symptoms and exudative CT lesions (however, lesions were less severe than on initial admission). [142]

The first case study involved a 78-year-old woman who initially presented with typical symptoms and ground glass lung opacities along with a positive RT-PCR test.[113] Symptoms resolved and SARS-CoV-2 RNA on day 23 was negative. The patient subsequently became febrile and lymphopenic on day 26 and RT-PCR became positive (with positive IgG serology). The second case study involved a 69-year-old woman who presented with typical symptoms and positive RT-PCR.[112] After resolution of symptoms and two negative RT-PCR tests, the patient was discharged. Patient was subsequently admitted for UTI 23 days later; four nasopharyngeal swab RNA tests for SARS-CoV-2 were negative at this time. Serological analysis revealed the presence of SARS-CoV-2-specific IgG, but not IgM. During recovery, the patient was accidentally in prolonged close contact with an undiagnosed patient with SARS-CoV-2. Subsequent analysis revealed positive RT-PCR and IgM seroconversion, although patient remained asymptomatic.

Research question 5: Are individuals reinfected with SARS-CoV-2 infectious?

No study was identified that directly addressed this research question. However, five studies were identified that partially addressed this research question as they examined onward transmission in individuals who retested positive for SARS-CoV-2, after having two previous negative RT-PCR tests.[3, 21, 53, 84, 85] These tests presumably used upper respiratory tract samples to determine whether patients satisfied discharge criteria; however, the sample site is not clearly reported. All five studies were case series studies conducted in China, examining the re-detection of SARS-CoV-2 in patients recovering from COVID-19. Four of these studies were pre-prints and are not yet peer-reviewed.[3, 21, 84, 85] No study was found that examined whether patients reinfected (or re-detected) with another human coronavirus were infectious. Full study details are provided in Table 4.

All five studies had small sample sizes, ranging from four re-detected cases[21, 53] to 38.[3] Two of the included studies sampled from larger populations of patients who were discharged from hospital after recovering from COVID-19.[3, 84] In all studies, patients were discharged in accordance with the Chinese clinical guidance

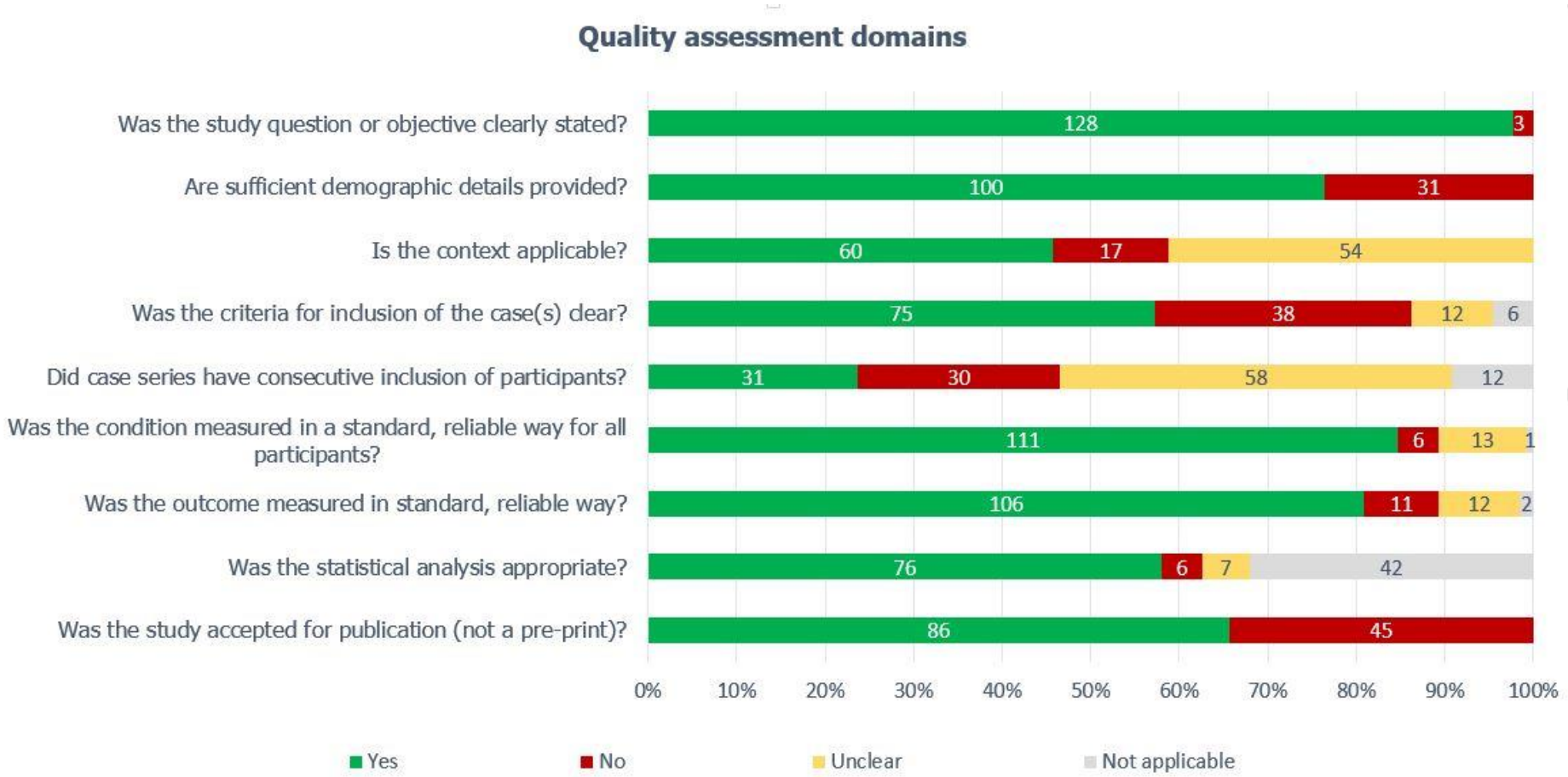
including improvement in symptoms and consecutive negative PCR tests taken 24 hours apart.[133]

None of the five 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, what testing was undertaken and how long the contacts were followed up for. Only one of the five studies explicitly reported conducting contact tracing, but provided limited details.[3] The other four studies simply stated that there were no reports of onward transmission, without providing any information on how this was established.[21, 53, 84, 85] As the convalescent patients were undergoing quarantine or self-isolation at home or in a hotel during the post-discharge period, it is not clear whether their contacts would have been in close enough contact to be infected. One study stated that they followed all 21 close contacts (of the 38 re-detected patients) until 10 March 2020, which was a median of 40-46 days since symptom onset.[3] However, no information is provided in this study regarding the timing and degree of exposure between the index case and their contacts.

Methodological quality

Figure 1 provides details of the quality appraisal of all (131) included studies, across nine critical domains. The overall quality of evidence was low due to the inherent biases in included study designs. In general, study questions were clearly stated (n=128/131) and the reporting of the condition (n=111/131) and outcomes (n=106/131) were conducted in a standard, reliable way. Sufficient demographic details were provided in 100 of the 131 studies. Of concern was the applicability of some studies to the Irish context, mostly due to the range of testing platforms used that may not be available for use in Ireland (n=17 were not applicable, and it was 'unclear' in n=54 studies). Forty-five studies included in this review were published as pre-prints, so have not yet been formally peer-reviewed raising additional concerns about overall quality and the potential for results to change prior to formal publication.

Figure 1 Quality assessment domains



Notes:
Data presented for all included studies (n=130); numbers on bars indicate number of studies that were deemed yes/no/unclear/not applicable for each question.
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.

Discussion

In this update, the evidence on the duration of antibody responses beyond 28 days and the reinfection rate following SARS-CoV-2 infection was summarised. In earlier versions of this review we also summarised the rate and timing of antibody detection, the duration of immune responses following SARS-CoV and MERS-CoV, and the association between these immune responses and the severity of initial infection (archived in appendices 1.1-1.3).

The overall quality of evidence is low based on pre-defined quality appraisal criteria and the nature of the study designs. The applicability of the majority of studies to the Irish context is uncertain. Concerns also exist regarding the methodological quality of pre-print studies that have not undergone a formal peer review process (45 of the 131 included studies were pre-prints). The evidence available to answer these research questions is evolving. Large-scale studies of population-based antibody responses with appropriate sample sizes and extended follow-up periods, that investigate the correlation with immunity and protection against reinfection, are not available yet.

Due to the recent emergence of SARS-CoV-2, the longest follow-up data on the immune response currently available is 94 days. While studies consistently demonstrated anti-SARS-CoV-2 IgG and neutralising antibody detection in most patients beyond 28 days, limitations of this review included potential 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, and limited duration of follow-up.

As of yet, there is no reference antibody standard for SARS-CoV-2. Reference standards are used to calibrate antibody testing systems against an international reference protocol.[135] Three reference standards are recommended for the ELISA: a strong positive standard, a weak positive standard and a negative serum standard. Without a reference standard, validation of tests is difficult. Earlier studies frequently employed tests that 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.[136] In May 2020; however, two IgG tests have been validated by Public Health England (Roche Diagnostics and Abbott Laboratories).[137] Evaluations concluded that each had a specificity of 100%; sensitivity, for samples taken at least 14 days since the onset of symptoms, stood at 93.9% for the Abbott test and 87.0% for the Roche test. The University of Washington has also validated the Abbott SARS-CoV-2 IgG test, finding 99.9% specificity on 1,020 patient samples and 100% sensitivity on 689

serum samples (from 125 people) when testing 17 days after symptom onset.[138] Performance data on commercially available in vitro diagnostic tests for SARS-CoV-2, that include independent validation of tests, are increasing in availability.[139]

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. For IgG, however, studies in this review consistently identified nearly all patients after two weeks post-symptom onset. Interim guidelines by the CDC have not identified an advantage of antibody tests whether they test for IgG, IgM and IgG, or total antibody.[140] Provided IgM or IgA are not the sole basis for detection of the immune response, and samples are taken a minimum of two-to-three weeks post-symptom onset, the testing platform used may not be a major issue.

While this review was limited by small sample sizes in a number of studies, it is notable that more recent studies typically included a larger number of participants with longer follow-up periods. The finding that IgG and neutralising antibodies were consistently detected beyond two weeks post-infection must be validated by larger studies.

It is not yet possible to conclude that reinfection can occur following recovery from SARS-CoV-2. Twenty-six studies were identified that reported on re-detection of SARS-CoV-2 following recovery. However, typically only a short time (< 14 days) elapsed between confirmatory negative tests and subsequent re-detection positive. Re-detected positive patients were asymptomatic in most studies. However, four studies reported unusual results; two case series and one case study reported re-detected cases that exhibited new signs and symptoms upon re-detection, and another case study reported new IgM seroconversion coinciding with RT-PCR re-detection.

Re-detected cases who are asymptomatic are unlikely to be clinically or epidemiologically important, unless evidence emerges that these re-detected cases are themselves infectious to others. Re-detection cases could reflect detection of non-viable viral material (which is being inconsistently shed) rather than viable virus. Only one study attempted live virus isolation with whole genome sequencing on re-detected positive samples; no live viruses were cultured and no full-length SARS-CoV-2 genome was attained.

It is possible that the confirmation of virus clearance in the initial infection was based on a false negative test result. There may be a number of explanations for this. 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 effect results with the use of different sample preparations, the presence of PCR inhibitors and operator errors.[141] 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.[142] 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

No evidence was found to determine whether patients who are re-detected as positive with SARS-CoV-2 or any other coronavirus are infectious. Although none of the five studies identified reported any evidence of onward transmission, discharged patients were aware of their prior infection and were undergoing quarantine or self-isolation, hence the potential for onward transmission via close contacts was limited. Viral dynamics are as yet uncertain for SARS-CoV-2, but in any case it is not possible to comment on the level of infectiousness as none of the studies reported the viral load, and this is a significant limitation of the included studies. These results are supported by the findings from the Korea Centers for Disease Control and Prevention (KCDC) in South Korea. They 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.[143] Of these, 59.6% were tested as a screening measure, and 37.5% were tested because of symptom onset. Of the 284 cases for which symptoms were investigated, 126 (44.7%) were symptomatic. From the 285 re-detected positive cases, a total of 790 contacts were identified (351=family; 439=others). From the monitoring of contacts, as of 19 May 2020, no case has been found that was newly confirmed from exposure during the re-detection positive period alone.

Conclusion

In conclusion, while the adequacy or long-term duration of the immune response is not yet known, SARS-CoV-2-specific IgG antibodies aredetected in nearly all individuals at the end of follow-up (up to 94 days), and over 90% of patients develop a neutralising antibody response. Many studies have reported the re-detection of SARS-CoV-2 in clinical samples following recovery from COVID-19. While most patients had no symptoms when the virus was re-detected, cases with new symptom onset and laboratory findings suggestive of potential re-infection (for example, new IgM seroconversion detectable in blood samples) have been reported. This suggests that re-infection with SARS-CoV-2 may be possible.

Tables of study characteristics and primary outcomes

Table 2: Duration of immune response following SARS-CoV-2 infection

Author DOI Country Study design	Virus type Test parameters	Population Patient demographics Clinical characteristics	Primary outcome results	Comments
Adams 2020[1] 10.1101/2020.04.15.20066407 UK Case series	SARS-CoV-2 ELISA and RT-PCR (used as reference test) Compared to 9 commercially available lateral flow immunoassay (LFIA) devices Plasma samples. RT-PCR from upper respiratory tract (nose/throat) swab Acute samples were collected from patients a median 10 (range 4-27) days from symptom onset (n=16), and from recovering healthcare workers median 13 [range 8-19] days after first symptoms; (n=6). Convalescent samples were collected from	N=40 adult positive for SARS-CoV-2 by RT-PCR. N=142 controls For SARS-CoV-2 patient: Age mean 60 (range 22-95) Severity: Mild 26(65%), Severe 4(10%), critical 9(22.5%), 1 asymptomatic (2.5%) N=18 convalescent cases (>28 days from symptom onset). N=16 case (≤ 28 days from symptom onset). N=6 convalescent health care worker (≤ 28 days from symptom onset)	**Duration of detection of serum immunoglobulin levels:** 40 SARS-CoV-2 samples and 50 controls tested by ELISA. 34/40 positive for IgG, other 6 where taken within 9 days of symptom onset. All samples taken >= 10 days after symptom onset positive for IgG. IgM positive in 28/40 samples (70%). No patient was IgM positive and IgG negative. N=9 patients had samples from between 50 and 60 days after onset of symptoms. In these 9 patients IgM (5 out of 9) and IgG (9 out of 9) still present. N=2 patients had samples ≥60 days, both were still positive. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Considering the relationship between IgM and IgG titres and time since symptom onset, univariate regression models showed IgG antibody titres rising over the first 3 weeks from symptom onset. The lower bound of the pointwise 95%CI for the mean expected titre crosses OD threshold between days 6-7. However, given sampling variation, test performance is likely to be optimal from several days later. IgG titres fell during the second month after symptom onset but remained above the OD threshold (at 60 days from symptom onset). No temporal association was observed between IgM titres and time since symptom onset. **Other outcome:** There was no evidence that SARS-2-CoV severity, need for hospital admission or patient age were	Not peer reviewed; medRxiv

	adults a median 48 [range 31-62] days after symptom onset and/or date of positive throat swab (n=18)		associated with IgG or IgM titres in multivariable models	
De Vriese 2020[18] Belgium Case series 10.1053/j.ajkd.2020.05.009	Nasopharyngeal swab RT-PCR ELISA for IgG (NovaLisa, NovaTec; validated in-house; approved by the Federal Agency for Drugs and Health Products)	N=282 patients on haemodialysis, of which N=7 PCR confirmed Samples taken from 6/7 patients (1 patient died before follow-up samples taken) until 29-35 days post-symptom onset	• IgG seroconversion rate was 100% • All patients sampled at 29-35 days positive (number tested not reported) • N=3/7 patients died; 1 on day 6, 1 on day 11 and 1 on day 36	Letter to the editor
Delliere 2020[19] France Case series 10.1128/JCM.01233-20	RT-PCR: Cobas® SARS-CoV-2 Test Two assays: Orient Gene Biotech (lateral flow assay) ASIA on Architect Abbott Instrument i2000SR	N=102 Mean age: 52 years (±16 years); 57.8% male N=19 followed for 28 days or longer	At 28 days or longer, 19/19 positive for IgG by either Abbott or Orient gene	Peer-reviewed
Dobano 2020[23] Spain Case series 10.1101/2020.06.11.147363	SARS-CoV-2 Diagnosis: RT-PCR Three quantitative suspension array technology (qSAT) assays to detect IgM, IgA and IgG to a panel	N=115 plasmas from individuals with a confirmed past/current diagnosis of COVID-19. Time since onset of symptoms ranged from 0 to 46 days.	Higher sensitivities were obtained when specificities were set to 98% or 99%, reaching 100% for samples ≥21 or ≥28 days since the onset of symptoms	Not peer-reviewed

	of eight SARS-CoV-2 antigens including spike (S), nucleoprotein (N) and membrane (M) protein constructs	Additional demographic details N/R		
Dobi 2020[24] Reunion Island (part of France) Prospective cohort 10.1101/2020.05.25.20112623	SARS-CoV-2 Immunofluorescence, Immunoblot, Western blot and ELISA Tested over a 2 month period (10 to 64 days)	N=20 hospitalised patients	**Rate and timing of seroconversion:** IgM and IgG detected 5-7 days post symptom onset. Mild non-ICU patients had a steady yet robust rise in specific IgG, whereas, over the full dilution set of the plasma (1/200 to 1/12800), severe (ICU) patients demonstrated a significant decrease (over 2.5-fold) of IgG. **Duration of immunity:** N=4/4 were IgG positive at end of follow up; 28-64 days post-symptom onset **Other:** IgG and IgM were initially against the nucleocapsid (50kDa band on the WB) and spreading to other major viral proteins Note: It is unclear how many patients are 'severe', though they say the reduction in IgG in severe patients is 'exemplified' by Patient 1 with results shown from 2 severe and 2 mild patients in Figure (B)	Not peer-reviewed
Dong 2020[25] 10.1101/2020.03.17.20036640 China Case series	SARS-CoV-2 RT-PCR and CT to confirm infected. ELISA for IgG/IgM (not commercial) Neutralising antibody assay Interferon gamma ELISpot FACS staining	N=12 SARS-COV-2 patients recently virus free and discharged from hospital. 6 were recently discharged and 6 had been discharged for 2 weeks(follow-up patients) n=4 controls 2 patients showed lymphopenia. Seven	**Duration of detection of serum immunoglobulin levels:** SARS-CoV-2 patients mounted IgG and IgM responses to SARS-CoV-2 proteins, especially NP and S-RBD, and also suggest that infected patients could maintain their IgG levels, at least for 2 weeks **Duration of detection of neutralising antibodies:** 4 of the recently discharged patients had high neutralising antibody titres. All bar 1 of the follow-up patients had lower lowers of neutralising antibody titres than the recently discharged patients, although all except 1 was positive (11/12). **B-cell/T cell responses:** Compared to discharged patients, there was a trend towards an increased frequency of NK cells in the follow-up patients. However, there was no significant difference in terms of the percentages of	Not peer reviewed; medRxiv

		patients were female. Age mean 41 years (range 26 to 68)	T cells among those 2 groups (discharged and follow-up) and the healthy donors. Compared to healthy donors, the number of IFN-gamma secreting NP specific t-cells in 4 of the recently discharged patients suggests that they had developed a SARS-CoV-2 specific T cell response. Only one of the follow-up patients (with lymphopenia) had a high number of IFN-gamma secreting T cells in response to NP, main protease and S-RBD, suggesting anti-viral T cells may not be maintained at high numbers in the PBMCs in the recovered patients. This suggests they may enter a quiescent state.	
Du 2020[26] 10.1002/jmv.25820 China Case series	SARS-CoV-2 Unclear which test performed, but IgG and IgM measured using a kit of some sort Doesn't specifically state if RT PCR used to confirm cases	N=60 convalescent patients (onset time of 6-7 weeks). N=10 patients tested at two time points (6-7 weeks after onset of symptoms and 7-8 weeks after symptom onset)	**Duration of detection of serum immunoglobulin levels:** All patients tested positive for the IgG against the virus, 13 patients tested negative for IgM, with the IgG titre being greater than the IgM titre. The IgM and IgG titres in 10 convalescent patients were tested twice (1 week apart); both titres showed a decrease, with the IgG titre being greater than the IgM titre. (drop also greater) **Other outcomes:** Antibody detection could act as an indicator of the stage of SARS-COV-2 progression and that the antibodies in convalescent patients are not always maintained at a high level.	Published in journal of medical virology as a letter to the editor
Fu 2020[29] 10.1101/2020.04.03.20051763 China Retrospective case series	SARS-CoV-2 Immunogold ICT device (INNOVITA Biotechnology Co. Ltd. Tangshan, China) 41 patients tested month after admission; 14 tested a second time (timing not stated)	50 severe patients; 27 male, 23 female; median age 64 years (IQR, 37-87); more than half had underlying disorders (hypertension 20%; diabetes 24%, CHD 22%;COPD 6%) 41 of 50 patients divided into 'good' n=12 (29.3%) or 'poor' n=29 (70.7%)	**Duration of immunity:** Day 53-55: 100% (N=5/5) positive for IgG Longest duration of IgM was 55 days from onset of illness, indicating that severe patients with poor recovery were more likely to have prolonged acute phase of the illness **Other:** Prolonged IgM positive was associated with poor recovery; 91.66% (11/12) patients with good recovery have positive IgG but negative IgM after hospitalisation for 1 month; 51.7% (15/29) patients with poor recovery had positive tests for both IgM and IgG	Not peer-reviewed

		recovery according to their clinical outcome and those with lung lesions were divided into 'partial resolution patient group' and 'significant resolution patient group' 14 patients were tested a 2nd time and 1 (7.1%) was in good recovery group and 13 (92.8%) were in poor recovery group Severity defined according to Chinese management guideline for SARS-CoV-2 (version 5.0)	Odds of impaired lung lesion resolutions were higher in patients with elevated IL-4 (as well as hyperproteinemia, hyperlipidemia and ferritin)	
Fujigaki 2020[31] Japan Case series 10.1101/2020.06.28.20140475	Three immunochromatography test kits: 2019-nCoV IgG/IgM Rapid Test Cassette (Hangzhou AllTest Biotech Co., Ltd., China), COVID-19 IgM/IgG Duo (SD BIOSENSOR, Korea), and 2019-nCoV IgG/IgM Detection Kit (Vazyme Biotech Co., Ltd., China).	N=29 PCR confirmed patients N=99 serum samples Mean age, 52.9 years ± 21.9 years; 14 males and 15 females	The IgG antibody-positive rates for samples (n=42) taken after 13 days of onset were 100%, 97.6%, and 97.6% for each test. One patient had samples at 35 days: positive for IgG in all 3 tests.	Not peer-reviewed

Gallais 2020[32] France Case series 10.1101/2020.06.21.20132449	SARS-CoV-2 At least 1 index case in each household had positive reverse-transcriptase polymerase chain reaction (RT-PCR) and /or serological evidence (contacts did not have RT-PCR testing) Three serological tests: 1. The Abbott Architect SARS-CoV-2 IgG chemiluminescent microparticle immunoassay for detection of IgG against the SARS-CoV-2 nucleoprotein 2. The Euroimmun Anti-SARS-CoV-2 Assay, an ELISA for the detection of IgG against the SARS-CoV-2 S1 domain of the spike protein including the immunologically relevant receptor binding domain (RBD) 3. Biosynex, a lateral flow assay for	N=7 households, comprising N=9 index patients and N=8 close contacts N=10 healthy controls The median age of index patients was 45 years (range, 34-65 years) and 4 were male Blood samples were collected from 47 to 69 days post symptom onset	**IgG** N=9/9 positive for IgG 47-69 days after symptom onset by Abbott and Euroimmun ELISA N=7/9 positive by Biosynex lateral flow assay Authors' Conclusions: Anti-SARS-CoV-2 antibodies and a significant T cell response detectable up to 69 days after symptom onset Contacts: N=6/8 contacts reported COVID-19 symptoms within 1 to 7 days after the index patients but all were SARS-CoV-2 seronegative. N=6/8 had SARS-CoV-2-specific T cell response, however	Not peer reviewed

	detection of IgM and IgG against the SARS-CoV-2 RBD of the Spike protein S (Abbott Architect assay: sensitivity 100% and specificity 100%; Euroimmun assay: sensitivity 100% and specificity 97.7%; Biosynx assay: sensitivity 95.6% and specificity 99.4%)			
Jin 2020b[49] China Case series DOI: 10.1016/j.ijid.2020.03.065	SARS-CoV-2 IgM and IgG chemiluminescence immunoassay (CLIA) kits (commercially available) SARS-CoV-2 confirmed by RT-PCR Serum taken before and after conversion to virus negative. Duration from first symptoms to hospital admission, to laboratory confirmation, and to first serological test in the SARS-COV-2 group patients was 3 days (IQR 2–7 days), 3 days (IQR 2–7 days)	N=43 SARS-COV-2 patients. N=33 controls (control group suspected of having COVID 19, but did not) Median age of the SARS-COV-2 patients was 47.0 years (IQR 34.0–59.0 years), ranging from 7 years to 74 years, and 39.5% were male. All cases were non-severe cases. Chronic disease: hypertension (10, 23.3%), diabetes (3, 7.0%), and liver disease (2, 4.7%). Fever was present in 62.8% of SARS-COV-2	**Duration of detection of serum immunoglobulin levels:** SARS-COV-2 group: 27 patients tested for viral antibody before becoming virus-negative. Median duration from first symptoms to serological testing in these 27 patients was 16 days (IQR 9–20 days). 13 were IgM-positive (48%) and 24 were IgG-positive (89%). 3 IgG-negative patients were also IgM-negative (these patients were test 0, 5 and 8 days from symptom onset). Days from laboratory confirmation to serological test: IgM-positive rate increased slightly at first (day 1-20) and then decreased as the number of days from laboratory confirmation to serological detection increased (up to 32 days); in contrast, the IgG-positive rate increased to 100% (by day 16-20) and was higher than IgM at all times. It remained at 100% by day 26-32. Meanwhile, the virus-positive rate tended to decrease over time As the duration from symptom onset to serological testing increased. It was found that both IgM and IgG levels were not high during the first 5 days following symptom onset. IgG positive rate reached 100% by day 11-15, and remained there by 31-55 days. IgM positive rate increased until days 16-20 and started to decrease around 26-30 days after symptom onset. By 31-55 days	Peer-reviewed; I Journal of infectious diseases

	and 18 days (IQR 11–23 days), respectively	patients before or on admission. The second most common symptom was cough (60.5%). Similarly, fever and cough were also the most common symptoms in the control group	after symptom onset less than half of the patients were IgM positive. The IgM-positive rate showed a trend to increase at first and then decline; however, the IgG-positive rate increased and then became stable over time. Furthermore, the IgG-positive rate was consistently higher than the IgM-positive rate. **Other outcomes:** According to molecular detection as the gold standard, the sensitivities of serum IgM and IgG antibodies to diagnose SARS-COV-2 were 48% (13/27) and 89% (24/27), respectively, and the specificities were 100% (33/33) and 91% (30/33).	
Jin 2020a[48] China Case series 10.1016/j.cmi.2020.05.022	SARS-CoV-2 Throat and/or nasal swabs collected upon admission and during hospitalisation were analysed by SARS-CoV-2 real-time RT-PCR Specific antibodies IgM and IgG to SARS-CoV-2 were analysed by chemiluminescent immunoassay	N=89 hospitalised patients N=43 in non-prolonged shedding group, n=46 in prolonged shedding group (Time to end of viral RNA shedding considered as the time period between symptom onset and the date of first negative RT-PCR test result. Over 30 days were categorized as prolonged viral RNA shedding.) All patients: median age 62 years (IQR 52–68); 44.9% male Non-prolonged conversion: 58 years	At week 8, serum IgM in both groups (prolonged: 19.4 ± 8.0 AU/mL and non-prolonged: 13.2 ± 4.0 AU/mL) declined almost to the reference level (10 AU/mL). Serum IgG persisted at a high level up to 8 weeks in both groups (prolonged: 130.6 ± 25.0 and non-prolonged: 115.6 ± 23.0). In the prolonged shedding group, serum IgG was slightly higher than that in the other group through week 4 to week 8. However, the difference between the 2 groups was not significant ($p > 0.05$)	Letter to the editor

		(IQR 44–68); 41.9% male Prolonged conversion: 67 years (IQR 63–70); 47.8% male		
Klein 2020[128] USA Cross-sectional study 10.1101/2020.06.26.20139063	SARS-CoV-2 1. Virus neutralization assay using Vero-E6-TMPRSS2 cells 2. Commercial IgG and IgA ELISA to Spike (S) protein S1 domain (Euroimmun) 3. IgA, IgG and IgM indirect ELISAs to the full-length S or S-receptor binding domain (S-RBD) 4. IgG avidity assay	N=126 convalescent plasma donors Median age = 42 years (IQR 29-53); 54% male Median days since PCR test=43 (IQR 38-48)	Sensitivity for IgG at 43 days post-diagnosis (IQR 38-48): S1-IgG: 96%, S-IgG: 98%, and S-RBD-IgG: 95%. NAbs positive in 101/126 (80%)	Not peer-reviewed
Kreer 2020[52] Germany Case series 10.1101/2020.06.12.146290.	SARS-CoV-2 ELISA for IgG Multiple antibody and cell responses tested using a variety of platforms	N=12 patients Mean age: 48.8 years (range: 28-59 years) 50% male, including N=5 patients for longitudinal analysis Mean age: 46.4 years (range: 28-58 years) 60% male	**IgG** For longitudinal analysis, n=5 patients sampled at 3 time points between 8–69 days post-diagnosis SARS-CoV-2 neutralization values of plasma IgG ranged from 78.8 to 1500 µg/ml, respectively At 69 days one person still positive for IgG	Not peer-reviewed

Liu 2020d[61] China Case series 10.1080/22221751.2020.1773324	SARS-CoV-2 RT-PCR for diagnosis along with clinical criteria for classification of severe COVID-19 Anti-SARS-CoV-2 IgG and IgM kits: manufactured by Chongqing Xinsaiya Biotechnology Company from Chongqing, China	N=32 patients (56.3% severe cases, 43.7% mild cases) N=217 samples Median age = 55 years 66.7% were male	N= 5/32 patients followed for 28 days (N=3 severe cases) N=5/5 IgG positive at 28 days Titres: • Anti-SARS-CoV-2 S-specific IgG antibodies were identifiable from day 7 onwards, peaking at approximately day 25 • Serum IgG antibodies were still maintained at a high level after 4 weeks of infection IgG antibody levels were not significantly correlated with clinical severity in the early stage of infection. However, the difference in IgG antibody levels between mild cases and severe cases from day 15 onward was found to be statistically significant. 21.4% of mild cases did not generate adequate IgG antibodies.	Peer-reviewed
Liu 2020e[63] China Case series 10.1093/clinchem/hvaa137	SARS-CoV-2 spike protein receptor binding domain (RBD)-specific IgM or total antibodies (IgA/IgG/IgM) using 2 commercial microparticle chemiluminescence immunoassays	N=192 PCR confirmed patients N=1,019 serum samples Of 192 patients, 83 (43%) classified as severe cases Demographic details not given	Total antibodies IgA/IgG/IgM seropositivity over time (from symptom onset) in mild and severe cases: **Day 31-36** Mild: 12/18 Severe: 103/103 **Day 37-42** Mild: 19/24 Severe: 79/80 **Day 43-48** Mild: 36/42 Severe: 86/86 **Day 49-54** Mild: 20/23 Severe: 54/54 **Day 55-60** Mild: 7/7 Severe: 39/39 **Day 61-65** Mild: 2/2 Severe: 14/14	Letter to editor

			After 25-30 days, all sampled severe patients (115/115) seropositive. At end of follow-up (61-65 days), both mild (2/2) and severe (14/14) all positive.	
Ma 2020[65] China Case series 10.1038/s41423-020-0474-z	SARS-CoV-2 RT-qPCR assay on throat swab samples for initial diagnosis Antibody testing: Chemical luminescence kits were made for detecting the presence of RBD-specific IgA, IgM, and IgG against highly purified receptor-binding domain (RBD) DTA: RBD-specific IgA, IgM, and IgG kits showed diagnostic sensitivities of 98.6%, 96.8%, and 96.8%, and specificities of 98.1%, 92.3%, and 99.8%, respectively	N=87 patients (37 with underlying illnesses) Age: Mean 47.5 years Median 48 years (range 21-91 years) N=216 serum samples	**IgA** N=23/23 positive for IgA 31-41 days after symptom onset **IgM** N=20/23 positive for IgM 31-41 days after symptom onset **IgG** N=23/23 positive for IgG 31-41 days after symptom onset (all RBD specific antibodies) **Severity:** Serum IgM and IgG levels in moderate and severe COVID-19 patients were significantly higher than mild cases, while no significant difference was observed between severe and moderate patients **IgG titre over time**: The median RLU of RBD-specific IgG was the lowest in early disease stages but raised at 15 days post illness onset, the IgG reached its peak during 21–25 days after illness onset, and stayed at a relatively high reading until 31–41 days	Published Correspondence Cellular & Molecular Immunology
Munitz 2020[67] Israel Case series	Authors developed an electrochemiluminescent assay for detecting IgM, IgA, and IgG antibodies	N=57 18 females and 39 males	IgG anti RBD and IgG anti NP detectable up to 50 days after symptom onset Seroconversion rate in individuals sampled ≥28 days not reported	Not peer-reviewed

10.1101/2020.06.28.20141838				
Okba 2020[69] 10.3201/eid2607.200841 Samples collected from France, the Netherlands, Germany Case series	SARS-CoV-2 Samples confirmed with RT-PCR as SARS-CoV-2 A plaque reduction neutralisation test (PRNT) was used as a reference for this study ELISA (developed in house and 2 commercially available ones) Serum samples taken between day 6 and 27 in mild and severe cases, days not specified but noted samples were taken 'at different time points' over this period	N=10 samples from 3 SARS-COV-2 cases from France (2 mild cases and 1 severe). N=31 serum samples from SARS-COV-2 cases from Berlin). N=31 controls from Berlin (controls were infected with other coronaviruses) Control samples from individuals infected with other coronaviruses (HCoV-229E, NL63 or OC43, SARS-CoV, MERS-CoV or other respiratory viruses)	**Duration of detection of neutralising antibodies:** With PRNT and all 3 ELISA kits the more severe case had higher response than the 2 mild cases. Based on PRNT results, the severe sample was positive 5-10 days after symptom onset. The titre peaked around 10-15 days after onset and declined gradually up to 30 days after symptom onset when the experiment ended. In the mild cases the titres increased more gradually and were positive at 10-15 days after symptom onset and still increasing at the end of the experiment (20-25 days after onset) **Other:** The aim of this study was to test in house ELISA kits. Antibody levels were higher following severe infection compared to the mild ones	Peer-reviewed; Emerging Infectious Diseases
Padoan 2020b[70] Italy Case series 10.1515/cclm-2020-0443	SARS-CoV-2 Validation study of MAGLUMI™ 2000 Plus 2019-nCov IgM and IgG assays 2019-nCoV IgM cut-off is 1.0 AU/mL, while the 2019-nCoV IgG cut-off is 1.1 AU/mL	N=37 PCR-confirmed hospitalised patients N=87 serum samples No other demographic details	The kinetics of COVID-19 antibodies confirmed previously reported findings. At 26-30 days post fever onset, mean & standard error AU/mL values for IgG >60 (above cut off) IgM mean & SE also above cut off at 26-30 days.	Peer-reviewed

Perera 2020[73] Hong Kong Case series 10.2807/1560-7917.ES.2020.25.16.2000421	SARS-CoV-2 IgG ELISA and IgM ELISA, and as confirmatory tests, micro-neutralisation (MN) and plaque reduction neutralisation tests ($PRNT_{90}$) Sera and plasma collected from patients within 4 weeks of illness onset. Serum and plasma were separated. Sera and plasma were available from controls and only sera available from SARS (2003) samples.	51 sera from 24 patients. 17 of these patients had 2 to 4 sequential serum samples available for study. Disease severity categorised as mild (5/24) (28-63 years), moderate (12/24) (25-80 years), severe (3/24) (60-72 years) and critical (4/24) (56-64 years); Sera from blood donors in 2017 used as controls, stratified by age 16-19;20-29;30-39;40-49;50-59;60-69 with 33-34 sera in each age group; 12 convalescent sera included as specificity controls. 7 convalescent sera from SARS in 2003 also included as controls.	**Rate and timing of seroconversion:** • Sera collected ≤ 4 days post-onset, 0 were positive by any assay • Sera collected 5-9 days post-onset: ○ 3/6 positive for IgG and IgM in ELISA ○ 0/6 positive by MN ○ 4/6 (including all 3 positive in ELISA) positive by PRNT • Sera collected 11-18 days post-onset: ○ 13/14 positive for IgM ○ 10/14 positive for IgG ○ 9/14 positive for MN ○ 13/14 positive for PRNT • Sera collected 19-28 days post-onset: ○ 9/11 positive for both IgM and IgG ○ 7/11 positive for MN ○ 11/11 positive for PRNT • Sera collected 29-42 days post-onset, 12/12 positive in all four assays. ○ 12/12 positive for IgM and IgG ○ 12/12 positive for MN and PRNT (Neutralising Antibodies) Correlation of antibody responses with disease severity assessed in serum samples after day 14 post-onset. PRNT and ELISA IgM were not correlated with disease severity but severe/critical cases had higher and statistically significant serum ELISA IgG than mild/moderate cases. **Duration of immunity:** Sequential serum samples available for 17 patients. Most developed detectable MN and PRNT antibody responses, provided they had sera collected beyond 28 days after illness. Note: 'While positive RBD ELISA result, even if specific, provides evidence of prior infection of SARS-CoV-2, it is no assurance of protective immunity, whereas the presence of neutralising	Peer-reviewed

			antibodies would provide greater assurance of protection. However, more research is needed on the correlates of protection in all these serological assays.' No detectable cross-reactivity noted	
Robbiani 2020[76] USA Case series 10.1038/s41586-020-2456-9	Plasma samples were tested for binding to the SARS-CoV-2 RBD and trimeric spike (S) proteins by a validated ELISA using anti-IgG or –IgM secondary antibodies for detection	N=157 N=111 (70.7%) were individuals diagnosed with SARS-CoV-2 infection by RT-PCR (cases), and N=46 (29.3%) were close contacts of individuals diagnosed with SARS-CoV-2 infection (contacts) Samples collected an average of 39 days after symptom onset	N=91/91 cases had IgG detected at 28-63 days post-symptom onset • Plasmas collected an average of 39 days after symptom onset had variable half-maximal pseudovirus neutralising titres: less than 1:50 in 33% and below 1:1,000 in 79%, while only 1% showed titres above 1:5,000 • Most convalescent plasmas obtained from individuals did not contain high levels of neutralising activity • Rare but recurring RBD-specific antibodies with potent antiviral activity were found in all individuals tested	Peer-reviewed
Seow 2020[111] 10.1101/2020.07.09.20148429 UK Case series	SARS-CoV-2 RT-qPCR confirmed ELISA for IgG, IgM and IgA response against spike (S), the receptor binding domain (RBD) and nucleocapsid (N) Neutralising antibodies: SARS-CoV-2 neutralisation potency using HIV-1 based virus particles, pseudotyped with SARS-CoV-2 S in a HeLa cell line stably	N=65 N=59 admitted patients and 6 staff Average age 55.2 years (range 23-95 years) 77.2% male A severity score was assigned to patients (ranged from asymptomatic to ECMO), score ranged from 0 to 5	**IgM, IgA and IgG: seroconversion** • N=2/65 individuals (3.1%) did not generate a detectable antibody response against any of the antigens; however samples only available up until 2- and 8-days post-symptom onset for these two individuals and the mean time to seroconversion against at least 1 antigen was 12.6 days post-symptom onset • IgG responses against S, RBD and N antigens were observed in 92.3%, 89.2% and 93.8% of individuals respectively • The frequency of individuals generating an IgM response • was similar to IgG, with 92.3%, 92.3% and 95.4% seropositive against S, RBD and N respectively • The frequency of individuals with an IgA response to RBD and N was lower, with only 72.3% and 84.6% seropositive respectively	Not peer reviewed; medRxiv

	expressing the ACE2 receptor		**IgM, IgA and IgG: longitudinal analysis** • Longitudinal analysis across sequential samples (number followed N/R) highlighted the rapid decline in the IgM and IgA response to all 3 antigens following the peak OD between 20- and 30-days post-symptom onset • In individuals sampled at time points >60 days post-symptom onset, the IgM and IgA responses were approaching baseline • The IgG OD (as measured at 1:50 dilution) remained high in the majority of individuals, even up to 94 days **Neutralising antibodies: titres and seroconversion** • The average time to detectable neutralization was 14.3 days post-symptom onset (range 3-59 days) • Increased neutralization potency was observed with increasing days post-symptom onset with each individual reaching a peak neutralization titre (ranging from 98 to 32,000) after an average of 23.1 days (range 1-66 days) • Only two individuals (3.1%) did not develop a response (ID50 <50) which was consistent with their lack of binding antibodies at the time points tested (<8 days post-symptom onset). • At peak neutralization, 7.7% had low (50-200), 10.8% medium (201-500), 18.5% high (501-2000) and 60.0% potent (2001+) neutralizing titres • For serum samples collected after 65 days, the percentage of donors with potent neutralising antibodies (ID50>2000) had reduced to 16.7% **Neutralising antibodies: longevity of response** • Following peak neutralisation, a waning in ID50 was detected in individuals sampled at >40 days • Comparison of the ID50 at peak neutralization and ID50 at the final time point collected showed a decrease in almost all cases • For some individuals with severity score 0, where the peak in neutralisation was in the ID50 range 100-300, neutralisation titres became undetectable (ID50 <50)	

			Severity & neutralising kinetics • ID50 values between individuals with 0-3 disease severity was compared with those in the 4/5 group • Magnitude of the neutralising antibody response at peak neutralization was significantly higher in the severity 4/5 group • Time taken to measure detectable titres and the time of peak neutralization did not differ between the two groups • This suggests disease severity enhances the magnitude of the antibody response but does not alter the kinetics	
Staines 2020[79] UK Case series 10.1101/2020.06.07.20124636	SARS-CoV-2 RT-PCR for diagnosis (nose/throat swab) ELISA for IgG (Omega Diagnostics, Cambridge UK) Authors report 'comparable' performance to other validated assays	N=177 patients (94% hospitalised) N=645 samples Median age = 64 years (IQR 52-77); 57% male	**IgG** 8.5% (15/177) did not seroconvert over the entire follow-up period. 4 of 15 who did not seroconvert were followed beyond 20 days, suggesting that 2-8.5% of patients may not develop detectable IgG antibody responses to SARS-CoV-2 for weeks following infection. In seroconverters, antibodies did not decline up to 60 days post-diagnosis Seroconverters were older (median age 65.5 vs 41 years, p<0.01), were more likely to have 1 or more comorbidities (p<0.01) and had higher BMI (25.7 vs 21.2, p=0.034)	Not peer-reviewed
Vogelzang 2020[82] Netherlands Case series 10.1101/2020.06.17.20133793	SARS-CoV-2 RT-PCR assay for confirmed cases Authors developed total antibody bridging assays for detection of SARS-CoV-2 antibodies to the 38 receptor-binding domain (RBD) and nucleocapsid protein (NP)	N=284: Study included PCR-confirmed hospitalised COVID-19 patients (n=41), PCR-confirmed hospitalised and non-hospitalised convalescent plasmapheresis donors (n=182), PCR-confirmed non-hospitalised	Authors state that, at least up to 60 days after symptom onset, substantial amounts of IgG to the RBD could be detected	Not peer-reviewed

	Conventional isotype assays also performed	healthcare workers (n=47), and a group of longitudinally sampled non-hospitalised symptomatic individuals highly suspect of COVID-19 (n=14) not PCR-confirmed		
Wang 2020a[120] China Case report DOI: 10.21203/rs.3.rs-23009/v1	SARS-CoV-2 RT-PCR to confirm SARS-CoV-2. Throat and nasopharyngeal swabs	N=1 SARS-COV-2 patient. Age 37 years old. Patient had fever, dry cough, fatigue, dizziness, runny nose and diarrhoea. Chest CT scan showed multiple nodules and mixed ground-glass opacification with consolidation in both lungs Laboratory findings showed that his lymphocyte and CD4+ counts were below the normal range	**Duration of detection of serum immunoglobulin levels:** In total the patient was monitored for 50 days from illness onset. New coronavirus-specific IgG antibody levels significantly increased by more than 3 times above those at illness onset, accompanied by decreased IgM levels. IgM and IgG measured 5 days after symptom onset were low (around 5 S/CO), IgM decreased to 0 by 12 days after illness onset, while IgG was still increasing by 31 days after illness onset (over 30 S/CO). **Other outcomes:** Treatment: antiviral treatment, including arbidol, lopinavir, IFN-α, and traditional Chinese medicine CD4+ T cell increased from around 260 c/μl to more than 400 c/μl from 5 days post-symptom onset to 31 days after symptom onset.	Not peer reviewed
Wang 2020b[86] 10.1101/2020.04.15.20065623	SARS-CoV-2 Neutralising antibody determined using cytopathogenic assay.	N=70 SARS-COV-2 inpatients (n=12) and convalescent patients (n=58). Patients for longitudinal changes in n= 8 convalescent	**Duration of detection of neutralising antibodies:** Seropositivity reached 100% within 20 days since illness onset and remained 100% until day 41-53. Based on 117 samples taken from 70 patients	Not peer reviewed; medRxiv

China Case series	Neutralising antibody test of 1st sample since onset in this study, the median time was 33.0 days (range 10.0-53.0). The time of convalescent patients (35.0 days) were longer than inpatients (13.5 days).	patients (4 mild, 4 moderate in severity) The mean age of the patients was 45 years (range 16-84). 59% were female. The number of patients having history of cardiovascular disease, diabetes, and hypertension was 2 (2.8%), 5 (7.1%) and 9 (12.9%), respectively. 1 (1.4%) patient was asymptomatic infected, 22 (31.4%) had mild clinical manifestations, 43 (61.5%) were moderate, and the remaining 4 (5.7%) were in severe condition	**Serum titres of neutralising antibodies over time:** The antibody level was highest during day 31-40 since onset, and then decreased slightly by day 41-53. The total GMT was 1:163.7 (95% CI, 128.5 to 208.6), of which 52.1% (61/117) had a titre between 1:64 and 1:512. The GMT of day 31-40 since onset (1: 271.2, 95% CI, 175.8 to 418.5) reached the highest, and decreased slightly after that time period (1:201.7, 96% CI, 144.1-282.2). Univariate GEE analysis showed that the antibody level during day 31-40 was significantly higher than other phases. **Other outcomes:** In multivariate GEE analysis, patients at age of 31-60 and 61-84 had a higher antibody level than those at age of 16-30 (β=1.0518, P=0.0152; β=1.3718, P=0.0020). Patients with a worse clinical classification had a higher antibody titre (β=0.4639, P=0.0227).	
Wang 2020e[85] China Case series 10.21203/rs.3.rs-38036/v1	SARS-CoV-2 RT-PCR Discharge criteria: [National Health Commission of China]: (1) normal temperature that lasts longer than 3 days, (2) significant improvement in respiratory symptoms, (3) substantially	N= 287 discharged patients, of which N=33 (11.5%) with recurrent PCR positivity Of the redetected, 21 (63.7%) female Mean age: 48.7 years (±19.7 years); range: 16-94 years	N=33 (11.5%) re-detected positive 22/33 (66.7%) asymptomatic Symptoms: cough, fatigue, sore throat, fever and expectoration. CT thorax: N=8 (24.2%) patients characterised by deterioration compared with prior admission (4 patients presented with stable lesions, 9 patients presented with improved lesions, and 12 patients presented with disappearance of original lesions) Median duration of positivity: 9.0 days (IQR: 6.0-15.0). IgG antibody titre (r=0.016, p=0.016) risk factor for prolonged positivity.	Not peer-reviewed

	improved acute exudative lesions on chest computed tomography (CT) images, and (4) the respiratory nucleic acid was negative for two consecutive times (with at least a 24-hour sampling time interval)		No new COVID-19 detected among close contacts of re-detected patients during the study period.	
Wölfel 2020[87] Munich, Germany Case series DOI: 10.1038/s41586-020-2196-x.	SARS-CoV-2 Seroconversion was detected by IgG and IgM immunofluorescence using cells expressing the spike protein of SARS-CoV-2 and a virus neutralisation assay using SARS-CoV-2 Testing for virus by RT-PCR	N=9 hospitalised patients	**Duration of detection of neutralising antibodies:** • Seroconversion in 50% of patients occurred by day 7, and in all by day 14, but was not followed by a rapid decline in viral load. • No viruses were isolated after day 7 • All patients showed detectable neutralising antibodies, the titres of which did not suggest close correlation with clinical courses **Other outcomes:** • Of note, case #4, with the lowest virus neutralisation titre at end of week 2, seemed to shed virus from stool over prolonged time • Results on differential recombinant immunofluorescence assay indicated cross-reactivity or cross-stimulation against the four endemic human coronaviruses in several patients	Peer-reviewed; Nature
Yang 2020a[94] USA Case series 10.1016/j.cca.2020.06.004	IgM/IgG: testing by cyclic enhanced fluorescence assay (CEFA)	Of N=42 RT-PCR positive patients, 28 inpatients had serial samples N=1 sample tested >32 days after symptom onset	Pylon CEFA: IgG positive in 1 patient (ventilated), tested >32 days post-symptom onset	Peer-reviewed

Yang 2020b[130] China Cross-sectional 10.1101/2020.07.01.20144030	Assay for IgM/IgG not described	N=72 clinically recovered patients, of which N=55 patients included with serology samples ≥28 days post-discharge Mean age: 48.8 years (range: 27-70 years) 62% female	IgG seropositive in 55 patients; (13 patients seronegative for IgG and IgM, 3 patients re-detected positive and 1 patient with a serious chronic condition all excluded from study). Of the 55 patients: N=1 at 76 days post-discharge (61-year old female) N=8 at 60-75 days post discharge N=10 at 50-59 days post discharge N=55≥28 days post discharge	Not peer-reviewed
Zeng 2020[101] China Case series 10.1016/j.jinf.2020.03.052	SARS-CoV-2 ELISA (Zhuhai Livzon Diagnostics INC.)	N=27 hospitalised cases (N=17 severe cases), N=36 controls Samples taken day 3 to 39 Serum SARS-CoV-2 specific IgG levels were tested within day 3 to 39 after the onset of COVID-19 every 3 days (ELISA) Median age =62 years (IQR, 46–67 years; range, 29–87 years) N=14 men	N=27/27 produced SARS-CoV-2 specific IgG between day 12 and 39 (samples tested every 3 days) Only severe cases (N=17) followed beyond 33 days Titre: SARS-CoV-2 specific IgG increased from day 9 to 39 after the onset of illness	Peer reviewed

Table 3: Reinfection rate

Author DOI Country Study design	Virus type Test parameters	Population Patient demographics Clinical characteristics	Primary outcome results	Comments
Reinfection rate				
An 2020[3] https://DOI.org/10.1101/2020.03.26.20044222. China Retrospective Case series	SARS-CoV-2 The discharge criteria of the recovered patients included: temperature returned to normal for >3 days, respiratory symptoms significantly improved, and significant absorption of pulmonary lesions of chest CT imaging, and at least 2 consecutive negative RNA test results at least 24 hours apart. RT-PCR was performed using a China Food and Drug Administration (CFDA) approved commercial kit specific for 2019-nCoV detection (GeneoDX Co., Ltd., Shanghai, China) or Sherlock kit gifted from Feng Zhang lab. The redetectable positive (RP) patients were confirmed by digestive (anal swab) and respiratory positive RT-PCR	N=262 confirmed SARS-COV-2 patients discharged from Shenzhen Third People's Hospital. Among them, mild, moderate and severe patients accounted for 11.4% (n=30), 81.0% (n=212) and 7.6% (n=20), respectively.	**Redetectable Positive (RP)/Reinfection rate** Up to March 10, 14.5% of convalescent patients (n=38) were re-detected to be SARS-CoV-2 respiratory RNA positive during their followed-up period. • The vast majority of RP patients (97.4%, n=37) were younger than 60 years of age. Among them, patients younger than 14 years old were more common compared with those between the ages of 14 and 60 years (35.0% vs 16.0%, p<0.01) • In addition, 36.7% (11/38) of RP patients were characterised by mild symptoms. The percentage was significantly higher than what was seen among non-RP patients (12.7%, 19/204, p<0.01). • There was no significant difference in the gender distribution • There were no RP cases in severe patients • RP patients showed no obvious clinical symptoms and disease progression upon re-admission	Not peer reviewed (pre-print)

	tests. All patients followed for minimum of 14 days.			
Bentivegna 2020[112] Italy Case study 10.1002/jmv.26160	Nasopharyngeal swab RT-PCR for diagnosis Chemiluminescence immunoassay assay for antibody detection	69-year-old woman Past medical history • Type 2 Diabetes • Urinary neoplasm	**Initial presentation:** • Mild fever, cough and positive RT-PCR • After symptoms resolution and 2 negative RT-PCR tests, the patient was discharged. **Second admission:** • 23 days later, admitted for UTI. • 4 nasopharyngeal swab RNA tests for SARS-CoV-2 were negative • Serological analysis revealed the presence of SARS-CoV-2-specific IgG but not IgM **Recovery period:** • During recovery, the patient was accidentally in prolonged close contact with a misdiagnosed COVID-19 patient • Subsequent analysis revealed positive RT-PCR and IgM seroconversion • Patient was asymptomatic HIQA interpretation: serological evidence suggestive of reinfection	Letter to the editor
Chen 2020a[14] 10.1002/jmv.26002. China Case series	SARS-CoV-2 Retested positive with either RT-PCR or serum antibody tests Serum antibody detected by colloidal gold immunochromatography	11 rehospitalised patients with positive RT-PCR or serum antibody following discharge; 3 males; mean age 48.45 years (33-72 years); 2 had diabetes, 1 had hypertension. Hospital discharge criteria: (1) normal	Rate and timing of re-detection positive: Average time between 1st discharge and 2nd admission was 16 days, ranging from 6 to 27 days. Average number of negative RT-PCR tests prior to discharge: 2.63 +/- 0.92 times (range 2-5 times) negative results. 1 patient was negative 5 times before discharge but positive on 8th day after discharge. Definition of re-detect positive: Following second hospitalisation: • 1 patient was RT-PCR, IgG and IgM, positive.	Peer reviewed; Journal of medical virology

		temperature without fever for over 3 days, (2) improved respiratory symptoms, (3) substantially improved acute exudative lesions on chest CT images, and (4) 2 consecutively negative results of RT-PCR analysis with 1 day interval at least	• 5 negative RT-PCR, but positive for IgG and IgM. • 3 positive for RT-PCR and IgG, but negative for IgM • 2 RT-PCR positive but IgM or IgG were not quantified. Symptomatic/asymptomatic on readmission: Main symptoms were cough (54.5%), fever (27.3%) and feeble (27.3%). Compared with 1st admissions, more of the symptoms were mild and relieved. Compared with 1st hospitalisation, there were decreases in gastrointestinal symptoms (5 vs. 0), elevated WBC and lymphocyte count, CRP and SAA. Additionally, 6 patients chest CT exhibited notable improvements in acute exudative lesions. Conclusion Hospital stay was shortened, clinical symptoms were relieved, laboratory outcomes were improved, and CT manifestations were ameliorated on the 2nd admission, which suggests that these rehospitalised patients were more likely to be in a status of recovery.	
Chen 2020b[13] China Case series 10.1101/2020.07.02.20144873	RT-PCR: COVID-19 RT-PCR detection kit (S1002) and COVID-19 nucleic acid detection kit Serology: COVID-19 IgM and IgG antibody detection kits (chemiluminescence method)	N=15 recurrent positive cases with moderate disease N=107 controls **Recurrent positive** Median age: 43 years (IQR: 35-54 years) 53% female Course of disease: median 36 days (IQR 34-45 days) **Controls** Median age: 60 years (IQR 43-69 years)	Recurrent-positive patients were significantly younger than control patients (p=0.011) Serum antibody levels were significantly lower in recurrent-positive patients than in control patients (IgM: 13.69 ± 4.38 vs. 68.10 ± 20.85 AU/mL, P = 0.015; IgG: 78.53 ± 9.30 vs. 147.85 ± 13.33 AU/mL, P < 0.0001), however data only available for one re-detection patient. Recurrent rate in hospital: 1.87% (denominator N/R)	Not peer-reviewed (preprint)

		45% female Course of disease: median 15 days (IQR: 7-30 days)		
Chen 2020c[127] China Case series 10.1016/j.jiph.2020.06.008	RT-PCR On discharge all patients had 2 negative RT-PCR test results at least 1 day apart	N=4 (of 17 patients) re-tested positive	**Case 1** 29-year-old male Nasopharyngeal swab was positive 3 days after discharge **Case 2** 49-year-old female Nasopharyngeal swab was positive 3 days after discharge **Case 3** 12-year-old female Anal swab was positive 3 days after discharge **Case 4** 38-year-old male Nasopharyngeal swab was positive 3 days after discharge Unclear if symptoms progressed on re-detection	Peer-reviewed
Deng 2020[21] China Case series https://europepmc.org/article/PPR/PPR122436	SARS-CoV-2 RT-PCR (device NR) using NP and anal swabs Discharge criteria: 2 negative RTPCR test results at least 1 day apart (sample site for discharge unclear) 3 days after discharge, patients were re-detected via NP swabs for 3 patients and via anal swabs for 1 patient	4 discharged patients with re-detected SARS-Cov-2 RNA 3 days after discharge **Demographics:** Case 1: 29-year old male Case 2: 49-year old female (mother of case 1) Case 3: 12-year old female	**Redetectable Positive (RP)/Reinfection rate** 17.6% (3/17) patients were found to be re-detectable positive by viral RNA RT-PCR of nasopharyngeal swabs. 4 patients from a total of 17 cases (23.5%) were found to be re-detectable positive by any means (nasopharyngeal or anal swab) • 3 patients showed nasopharyngeal swabs result positive after 3 days of discharge. The remaining 1 showed anal swab result positive after 3 days of discharge. • No patient presented with symptoms upon re-detection	Not peer-reviewed (pre-print)

	Viral RNA was not consistently detected in subsequent tests in 3 of 4 patients.	Case 4: 38-year old male **Clinical characteristics:** Initial Presentation: Case 1: Fever and cough Case 2: Cough Case 3: No symptoms Case 4: Fever, fatigue and cough Re-admission Case 1: No symptoms Case 2: No symptoms Case 3: No symptoms Case 4: No symptoms **SARS-COV-2 Clinical syndromes (National Health Commission of the People's Republic of China definition):** Case 1: NR Case 2: NR Case 3: Mild Case 4: NR	• 3 patients returned to the designated hospital for quarantine again. 2 patients were discharged again from the hospital on March 2nd, 2020, and tested negative. • The other (case 4) was still under medical observation at the time of writing. • The third case was quarantined in the hospital due to positive results of anal swab.	
Fu 2020b[30] China Case series	SARS-CoV-2 SARS-CoV-2 RNA test (Type of test not stated)	3 confirmed cases; 2 female; Aged 36, 74 and 34 years; Case 2 had history of hypertension	**Rate and timing of re-detection positive:** 3 confirmed cases whose IgM was negative and IgG was positive before 1st discharge, while PCR turned positive again during hotel isolation. All 3 presented negative for IgM and positive for IgG during re-admission period.	Published letter to the editor

DOI: 10.1002/jmv.25968	IgM and IgG antibody test (type of test not stated) Timing of test is unclear	**Criteria for discharge/re-detection:** Nasopharyngeal swab tests for SARS-C0V-2 RNA were negative for at least 2 consecutive times (sampling interval >= 1 day (which meets discharge standard.	Time from first discharge to second admission was 7, 12 and 9 days respectively. **Antibody response in re-detection positive patients :** For 1st test, IgM was negative for cases 1 and 2 and weakly positive in case 3, while IgG was positive in all 3. The results for IgM were negative and IgG were positive for all 3 on discharge. During re-admission to hospital, the results were still negative for IgM and positive for IgG antibodies. Comparing with the 1st admission, IgG levels declined in Case 1 and 3, while it increased in Case 2. **Symptomatic/asymptomatic on readmission:** During re-admission, patients' temperature and respiratory rates were normal, and 'there was no special symptom'. Only 1 patient has developed the symptom of cough. Blood routine, urine routine, and stool routine tests, coagulation function, liver and renal function, electrolytes, inflammation indicators were completed and the results were normal. Lung lesions in all were further absorbed than during 1st admission.	
Garnier-Crussard 2020[113] France Case report 10.21203/rs.3.rs-34694/v1	SARS-CoV-2 RT-PCR, cobas® SARS-CoV-2 Test, Roche Diagnostics, Switzerland, Nasopharyngeal IgG test: Architect, Abbott, USA	78-year-old woman Past medical history: Metastatic breast cancer with bone metastases	Initial diagnosis: RT-PCR positive with symptomatology & ground glass lung opacities Symptoms resolved and SARS-CoV-2 RNA on Day 23 was negative (only 1 sample taken, not 2 consecutive negatives) Patient became febrile and lymphopenic on Day 26 and RT-PCR changed to positive (with high cycle threshold) Patient had positive IgG serology Patient transferred back to acute COVID ward and made full recovery	Not peer reviewed

Loconsole 2020[117] Italy Case report DOI: 10.1007/s15010-020-01444-1	SARS-CoV-2 Vivadiag, VivaChek Laboratories, INC, USA *and* Anti-SARS-CoV-2 ELISA IgG Test, Euroimmun, Lubeck, Germany	48 year old male	**Rate and timing of re-detection positive:** Patient discharged 31st March. PCR negative on April 15th, and IgG/IgM present. April 30th dyspnoea and chest pain. Imaging showed ground-glass area. He was PCR positive and IgG (not IgM) positive. **Criteria for discharge/re-detection:** Hospital required two consecutive negative SARS-CoV-2 molecular tests, normal body temperature, resolution of respiratory symptoms and improvement in lung imaging. **Symptomatic/asymptomatic on readmission:** Dyspnoea and chest pain on readmission. Pulmonary embolism noted on readmission.	Peer reviewed; Infection
Lu 2020[64] China Case series 10.1101/2020.06.15.20131748	SARS-CoV-2 RT-PCR: QIAamp Viral RNA mini kit (QIAGEN, Germany) Discharge criteria for COVID-19 cases in Guangdong: 1) Body temperature is back to normal for more than 3 days; 2) Respiratory symptoms improve; 3) Pulmonary imaging shows obvious absorption of inflammation, and 4) Nuclei acid tests negative twice consecutively on both respiratory tract samples such as sputum and nasopharyngeal swabs and digestive tract samples such as stool and anal swabs (sampling interval being at least 24 hours).	N=87 re-detected positive cases out of N=619 discharged patients Mean age of re-detected cases=30.4 years, range 11 months to 68 years N=45 Males, N=42 Females	Of 619 discharged COVID-19 cases, 87 were re-tested as SARS-CoV-2 positive (14%) 58/59 (98.3%) serum samples of re-positive cases collected at a median of 35 days post illness onset (range 23-47 days) developed NAbs with a titre >4, ranging from 4 to >1024. All re-positive cases had mild or moderate symptoms in initial diagnosis Duration from discharge to the time tested as re-positive can range from 6 to 28 days **Live virus isolation** Live virus isolation attempted on N=36 RT-PCR positive samples including 14 nasopharyngeal swabs, 3 throat swabs and 19 anal swabs. These RT-PCR positive samples were inoculated into Vero-E6 cell line No live viruses could be cultured following two 193 rounds of cell passage **Whole genome sequencing** Virus whole genome sequencing in re-positive cases	Not peer-reviewed

			None of full-length SARS-CoV-2 genome could be obtained by sequencing 94 samples from 54 patients and the sequencing coverage ranged from 0.00–75.48%	
Huang 2020a[44] Case series China DOI: 10.1101/2020.05.06.20089573	SARS-CoV-2 Chemiluminescent microparticle immunoassay (CMIA) kit (Innodx, Xiamen, China, catalog no. Gxzz 20203400198) SARS-CoV-2 qRT-PCR (Shanghai GeneoDx Biotech Co., Ltd); testing was performed every 3 days during the hospitalisation, every 3 to 5 days during mandated quarantine at a designated centre, and weekly during quarantine at home. **Definition of reinfection:** Positive qRT-PCR nasopharyngeal test. **Readmission criteria:** Positive qRT-PCR nasopharyngeal test.	417 SARS-COV-2 in-patients who were discharged; mild (n=16), moderate (n=309), severe (n=73), critical (n=19) N=3 died and remaining 414 included in study Patients who had positive nasopharyngeal swab post-discharge were defined as 'case' patients. Case patients were generally younger than controls and 93% had mild or moderate illness at first admission. Controls 13.6% 0-29 years; 47.5% 30-54 years; 38.8% 55-86 years; 48.4% male; 3.8% mild; 71.9% moderate;19.7% severe; 4.6% critical. Cases: 33% 0-29 years; 49% 30-54 years; 17% 55-86 years; 41% male; 4%	**Rate and timing of re-detection positive:** Of 414 patients, 69 re-test positive (16.7% (95% CI 13.0-20.3%)) (53 with 1 readmission, 13 with 2 readmissions and 3 with 3 readmissions). Median time from new onset of symptoms to first positive nasopharyngeal swab PCR test after admission: 3 days Median time to PCR test negative after treatment: 12 days. 70% overall in the case group retested positive within 5-25 days after the first negative test, with a peak occurring at 10-15 days. Of the 16 who retested positive again during second period of post-discharge observation there was a median of 8.5 days from test negative to retest positive. Of the 3 patients who retested positive for the fourth time, median time from prior testing to retest positive was 5.5 days. A subset of 154 patients had IgG/IgM antibody testing at initial discharge. 85 and 153 were IgG and IgM positive respectively. 1/154 had repeated negative antibody tests (n=5) of both IgM and IgG. Of the 154 patients tested, 40 (100%) of the case group were IgG positive, and 30 (75%) of were IgM positive. **Symptomatic/Asymptomatic (overall and at time of re-detection)** Patients who had positive nasopharyngeal swab post-discharge were defined as 'case' patients. Case patients were generally younger than controls and 93% had mild or moderate illness at first admission and had respiratory symptoms including cough and increased sputum at the readmission of PCR positivity. 2/69 were febrile with typical clinical manifestations satisfying the first admission criteria. **Other:**	Not yet peer reviewed

		mild; 88% moderate; 7% severe; 0% critical. **Definition of recovery/Discharge criteria:** Being afebrile for at least 3 days; improvement of radiological abnormalities on CT or X-ray, 2 consecutive negative qRT-PCR tests sample >1 day apart. A subset of 154 patients had IgG/IgM antibody testing at initial discharge	Multivariable model developed to predict the risk of recurrence **Prediction of PCR re-detection using mathematical modelling** Mild or moderate patients more likely to recur with PCR positivity post discharge. Serum concentrations of cholinesterase, calcium, and eGFR associated with the risk of recurrence of PCR positivity.	
Kim 2020[51] South Korea Case series https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7036338/pdf/jkms-35-e86.pdf	SARS-CoV-2 rRT-PCR (Thermo Fisher Scientific, MA, USA) using URT, LRT, serum, plasma, urine, stool samples. Discharge criteria not provided, as patients remained in-patients for the duration of the study Re-detected using URT and LRT samples	2 hospitalised patients **Demographics:** Patient 1: 35 year old woman Patient 2: 55 year old man **Clinical characteristics:** Presentation: Patient 1: fever, chills, and myalgia	• Patient 2 had undetectable virus RNA across all tested samples for 7 consecutive days (from days 18-24 post-symptom onset inclusive) having had several days of consecutively positive test results across multiple sample sites • Patient 2 subsequently tested positive one more time via both URT (on day 25) and LRT samples (on day 26), while an in-patient. • Patient was discharged on day 27 post-symptom onset. • Patient 1 experienced relatively stable patterns of virus detection from admission through to discharge	Peer-reviewed; J Korean Med Sc

		Patient 2: sore throat and intermittent myalgia SARS-COV-2 Clinical syndromes: Patient 1: Moderate Patient 2: Mild (not defined)		
Li Y 2020[57] China Case series DOI: 10.1002/jmv.25905	**Test:** RT-PCR **Sample site(s):** Oral, nasal, sputum, blood, faeces, urine, vaginal secretions and milk SARS-COV-2 Clinical syndromes (National Health Commission of the People's Republic of China definition): Not reported	**Population setting:** 13 discharged SARS-COV-2 patients who were quarantined for 4-weeks at home **Demographics:** *Adults* *Sex:* Male, 6 (46%) Female, 7 (54%) *Age:* Mean: 52.8 (± 20.2) **Clinical characteristics:** *Presentation* Fever, 13 (100%) Cough, 9 (69.2%) Fatigue, 3 (23.1%) Sore throat, 3 (23.1%) Diarrhoea, 1 (7.7%)	**Duration of virus detection** *Days from onset of symptoms to the first of two consecutive negative tests:* Respiratory sample (unclear whether upper or lower): Mean (±SR): 25 (±6) days Range: 18-44 Blood, urine, vaginal secretions and milk: N/R *Post discharge* Faeces: 2 (15.4%) patients tested positive at day 14 day and 15 after sputum was negative. Sputum: 4 (30.7%) patients positive between 5 – 14 days after discharge One of the patients experienced recurrence followed by a negative test result, which turned positive again at a later stage.	Peer reviewed (Zhongguo Wei Zhong Bing Ji Jiu Yi Xue)
Lim 2020[116] South Korea	SARS-CoV-2 RT-PCR (Quantstudio 1 Applied Biosystems, Foster	**Population setting:** 1 patient admitted to hospital	• Patient experienced 2 consecutive days of undetectable virus RNA from sputum samples on days 11 and 12 since	Published

Case report DOI: 10.3346/jkms.2020.35.e79	City, CA, USA) and PowerCheck™ SARS-CoV-2 Real-Time PCR kit, KogeneBiotech, Seoul, Korea) using sputum sample. Discharge criteria not provided, as patient remained in-patients for the duration of the study Re-detected using sputum samples	**Demographics:** 54 year old man **Clinical characteristics:** Presentation: Chills and muscle pains **SARS-COV-2 Clinical syndromes (WHO definition):** Pneumonia	symptom onset, having had 2 previous days of positive test results. • Patient subsequently had 4 more consecutive days of positive test results	J Korean Med Sc
Qu 2020[119] China Case report DOI: 10.1016/j.tmaid.2020.101619	SARS-CoV-2 real-time RT-PCR (device NR) using throat swabs and sputum **Discharge criteria:** 2 successive negative results of Sars-Cov-2 nucleic acid detection, in addition to normal body temperature for 3 days as well as obvious improvement in respiratory symptoms and CT scan Re-detected by throat and sputum samples	**Population setting:** 1 patient admitted to hospital **Demographics:** 49 year old man **Clinical characteristics:** Presentation: Fever SARS-COV-2 **Clinical syndromes:** NR	• After the active treatment, the patient recovered from fever and other respiratory symptoms on February 4 (day 13 of hospitalisation). • On February 9 and February 10 (days 18 and 19 of hospitalisation), the SARS-CoV-2 nucleic acid detection was successively negative in throat swab samples. CT scan result showed that the inflammation was significantly decreased in both lungs. Both the results of SARS-CoV-2 nucleic acid detection and CT scans indicated a recovery trend, and the patient was ready for discharge. • On February 13 (Day 22 of hospitalisation), the throat swab and sputum by nebulization were collected before the patient was discharged. Notably, SARS-CoV-2 nucleic acid was still detected in sputum from the patient although negative result of throat swab detection	Published Travel Medicine and Infectious Disease Journal
To 2020[124] Hong Kong, China Cohort study	SARS-CoV-2 qRT-PCR (QuantiNova Probe RT-PCR Kit (QIAGEN, Hilden, Germany)) using blood, urine,	**Population setting:** 23 patients at 2 hospitals in Hong Kong **Demographics:**	1 patient (of 23) with complete resolution had undetectable viral load on days 21 and 22 after symptom onset, with rebound of viral load on days 23 and 24, followed by 5 days of undetectable viral load	Peer-reviewed; The Lancet Infectious Diseases

DOI: 10.1016/s1473-3099(20)30196-1	posterior oropharyngeal saliva, and rectal swab samples **Discharge criteria:** A criterion for discontinuation of transmission-based precautions is a negative RT-qPCR result from two sets of nasopharyngeal and throat swab specimens. Other criteria not specified. Re-detected via rectal swab	13 male, 10 female Median age 62 years (range 37–75) **Clinical characteristics:** Fever, 22 (96%), cough, 5 (22%), chills, 4 (17%), dyspnoea, 4 (17%) SARS-COV-2 **Clinical syndromes (author definitions):** Severe disease, 10 (43%), Mild disease, 13 (57%) Severe disease defined as the need for supplemental oxygen, admission to ICU, or death.		
Wang 2020c[84] China Case series DOI: 10.21203/rs.3.rs-22829/v1	SARS-CoV-2 RT-PCR (BioGerm) using NP and anal swabs **Discharge criteria:** 1. Temperature below 37 degrees lasting at least 3 consecutive days; 2. Resolved respiratory symptoms;	**Population setting:** 182 post-discharge patients recovering from SARS-COV-2 under medical isolation **Demographics** (n=20 re-detected patients):	• Fourteen of the 20 (70%) re-detected patients tested positive from nasopharyngeal swabs and the other six patients (30%) tested positive from anal swabs. No patient tested positive from both samples. Therefore, 20 patients overall (11%) re-tested positive for SARS-CoV-2 within 14 days of meeting discharge criteria • Patients that were re-detected for SARS-CoV-2 had significantly shorter lengths of stay during their index admission than patients who were not re-detected	Not peer-reviewed (Pre-print)

	3. Substantially improved in chest lesions CT images, and 4. 2 consecutively negative RT-PCR test results with at least 1 day interval (sample site not reported)	Mix of children and adults Sex: Male, 7 (35%) Female, 13 (65%) **Age:** Median, 41.5 (Range 1-72) **Clinical characteristics:** *Initial presentation:* NR *Upon re-admission:* No symptoms, 20 (100%) SARS-COV-2 Clinical syndromes (n=20 re-detected patients) (Definition not reported): Non-severe, 20 (100%)		
Xiao 2020a[90] China Case series DOI:10.1002/jm25855	Throat swab samples or deep nasal cavity swab samples were collected from patients on different dates after the onset of symptoms SARS-CoV-2 were detected by RT-PCR assay using a SARS-COV-2 nucleic acid detection kit (Shanghai Huirui Biotechnology Co., Ltd)	N=70 patients Age (median): 57 (IQR 44-65) Male: 44% All patients were mild to moderate Time from onset of symptoms to nucleic acid conversion (2	• 15 (21.4%) patients experienced a positive of nucleic acid detection by RT-PCR test for SARS-CoV-2 after 2 consecutive negative results • Authors report this may be related to false negative RT-PCR tests	Letter to the editor Peer-reviewed; Journal of Medical Virology.

		negative RT-PCR): median 36 days (IQR: 28-40)		
Xing 2020[93] China Case series DOI: 10.2807/1560-7917.ES.2020.25.10.2000191	SARS-CoV-2 RT-PCR assay for SARS-CoV-2 SARS-CoV-2 nucleic acid in throat swab samples were taken according to the manufacturer's protocol (Shanghai BioGerm Medical Technology, Shanghai, China).	N=62 SARS-CoV-2 cases among medical personnel, of which 2 were repeat positive after discharge. All confirmed cases were hospitalised and isolated for treatment. The discharge criteria were: (i) afebrile for at least 3 days, (ii) obvious alleviation of respiratory symptoms, (iii) improvement in radiological abnormalities on chest CT or X-ray and (iv) 2 consecutive negative detections of SARS-CoV-2 at least 24 h apart	• Case 1 was a male doctor in his 40s After discharge on 10 February, he was kept under surveillance and quarantined at home. He did not experience discomfort during the follow-up period. The results of consecutive throat swab tests were negative on 13 February, weakly positive on 14 February, positive on 15 February, negative on 16 February, weakly positive on 18 February, negative on 20 February and negative on 22 February. • Case 2 was a female nurse in her 20s. After discharge on 13 February, Case 2 was kept under surveillance and quarantined at home. She did not experience discomfort during the follow-up. The results of consecutive throat swab tests were weakly positive on 14 and 15 February, negative on 16, 17 and 18 February, positive on 19 February and negative on 20, 21 and 22 February.	Eurosurveillance Peer-reviewed
Ye 2020[96] China Case series DOI: 10.1016/j.jinf.2020.03.001	SARS-CoV-2 RT-PCR on samples from throat swabs (device NR) Discharge criteria: NR Re-tested positive from throat samples (RT-PCR)	**Population setting:** N=55 hospitalised patients with SARS-COV-2 pneumonia, 5 (9%) re-tested positive after discharge	• 5 of the total of 55 hospitalised patients (9%) re-tested positive after discharge • Symptoms on presentation (it is unclear if these symptoms were at initial admission or at time of re-detected positive): 4 of the 5 patients presented with fever without chills and 1 was afebrile. Of the febrile patients, 1 had a high fever (39.3 °C). Patients' body temperatures fluctuated within a range from 36.2 to 39.3	Peer reviewed; Journal of Infection

		Demographics: Adults Age: for n=55 Median 37 (range 22-67) The age range of the 5 SARS-CoV-2 reactivated patients was 27–42 years Sex, for n=55: Male, 19 (34.5%) Female, 36 (65.5%) The sex of the 5 SARS-CoV-2 reactivated patients were 2 males and 3 females.	°C. 1 patient showed normal body temperature. Other symptoms of an upper respiratory tract infection were also observed: 1 patient had cough, 1 had sore throat and all patients reported fatigue. Additionally, 1 patient had constipation. • Time from testing negative to testing positive again ranged from 4 to 17 days.	
Yuan 2020[99] China Case series DOI: 10.21203/rs.3.rs-22829/v1	SARS-CoV-2 RT-PCR for viral load Performed by nasopharyngeal swabs and anal swabs 7 and 14 days post-discharge RT-PCR test kits: Bio-Germ Ig detection: The total immunoglobulin, IgA, IgG and IgM of 14 re-positive patients were tested on the 7th day by a SARSCoV-2 testing kit (WANTAI BioPharm) based on Chemiluminescence method	N=182 recovered patients under medical isolation observation Among all the recovered and isolated, there are 182 of them has been re-tested for at least 1 time, 84 (46.2%) of the 182 male and 98 (53.8%) female, mean age was 46.4±17.1	20 (10.99 %) patients out of the 182 were re-detected SARS-CoV-2 RNA positive. Thirteen of them tested to be re-positive on the 7th day, and another 7 on the 14th day; 14 were tested as nasopharyngeal swabs positive, and 6 were anal swabs positive, none has found both swabs positive None became symptomatic on re-detection Females and young patients aged under 15 have higher re-positive rate than the average, and none of the severe patients turned re-positive. Notably, most of the re-positive cases turn negative in the followed tests **IgA/M/G**	Not peer-reviewed

		(median 49, range 1-81); 39 (21.4%) had severe symptoms, 143 (78.6%) mild and moderate **Discharge criteria:** 1. Temperature <37 degrees lasting at least 3 consecutive days; 2. Resolved respiratory symptoms; 3. Substantially improved in chest lesions CT images; 4. 2 consecutively negative RT-PCR test results with at least 1 day interval	14 out of the 20 re-positives were assessed for Igs Total immunoglobulin, IgA and IgG were positive in 14/14 IgM positive in 10/14 The re-positives are transferred to designated infectious hospital for quarantine treatments, and again their RT-PCR testing results of blood, nasopharyngeal swabs and anal swabs were collected on the 1st, 4th and 7th day (some were taken on 2nd and 6th) N=5/14 still positive.	
Zhang 2020a[104] China Case series DOI: 10.1101/2020.03.28.20043059	SARS-CoV-2 rRT-PCR (Mabsky Biotech Co., Ltd) using upper respiratory (nasal-throat mixed), faeces, urine, plasma samples Discharge criteria not provided	**Population setting:** 23 patients treated in hospital in Beijing **Demographics:** Adults Age: 48 years (IQR 40 to 62) Sex: Male, 12 (52%); Female, 11 (48%) **Clinical characteristics:**	At 26 days after discharge, 1 case was detected positive again in faeces samples, but appeared healthy and negative for respiratory swabs.	Not peer-reviewed (Pre-print)

		Presentation: Fever 20 (87%), cough 13 (57%), weakness 9 (39%), myalgia 5 (22%), pharyngalgia 5 (22%), headache 3 (13%) SARS-COV-2 **Clinical syndromes (National Health Commission of the People's Republic of China definition):** Severe, 2 (9%) Mild-to-moderate, 21 (91%)		
Zhu 2020[108] China Case series 10.1002/jcla.23392	SARS-CoV-2 RT-PCR of sputum and nasopharyngeal swab specimens Patients have to meet the following criteria for hospital discharge: (a) temperature returned to normal for more than 3 days, (b) respiratory symptoms are relieved or resolved, (c) pulmonary computed tomography (CT) images show significant improvement in acute exudative lesions, and (d) two consecutive negative	N=98 convalescent patients, of which N=17 re-detected positive Of entire sample (N=98), median age 52 years (IQR, 37.8-59); 67.3% female Of re-test group (N=17), median age 54 years (44-63); 70.6% female Among 17 cases with re-positive RT-PCR test results, the median time from	• 17.3% (17/98) retested positive • Re-tested positive were asymptomatic except one person with recurrent symptoms and exudative CT lesions (however, lesions were less severe than initial admission). • Median time from symptoms onset to final respiratory SARS-CoV-2 detection of negative result was significantly longer in re-positive group (34 days [IQR, 29.5-42.5]) than in non-re-positive group (19 days [IQR, 16-26]) • Median time from discharge to SARS-CoV-2 nucleic acid re-positive was 4 days (IQR, 3-8.5)	Peer-reviewed

	detections of respiratory SARS-CoV-2 (sample collection interval of at least 1 day)	discharge to nucleic acid re-positive was 4 days (IQR, 3-8.5), and notably, 1 of the cases had re-positive results 17 days after discharge.		

Table 4: Infectiousness of re-detected cases

Author Country Study design Study URL	Population setting	Primary outcome results	
An 2020[3] China Case series https://www.medrxiv.org/content/10.1101/2020.03.26.20044222v1	**Population setting:** 262 discharged SARS-COV-2 patients (38 (14.5%) of whom had re-tested positive for SARS-CoV-2 after meeting the discharge criteria). **Demographics:** *Mix of adults and children* *Sex:* n=242 patients with mild or moderate initial disease presentation Male, 116 (47.9%), Female, 126 (52.1%) Severe disease: NR *Age* Mild disease, Median (range) Re-detected patients (n=11), 20 (5-64) Not re-detected (n=19), 23 (2-63) Moderate disease, Median (range) Re-detected patients (n=27), 38 (2-60) Not re-detected (n=185), 48 (1-86) Severe disease: NR **Initial Infection** ***Initial Presentation (n=242 mild and moderate patients):*** Fever, 165 (68.1%) Upper respiratory symptoms, 45 (18.6%) Lower respiratory symptoms, 121 (50%) Digestive tract symptoms, 20 (8.3%) Severe patients: NR	**Test parameters**	**Infectiousness outcomes**
		Virus: SARS-CoV-2 **Test:** qRT-PCR (GeneoDX Co., Ltd., Shanghai, China) and Sherlock assay (hypersensitive test) (Feng Zhang lab) for SARS-CoV-2 RNA detection ELISA assay for anti-SARS-CoV-2 IgG and IgM antibody (Sangon Biotech) **Thresholds:** Ct value ≤ 37 = positive **Gene Targets:** Sherlock assay: S, ORF, Commercial qRT-PCR kit: N, ORF1 **Sample site(s):** NP and anal (RNA) Serum (antibodies) **Discharge criteria:** Temperature returned to normal for more than three days, respiratory symptoms significantly improved, and	**Location of patients after discharge:** Discharged from hospital (at home or under intensive isolation for 14 days). **Post-discharge follow-up for re-detection of SARS-CoV-2:** At least 14 days (however unclear exactly how long patients were followed up for in total). Patients who tested positive again (n=38) were re-admitted to hospital for observation. **Number of people in close contact with re-detected patients:** 21 close contacts identified from the 38 who re-tested positive. **Number of close contacts subsequently infected:** None **Method of contact tracing undertaken:** NR **Duration of follow-up of contacts:**

	SARS-COV-2 ***Clinical syndromes (National Health Commission of the People's Republic of China definition):*** All 262 patients: Mild, 30 (11.4%) Moderate, 212 (81%) Severe, 20 (7.6%) 38 re-detected patients Mild, 11 (28.9%) Moderate, 27 (71.1%) Severe, 0 (0%) ***Length of stay:*** *Symptom onset to hospital discharge* *Mild disease (n=30),* median 15 days, range 14-22 (re-detected) median 16 days, range 10-23 (not re-detected) *Moderate disease (n=212),* median 17 days, range 9-29 (re-detected) median 18 days, range 7-35 (not re-detected) *Severe disease, NR* **Re-detected Cases** *Clinical characteristics (n=38 mild and moderate patients)* Fever, 0 (0%) Cough, 6 (15.7%) Chest tightness, 2 (5.3%) Other symptom, 3 (7.9%)	significant absorption of pulmonary lesions of chest CT imaging, and at least 2 consecutive negative upper respiratory tract sample (plus anal swab from February 22) RNA test results at least 24 hours apart. **Re-detection:** Within 14 days of discharge via NP and anal swabs (unclear whether positive detection in both sampled required for re-detection). **Genome testing:** Not conducted	Authors report follow-up of close contacts until 10 March 2020, which is a median of 40-46 days since symptom onset for all patients.
Deng 2020[21] China Case series https://europepmc.org/arti	**Population setting:** 4 discharged patients with re-detected SARS-Cov-2 RNA 3 days after discharge. **Demographics:** *Mix of adults and children* Case 1: 29-year old male Case 2: 49-year old female (mother of case 1)	**Test parameters** **Virus:** SARS-CoV-2 **Test:** RT-PCR (device NR) **Thresholds:** NR	**Infectiousness outcomes** **Location of patients after discharge:** NR **Post-discharge follow-up for re-detection of** SARS-CoV-2**:**

cle/PPR/PPR122436	Case 3: 12-year old female Case 4: 38-year old male **Initial Infection** *Initial Presentation:* Case 1: Fever and cough Case 2: Cough Case 3: No symptoms Case 4: Fever, fatigue and cough SARS-COV-2 ***Clinical syndromes (National Health Commission of the People's Republic of China definition):*** Case 1: Mild Case 2: Mild Case 3: Mild Case 4: Pneumonia ***Length of stay*:** Case 1: 14 days Case 2: 14 days Case 3: 14 days Case 4: 23 days **Re-detection** *Clinical characteristics* Case 1: No symptoms Case 2: No symptoms Case 3: No symptoms Case 4: No symptoms	**Gene Targets:** NR **Sample site(s):** NP and anal swabs **Discharge criteria:** 2 negative RT-PCR test results at least 1 day apart (sample site not reported). **Re-detection** 3 days after discharge via NP swabs for 3 patients and via anal swabs for 1 patient Viral RNA was not consistently detected in subsequent tests in 3 of 4 patients. **Genome testing:** Not conducted	3 days (all 4 patients were returned to hospital for quarantine) **Number of people in close contact with re-detected patients:** NR **Number of close contacts subsequently infected:** None **Method of contact tracing undertaken:** NR **Duration of follow-up of contacts:** NR

Lan L 2020[53] China Case series https://jamanetwork.com/journals/jama/fullarticle/2762452	**Population setting:** 1 hospitalised and 3 quarantined (at home) healthcare professionals, with re-detected SARS-Cov-2 RNA. **Demographics:** *Adults* Sex Male, 2 (50%) Female, 2 (50%) *Age* Range, 30-36 **Initial Infection** *Initial Presentation:* Among 3 of the patients, fever, cough, or both occurred 1 patient had no symptoms. **SARS-COV-2 *Clinical syndromes (Definition not reported):*** Mild to moderate, 4 (100%) ***Length of stay:*** NR **Re-detection** *Clinical characteristics* No symptoms	**Test parameters** **Virus:** SARS-CoV-2 **Test:** RT-PCR (BioGerm) **Thresholds:** NR **Gene Targets:** NR **Sample site(s):** Throat **Discharge/end of quarantine criteria:** 1. normal temperature lasting longer than 3 days, 2. resolved respiratory symptoms, 3. substantially improved acute exudative lesions on CT images, and 4. 2 consecutively negative RT-PCR test results separated by at least 1 day (sample site not reported). **Re-detection** Throat sample RT-PCR tests were repeated 5 to 13 days post-discharge and all were positive. All patients had 3 repeat RT-PCR tests performed over the next 4 to 5 days and all were positive. **Genome testing:** Not conducted	**Infectiousness outcomes** **Location of patients after discharge:** Home quarantine for 5 days. **Post-discharge follow-up for re-detection of** SARS-CoV-2: Up to 13 days after discharge (not clear whether patients were re-admitted to hospitals). **Number of people in close contact with re-detected patients:** NR **Number of close contacts subsequently infected:** None **Method of contact tracing undertaken:** NR **Duration of follow-up of contacts:** NR
Wang 2020a[84] China Case series https://europepmc.org/arti	**Population setting:** 182 post-discharge patients recovering from SARS-COV-2 under medical isolation (20 of whom (11%) re-tested again for SARS-CoV-2 within 14 days of meeting discharge criteria).	**Test parameters** **Virus:** SARS-CoV-2 **Test**: RT-PCR (BioGerm) Total Ig, IgA, IgG and IgM (WANTAI BioPharm) **Thresholds:**	**Infectiousness outcomes** **Location of patients after discharge:** 14 days of medical isolation observation in a hotel or at home. **Post-discharge follow-up for re-detection of** SARS-CoV-2**:**

cle/PPR/PPR150648	**Demographics (n=20 re-detected patients):** *Mix of children and adults* Sex: Male, 7 (35%) Female, 13 (65%) **Age:** Median, 41.5 (Range 1-72) **Initial Infection:** ***Initial presentation:*** NR **SARS-COV-2 *Clinical syndromes (n=20 re-detected patients) (Definition not reported):*** Non-severe, 20 (100%) **Length of stay:** Re-detected (n=20): Average ± SD, 20.8 ± 7.1 days Not re-detected (n=162): Average ± SD, 25.6 ± 7.6 days **Re-detection** *Clinical characteristics* No symptoms, 20 (100%)	Ct-value< 37 = positive Ct-value ≥ 40 was defined as negative. A medium load, >37 and < 40, was defined as weak positive and required re-testing. **Gene Targets:** ORF1ab and N genes **Sample site(s):** NP and anal Blood for antibody testing **Discharge criteria:** 1. Temperature < 37 degrees lasting at least 3 consecutive days; 2. Resolved respiratory symptoms; 3. Substantially improved in chest lesions CT images, and 4. 2 consecutively negative RT-PCR test results with at least 1 day interval (sample site not reported) **Re-detection** NP and anal swabs taken on day 7 and 14 post-discharge medical isolation. 14 were tested as NP swabs positive, and 6 were anal swabs positive, none had both positive. 13/20 tests were positive on day 7 post-discharge. 7/20 tests were positive on day 14 post-discharge. **Genome testing:** Not conducted	14 days (20 patients who tested positive were re-admitted to hospital for quarantine). **Number of people in close contact with re-detected patients:** NR **Number of close contacts subsequently infected:** None **Method of contact tracing undertaken:** NR **Duration of follow-up of contacts:** NR
Wang 2020e[85] China Case series 10.21203/rs.3.rs-38036/v1	SARS-CoV-2 RT-PCR Discharge criteria: [National Health Commission of China]: (1) normal temperature that lasts longer than 3 days, (2) significant improvement in respiratory symptoms, (3) substantially improved acute exudative lesions on chest	**Test parameters**	**Infectiousness outcomes**
		N= 287 discharged patients, of which N=33 (11.5%) with recurrent PCR positivity Of the redetected, 21 (63.7%) female Mean age: 48.7 years (±19.7 years); range: 16-94 years	N=33 (11.5%) re-detected positive 22/33 (66.7%) asymptomatic Symptoms: cough, fatigue, sore throat, fever and expectoration. CT thorax: N=8 (24.2%) patients characterised by deterioration compared

	computed tomography (CT) images, and (4) the respiratory nucleic acid was negative for two consecutive times (with at least a 24-hour sampling time interval)		with prior admission (4 patients presented with stable lesions, 9 patients presented with improved lesions, and 12 patients presented with disappearance of original lesions) Median duration of positivity: 9 days (IQR: 6-15). IgG antibody titre (r=0.016, p=0.016) risk factor for prolonged positivity. No new COVID-19 detected among close contacts of re-detected patients during the study period.

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Appendix 1.1 Research questions 1 and 2: Rate and timing of antibody detection following acute infection

It is widely accepted that immunoglobulin M (IgM) antibodies provide the first line of defence following infection.[144] This response is followed by the generation of virus-specific immunoglobulin G (IgG), the most abundant antibody class in humans.[145] IgG responses are crucial for immunological memory and long-term immunity.[144]

Seroconversion is the transition from a seronegative (no detectable SARS-CoV-2 - specific antibodies in the serum sample) to a seropositive condition (detectable SARS-CoV-2 specific antibodies in the serum sample). This section reviews the rate and timing of seroconversion of IgM and or IgG detection. Where there is an absence of serial 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 is taken as a proxy for seroconversion timing.

Characteristics of included studies

In total, 43 studies were identified that assessed the rate and or timing of IgM and or IgG antibody detection in patients with acute SARS-CoV-2 infection, including 34 case series,[1, 3, 5-7, 15, 20, 22, 25-27, 29, 33-35, 37, 40, 42, 43, 46, 47, 50, 69, 71, 78, 80, 84, 87, 97, 102, 103, 106, 110, 122] five case reports,[54, 114, 115, 118, 121] two cohort studies[124, 146] and two cross-sectional studies.[129, 131] Due to the abundance of data relating to SARS-CoV-2, evidence relating to other coronaviruses was not considered. Sixteen of the 43 studies have not yet been peer reviewed.

The largest number of patients enrolled in a study was 338[40] and the largest number of samples taken was 535.[106] The median age ranged from 37[131] to 68 years,[60] and a similar number of males and females were followed across studies.

A diverse range of serological tests (blood tests that look for antibodies in your blood) were used, including chemiluminescent immunoassay (CLIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), gold immunochromatographic assay (GICA), immunofluorescence assays (IFA), immunochromatography (ICG) strip assay, lateral flow immunoassay (LFIA), magnetic chemiluminescence enzyme immunoassay (MCLIA), modified cytopathogenic assay (MCA), proteomic microarrays and SARS-CoV-2 antibody detection kits. Two studies used rapid test kits (Biosynex rapid immunodiagnostic test and ALLTEST 2019-nCoV IgG/IgM Rapid Test Cassette).[27, 115]

Table 1 summarises the characteristics, testing methodology and primary outcome findings of the included studies.

Seroconversion rate

Seroconversion rate (proportion of individuals who seroconvert) for SARS-CoV-2-specific antibodies varied across studies and stage of disease. One peer-reviewed case series reported daily serial antibody samples to identify the exact day of seroconversion post-symptom onset.[20] In this study, four immunochromatographic tests were used for the detection of IgM and IgG directed against SARS-CoV-2 in 22 convalescent patients; tests were obtained from Biotime Biotechnology Co, Autobio Diagnostics Co, ISIA BIO-Technology Co and Biolidics. On day 15, IgM was 100% positive in two tests, 86% in one (Autobio) and 82% in one (ISIA). On day 15, 100% seropositivity for IgG was noted in all four tests.

Eight studies investigated the IgM and IgG detection rate at three different stages of the disease.[33, 74, 80, 97, 102, 110, 131, 146] The detection rate for IgM ranged between 11% and 71% at the early stage (1-7 days) after symptom onset, between 36% and 87% at the intermediate stage (8-14 days), and between 56% and 97% after 14 days. The detection rate for IgG ranged between 4% and 57% at the early stage, between 54% and 88% at the intermediate stage, and between 91% and 100% after 14 days. Figures A.1 and A.2, below, illustrate these findings.

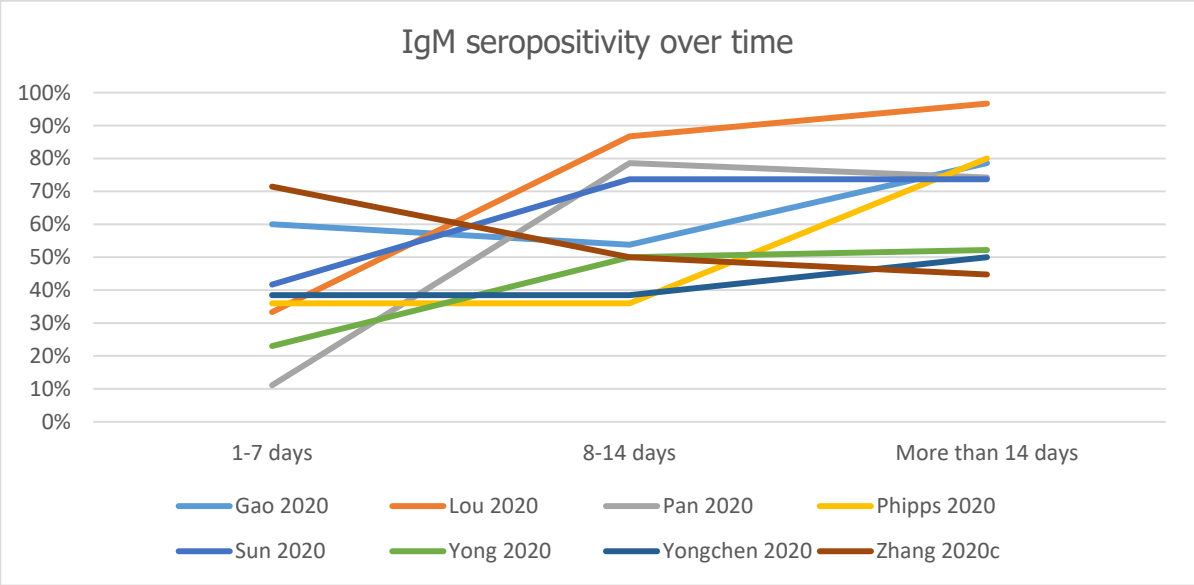
One study (n=34) evaluated antibody detection at two points in time;[15] at week three all patients tested positive for IgG and IgM, whereas at week five, all tested positive for IgG and 83% for IgM.

Seventeen studies reported the antibody detection rate at one point in time.[26, 46, 47, 69, 124, 147] This ranged from 74% to 100% for IgM and from 64.7% to 100% for IgG. However, the timing of samples varied widely (from one to 51 days post-symptom onset). The IgM detection rate was lowest at the later time-points, whereas nearly all patients were reported to have seroconverted for IgG when samples were taken beyond 14 days.

Two studies used rapid antibody testing. In the first study, IgM positivity was 90% (n=75/83) at 21-27 days and IgG positivity was 85% (n=41/48) after 28 days.[27] Another case study found the patient tested positive for IgG on the seventh day.[115]

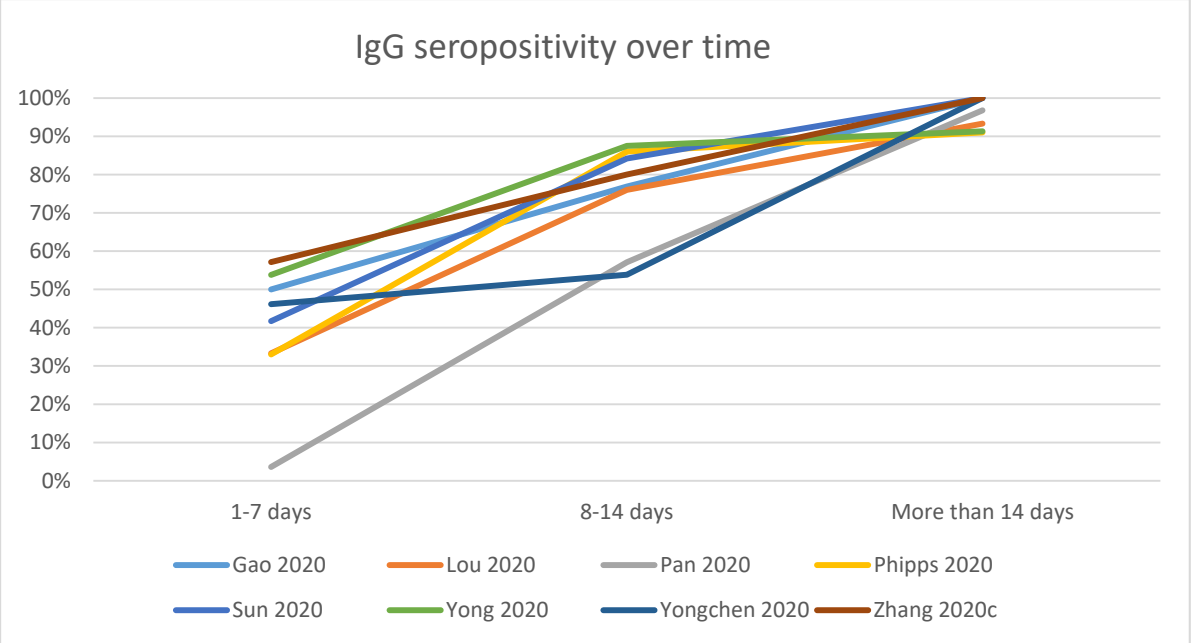
Two studies also reported IgA antibody detection; seroconversion rates were 93% at a median time of five days[35] and 74% at a median time of 22 days.[6]

Figure A.1 IgM detection rate over time



Note – Zhang 2020 collected data at following time points: <10 days, 10-20 days and 20-30 days.

Figure A.2 IgG detection rate over time



Note – Zhang 2020 collected data at following time points: <10 days, 10-20 days and 20-30 days.

Seroconversion timing

Across studies, IgM titres (concentration of antibody in the blood) were typically the first to rise in acute infection, followed by IgG, with IgG tending to persist for much longer in the body. However, the timing for IgM and IgG detection varied significantly across studies with virus-specific antibodies detected at an early stage after symptom onset in some cases, but not until the intermediate or late stage in others.

The median time for antibody detection, following symptom onset, ranged from five days[35] to 17 days[42] for IgM and from six days[42] to 14 days[35] for IgG. Antibody detection timing was typically shorter for IgM than for IgG, while one study found IgG seroconversion before IgM.[147] While steady decreases in IgM titres after one week were reported in most studies, IgG titres did not wane and remained positive for the duration of follow-up (that is, for up to seven weeks) in four studies.[26, 42, 122, 131]

Of the two studies that reported IgA antibody detection, the median seroconversion times were between five days[35] and 22 days.[6]

Four studies reported neutralising antibody data (sample sizes ranged from nine patients[87] to 162[27]). The first found that all patients tested positive for neutralising antibodies by day 14,[87] the titres of which did not suggest close correlation with clinical courses. Additionally, one patient with the lowest virus neutralisation titre at end of week two was RT-PCR positive in stool samples for a prolonged time. A second study found a neutralising antibody detection rate of 100% within 20 days of symptoms onset, which remained at 100% for the duration of follow-up (day 41-53).[86] In a third study, IgG and IgA responses detected by different assays correlated strongly with neutralising antibody response, with all patients eventually developing neutralising antibodies.[148] In a fourth study, neutralising antibodies were detected in 79%, 92% and 98% of samples collected on days 13-20, 21-27 and 28-41 after symptom onset, respectively.[27]

Finally, a case series involving nine COVID-19 cases measured antibody titres (by immunofluorescence), viral load (by RT-PCR) and infectivity (live virus isolation).[87] In this study, live virus isolation was attempted on multiple occasions from clinical samples. Whereas virus was readily isolated during the first week of symptoms from a considerable proportion of samples (16.7% in swabs, 83.3% in sputum samples), no isolates were obtained from samples taken after day eight despite persistent high viral loads. Seroconversion was detected by IgG and IgM immunofluorescence using cells expressing the spike protein of SARS-CoV-2 and a virus neutralisation assay using SARS-CoV-2. Antibody detection (IgM and or IgG) in 50% of patients occurred

by day seven, and in all by day 14. All patients showed detectable neutralising antibodies, the titres of which did not suggest close correlation with clinical courses. This study supported the hypothesis that an appropriate antibody response is associated with clearance of infectious virus

Appendix 1.2 Research question 3: Duration of immune response following SARS-CoV or MERS-CoV infections

SARS-CoV and MERS-CoV, share similar clinical genetic and epidemiological features with SARS-CoV-2.[149, 150] As the process of generating SARS-CoV-specific and MERS-CoV-specific antibodies may be similar to that of SARS-CoV-2-specific antibody production, the duration of detection of these antibodies is of interest. Whether or not the immune response to SARS-CoV-2 follows a similar trajectory has yet to be determined.

SARS-CoV

Twenty-five studies provided data on the duration of the immune response to SARS-CoV; maximum follow-up was up to seventeen years in one study,[4] up to twelve years in two studies,[36, 68] between one and six years in twelve studies,[8, 9, 12, 56, 58, 66, 72, 81, 88, 95, 109, 126] and up to one year in ten studies.[10, 11, 39, 41, 45, 55, 77, 92, 125, 151]

All studies were conducted in China apart from two in Taiwan,[11, 41] one in the Philippines [58] and two in Singapore.[4, 68] All studies were case series or prospective cohort studies, with sample sizes ranging from two[58] to 311[28] participants. Table 4 provides additional details of included studies.

For studies with less than one year follow up, IgM antibodies were reported to begin to decline 2-3 weeks after the onset of symptoms[11, 39, 41, 45, 152] and had disappeared by three to twelve months after infection.[11, 41, 55] In all studies IgG antibodies were detectable at the end of follow-up, which ranged from 12 weeks to one year.[10, 11, 28, 39, 41, 45, 55, 152] Two studies reported on the magnitude and duration of T cell immunity one year after the onset of symptoms.[45, 92] T cell populations were said to be decreased in convalescent patients compared with healthy controls in the early post-infection period in both studies.[45, 92] In the second study with longer follow-up, T cell populations later rapidly recovered, but at one year T cell counts were still reduced compared with healthy controls. The number of CD8+ T cells recovered significantly faster than CD4+ T cells.[92]

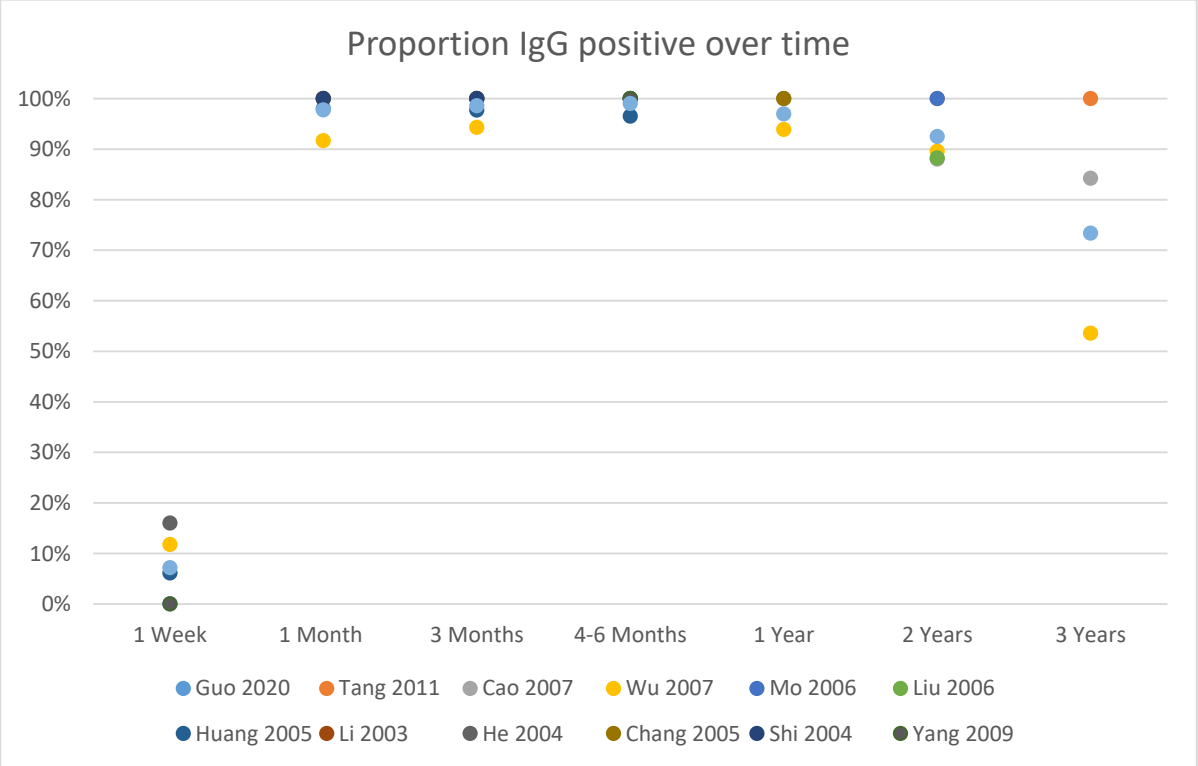
For studies with 1-2 years follow-up, IgG antibodies were still detectable at the study end point.[95, 126] Additionally, SARS-CoV infection was reported to induce a strong memory T-cell response approximately one year after infection in both studies.[12, 95] Furthermore, cross-reactive memory T cells to SARS-CoV may exist in the T cell repertoire of a small subset of healthy individuals in one study.[12]

Five studies reported follow-up data at approximately two years after SARS infection.[56, 66, 72, 109] In the first study, SARS-specific IgG and neutralising antibodies

were detectable at the study end-point in all 30 patients.[56] High and sustainable levels of immune responses were found to be strongly correlated with disease outcome.[56] In a second study, IgG antibody and neutralising antibody titres were found to be highly correlated.[109] Neutralising antibodies were detectable in all patients at 24 months, however 11.8% of serum samples were negative for SARS-CoV-specific IgG antibodies at the final visit. A third study reported that IgG and neutralising antibodies were still detectable at 720 days; however, titres were close to the cut-off point for positivity.[66] In addition to evidence of persistent humoral immunity at two years post-infection, three of these studies investigated T cell-mediated immunity in recovered SARS patients up to 30 months after infection. In the first study, despite the potent immune responses and clinical recovery observed in patients, peripheral lymphocyte counts were not restored to normal levels compared with matched controls at 24 months,[56] in line with findings previously reported at one year follow-up. A second study reported that SARS-CoV N-protein-specific memory CD4+ and CD8+ T cells were maintained for two years after SARS-CoV infection,[72] while in the final study, T cell cytotoxic activity could be detected after *in vitro* stimulation at 12 months, but not at 24 or 30 months.[58]

Figure A.3 illustrates the proportion of patients detected to be IgG positive over the first three years post-symptom onset.

Figure A.3 Proportion IgG positive over time following SARS-CoV infection



Of the four studies that followed patients for three to six years, in general, antibody levels were reported to decrease over time. One study reported a decline in SARS-specific IgG antibody titres and neutralising antibodies with IgG GMTs dropping from 244 at month four to 28 at month 36 (that is, study end-point) and neutralising antibodies dropping from 1,232 at month four to 32 at month 36.[8] Another study reported that SARS-CoV–specific IgG antibodies were detectable in >90% of patients at two years follow-up, but at three years, approximately 50% of the convalescent population had no detectable SARS-CoV–specific IgG. IgM became undetectable at approximately 90 days.[88] In another study, only two of 23 patients maintained a low level of SARS-CoV-specific IgG antibodies at six years post-infection.[81] However, memory T cell responses to a pool of SARS-CoV S peptides were identified in the majority (60.9%) of recovered patients. There was evidence to suggest that the memory T cell response was correlated with clinical severity.[81] No SARS-CoV antigen-specific memory B cell responses were detected. Of note, a fourth study reported that SARS-CoV-specific antibodies could be detected at high titres through three years follow-up using ELISA with RBD-based ELISA, while the positivity rate was only 42% using a commercially available viral lysate-based ELISA kit, suggesting that differences in positivity rates reported across studies may be attributable to differences in the sensitivity of the tests used.[9]

Three studies had greater than 10 years follow-up. These studies assessed the long-term duration of IgG,[36] neutralising antibodies[4] and T-cells[68] among SARS-CoV survivors. SARS-CoV specific IgG antibodies against the whole virus were detected for at least 12 years in one study.[134] In general, IgG levels 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).[134] The second study reported on the response of memory T cells, and found that SARS-CoV-specific memory T cells targeted against SARS-CoV structural proteins persisted up to 11 years post-infection in all three recovered patients.[68] SARS-specific T cells were not activated by MERS-CoV peptides suggesting that T cell immunity against SARS-CoV is highly specific and SARS-specific T cells are unlikely to provide cross-protection against infection with other distantly related coronaviruses. The third study found significant levels of anti-SARS CoV-1 neutralising antibodies in recovered patients from nine to 17 years post-infection.[4] However, cross-neutralisation of SARS-CoV sera against SARS-CoV-2 was not achieved. The strong cross-reactivity of N-directed antibodies proved the close relatedness of the two viruses, which should be taken into consideration when developing serological tests and vaccine candidates.

MERS-CoV

Three case series examining the duration of the immune response following MERS-CoV infection were identified, with the longest follow-up 24 months post-symptom onset.[105] Two studies were conducted in Saudi Arabia[2, 105] and one in South Korea.[16] Details of study characteristics can be found in Table 5.

One study (n=9) reported a rigorous antibody response in all survivors who had severe disease, but not in survivors of mild disease.[2] In this study, patients with severe MERS-associated pneumonia had a persistent antibody response detected for more than 18 months after infection, whereas patients with disease confined to the upper respiratory tract or who were asymptomatic had no detectable MERS-CoV antibody response. Similar findings were reported in another study of 11 patients (five with severe disease and six with mild disease) who were followed up for one year.[16] While all had an initial antibody response, the majority of those with mild disease (4/6) had negative results for antibodies using four different assays at one year follow-up, while all five patients with severe disease had positive antibody tests. Antibody titres waned during the first six months after disease onset, especially in patients who had had high antibody titres at 21-50 days after onset. The waning of antibody titres between six months and one year after disease onset was less pronounced.

A third study included 21 patients (14 had samples taken at six months, seven at 24 months), antibody responses were present, but at a lower titre at 24 months compared with those who had samples taken at six months.[105] The difference was not statistically different. Virus-specific CD8+ and CD4+ T cell responses were present at six months and 24 months even in those with mild or subclinical illness.

Appendix 1.3 Research question 6: Immune response and severity of initial disease

Seventeen studies were retrieved that described the impact of the severity of initial infection with SARS-CoV-2 and the immune response.[1, 15, 17, 21, 29, 35, 38, 44, 54, 69, 74, 75, 80, 98, 123, 129, 131] Studies investigated a range of associations, including the potential link between severity of COVID-19 and the seroconversion timing, immunoglobulin titres, antibody levels over time, re-detection positive rate, lymphocyte counts and other pro-inflammatory markers. Unsurprisingly, as the virus has only recently been identified, none described how initial severity impacted the long-term duration of immunity. All were either case series or cross-sectional studies, and 10 of the 17 studies have not yet been peer-reviewed. Overall, eight studies reported a stronger antibody response in severe compared with mild cases, while six reported no or an inverse relationship. Table 8 summarises study characteristics and primary outcome data of included studies.

Eight studies reported that antibody titres were higher in severe compared with mild cases.[29, 35, 54, 69, 75, 98, 123, 129] The first study reported that among 285 patients, whose serum samples were taken in three-day intervals during their hospital stay, IgG and IgM titres in the severe group were higher than in the non-severe group, although a statistical difference was only observed in IgG levels at two weeks.[129] The second study, reporting on one 'mild' case and two 'severe' cases, found that antibody levels were higher following severe infection compared with the mild.[69] The third study reported on 70 Covid-19 patients, 12 of whom were inpatients and 58 'convalescent' patients.[35] After adjusting for other factors associated with antibody levels, patients with more severe symptoms tended to have higher antibody titres than those who were classified as moderate. The fourth study found a delayed but stronger antibody response in critical (n=10) compared with non-critical (n=31) cases.[75] The fifth study compared 20 severe cases with 17 'non-severe' cases, and found that the relative levels of IgA and IgG were markedly and statistically significantly higher in severe cases.[98] In contrast, no statistically significant changes occurred in the levels of IgM between severe and non-severe cases after disease onset. The sixth study, which stratified patients into those with 'good' versus 'poor' recoveries, reported that prolonged IgM positive status was associated with poor recovery.[29]

The seventh study compared six symptomatic patients with eight asymptomatic or 'mild' patients.[54] All of the six symptomatic patients had positive IgG and four had positive IgM responses. None of the eight asymptomatic/mild patients had positive IgM responses and three had negative IgG responses. Patients with prominent symptoms and development of anti-SARS-CoV-2 IgM antibodies had a shorter

duration of positive results and no worsening of clinical conditions compared to those without IgM antibodies. The eighth study reported findings for 67 hospitalised SARS-CoV-2 infected patients with 'severe' and 'non-severe' disease.[123] Patients were classified as 'strong responders' if their peak titre was greater than 2-fold of the cut-off point, 'weak responders' if their peak titres were 1-2 fold of the cut-off point and 'non-responders' if their peak titre was below the cut-off point. The proportion of strong responders was significantly higher and proportion of weak responders significantly lower in patients with severe disease than patients with non-severe disease. IgM and IgG appeared earlier and were continuously significantly higher in patient with severe disease compared with those with non-severe disease. A higher proportion of non-severe cases had cleared the virus at day seven than severe patients (by RT-PCR). IgM was detectable in severe cases at 11.6 days (+/- 3 days) after illness onset compared with 14 days (+/- 5.3 days) in non-severe cases, and IgG was detectable in severe cases 13.4 days (+/- 4 days) after illness onset compared with 15.3 days (+/- 5.7 days) in non-severe cases.

Six studies reported antibody findings that were inconsistent with this general trend.[1, 17, 38, 74, 80, 131] One case series compared a 'more severe' case with a 'mild' case as well as three controls (a 'mild', a 'mild/moderate' and a 'negative' control).[17] Patients with mild symptoms displayed a much stronger IgA response soon after onset of symptoms that decreased seven to 14 days later, with the more severe case showing a delayed, but eventually very strong SARS-CoV-2 specific IgA response. A similar, but less pronounced trend was observed for IgG antibodies. The memory B-cell population increased after approximately 15 days post onset in both cases, but persisted in the severe case to day 32. A further two studies found that there was no association between antibody titres (IgM/IgG) and disease severity.[1, 74] A fourth study found that while higher levels of IgG were found in severe cases compared with non-severe, lower levels of IgM were found in severe cases.[38] A fifth study, comparing 'non-ICU' with 'ICU' patients, reported that N- and S-specific IgM and IgG (N-IgM, N-IgG, S-IgM, S-IgG) in non-ICU patients increased after symptom onset, but that in ICU patients, the dynamic patterns of N- and S-IgM and IgG were more erratic.[80] S-IgG was significantly higher in non-ICU patients than in ICU patients in the third week, however, in contrast, N-IgG was significantly higher in ICU patients than in non-ICU patients. The sixth study did not identify a strong association between seroconversion and disease severity.[131] However, the timing of seroconversion appeared to differ between the groups. Of the non-severe cases, 27.2% seroconverted within one week; 63.6% within two weeks; 81.8% within three weeks and 100% within six weeks, whereas all severe cases seroconverted within two weeks. In addition, only one (20%) out of five asymptomatic cases generated SARS-CoV-2 specific antibody responses, and this patient did not seroconvert until week three of her diagnosis. For 72.7% of non-severe cases, the

first detection of antibody responses occurred during the period when their swab samples converted to RNA negative, suggesting that antibody responses might facilitate viral clearance especially in non-severe cases. Of note, three out of five severe cases generated viral specific IgG responses prior to viral clearance. Well-maintained antibody responses were observed for all seroconverted individuals for at least six weeks.

The association between lymphocyte counts (CD4+ and CD8+ subsets) and the severity of infection was investigated in two studies.[38, 62] In both studies, authors reported that CD4+T cell and CD8+ T cell counts were 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 reported that CD3+, B cell (CD19+) and NK cell (CD16+56+) counts were significantly lower in severe cases.[38] This study also reported a negative correlation between levels of TNF-α, IL-4, IgG and C3 and the counts of T cell in severe cases.

The association between the detection rate of viral RNA in blood and anal swab specimens and disease severity (patients classified as either mild or severe) was investigated in one study.[15] In the blood detection cohort, six cases had detectable virus in the blood, all of which were classified as severe; 51 had no virus detectable in the blood of which only 12 (23.5%) were classified as having severe disease. In the anal swab cohort, 11 of 28 were anal swab positive, eight of which (72.7%) were classified as having severe disease. This was significantly higher than that those who were anal swab negative (n=17), only 4 (23.5%) of which were classified as severe disease. The authors noted that detectable SARS-CoV-2 viral RNA in blood is a strong indicator for clinical severity.

Finally, the association between re-detection positive and severity of initial disease was investigated in two studies.[21, 44] In the first study, authors found that 36.7% (11/38) of re-detected positive patients had a disease course characterised by mild initial symptoms. The percentage was significantly higher than what was seen among non-re-detected positive patients (12.7%, 19/204, $p<0.01$). Additionally, there were no re-detected positive cases in patients with severe initial infection. In the second study, mild or moderate cases were found to be more likely to re-present with RT-PCR positivity post-discharge.[44] Through mathematical modelling, elevation of serum concentrations of cholinesterase, calcium and eGFR were found to be predictors of recurrence of RT-PCR positivity.

Appendix 1.4: Tables of study characteristics and primary outcomes – questions 1, 2 and 6 (SARS-CoV-2) and question 3 (SARS-CoV and MERS-CoV)

Table 5 Rate and or timing of IgG/IgM detection following acute SARS-CoV-2 infection

Author DOI Country Study design	Virus type Test performed	Population Patient demographics	Primary outcome results	Comments
Rate/timing of seroconversion				
Adams 2020[1] 10.1101/2020.04.15.20066407 UK Case series	SARS-CoV-2 ELISA and RT-PCR (used as reference test) Compared to 9 commercially available lateral flow immunoassay (LFIA) devices Plasma samples. RT-PCR from upper respiratory tract (nose/throat) swab Acute samples were collected from patients a median 10 (range 4-27) days from symptom onset (n=16), and from recovering healthcare workers	N=40 adult positive for SARS-CoV-2 by RT-PCR. N=142 controls For SARS-CoV-2 patient: Age mean 60 (range 22-95) Severity: Mild 26(65%), Severe 4(10%), critical 9(22.5%), 1 asymptomatic (2.5%) N=18 convalescent cases (>28 days from symptom onset). N=16 case (≤ 28 days from symptom onset). N=6 convalescent health care worker (≤ 28 days from symptom onset)	**IgM/IgG seroconversion:** 40 SARS-CoV-2 samples and 50 controls tested by ELISA. 34/40 positive for IgG, other 6 where taken within 9 days of symptom onset. All samples taken >= 10 days after symptom onset positive for IgG. IgM positive in 28/40 samples (70%). No patient was IgM positive and IgG negative. N=9 patients had samples from between 50 and 60 days after onset of symptoms. In these 9 patients IgM (5 out of 9) and IgG (9 out of 9) still present. N=2 patients had samples ≥60 days, both were still positive. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Considering the relationship between IgM and IgG titres and time since symptom onset, univariable regression models showed IgG antibody titres rising over the first 3 weeks from symptom onset. The lower bound of the pointwise 95%CI for the mean expected titre crosses OD threshold between days 6-7. However, given sampling variation, test performance is likely to be optimal from several days later. IgG titres fell during the second month after symptom onset but remained above the OD threshold (at 60 days from symptom onset). No temporal association was observed between IgM titres and time since symptom onset.	Not peer reviewed; medRxiv

	median 13 [range 8-19] days after first symptoms; (n=6). Convalescent samples were collected from adults a median 48 [range 31-62] days after symptom onset and/or date of positive throat swab (n=18)		**Other outcome:** There was no evidence that SARS-2-CoV severity, need for hospital admission or patient age were associated with IgG or IgM titres in multivariable models	
Baettig 2020[5] Switzerland Case series/ follow-up study	SARS-CoV-2 Immunochromatography rapid test	N=2 members of Swiss Armed Forces; 54 close contacts Cases were mild N=One test each 14 days after the first person was diagnosed	The two confirmed cases were seropositive IgM/IgG after 14 days None of the 54 contacts tested positive for antibodies	Peer-reviewed; BMJ Health
Burbelo 2020[7] 10.1093/infdis/jiaa273 Case series USA	SARS-CoV-2 Luciferase immunoprecipitation assay systems (LIPS) with and without heat activation. A minimum of >14 days between onset of symptoms and time of blood	100 samples from SARS-CoV-2 anonymised patients 35 PCR confirmed cases and 10 subjects with Covid-like symptoms or household contacts of persons with SARS-CoV-2 (not tested by PCR). 32 blood donors who donated samples before 2018 were used as	**Rate and timing of seroconversion:** Antibodies (ABs) to nucleocapsid and spike appearing between day 8 and 14 after initial symptoms. Immunocompromised patients had a delayed AB response compared to immunocompetent patients. Seropositive anti-nucleocapsid ABs were detected in 35/35 samples (sensitivity and specificity of 100%). Seropositive anti-spike Abs were detected in 32/35 samples (sensitivity and specificity of 91%). Evaluation of ≤ 14 days showed reduced sensitivity but specificity was maintained. (Sensitivity for anti-nucleocapsid 51% (33/65)	Peer-reviewed; The Journal of infectious diseases

	collection in the SARS-CoV-2 PCR positive patients.	controls. 87% confirmed cases male: median age 44 years (range 32-50 years) Subgroup analysis of 6 patients, 3 immunocompromised and 3 immunocompetent.	andante-spike 43% (28/65)). Thus, detection of Abs against anti-nucleocapsid is more sensitive than anti-spike ABs. 9 of 10 suspected cases (including contacts with confirmed cases) were seronegative and 1 contact was seropositive for both nucleocapsid and spike ABs. **Duration of immunity:** Not reported.	
Brandstetter 2020[6] 10.1111/pai.13278 Germany Case series Described in paper as cross sectional	SARS-CoV-2 ELISA (EUROIMMUN AG, Lubeck, Germany) Blood sample	201 study participants, 31 (15.4%) were SARS-CoV-2 cases; Following outbreak in hospital, 36 staff tested positive, 34 with mild or moderate forms and 2 asymptomatic. Socio-demographic information and symptoms collected by structured interview and securely documented in a qnome database (www.qnome.eu)	**Rate and timing of seroconversion:** 80% of SARS-CoV-2 cases developed some specific antibody response (IgA and IgG) approximately 3 weeks after symptom onset. Subjects in the non-SARS-CoV-2 groups had also elevated IgG (1.8%) and IgA (7.6%) irrespective of contact history with cases. Within the SARS-CoV-2 cases 22.5% showed no antibody response, IgG was elevated in 75% and IgA in 74.2%. Overall, 77% of cases had some kind of antibody response. 14 individuals (8.2%) in the non-SARS-CoV-2 group (i.e. exposure only) showed 'some kind of' elevated IgG or IgA. IgG was borderline in 3 individuals (2 were close contacts) while borderline or elevated IgA was measure in 13 individuals. It cannot be ruled out that especially these IgA responses were directed against common cold Corona viruses, as results from the manufacturer indicate that approximately 10% of sera from the era before SARS-CoV-2 showed unspecified IgA measurements. Timespan between onset of symptoms and antibody test ranged from 15 to 28 days (median 22, IQR 20-24) **Duration of immunity:** Not reported Other:	Peer-reviewed; Pediatric allergy and immunology

			Antibody responses neither related to the degree of exposure to SARS-CoV-2 nor to the duration in which SARS-CoV-2 was still observable in the throat by RT-PCR testing after convalescence. Level of IgG was not related to the severity of the disease.	
Dong 2020[25] 10.1101/2020.03.17.20036640 China Case series	SARS-CoV-2 RT-PCR and CT to confirm infected. ELISA for IgG/IgM (not commercial) Neutralising antibody assay Interferon gamma ELISpot FACS staining	N=12 SARS-COV-2 patients recently virus free and discharged from hospital. 6 were recently discharged and 6 had been discharged for 2 weeks(follow-up patients) n=4 controls 2 patients showed lymphopenia. Seven patients were female. Age mean 41 years (range 26 to 68)	**IgG:** Authors report high titers of IgG antibodies recorded at 2 weeks post-discharge **IgM** Seroconversion of IgM not reported	Not peer reviewed; medRxiv
Demey 2020[20] 10.1016/j.jinf.2020.04.033 France Case series Dynamic profile for the detection of anti-SARS-CoV-2 antibodies using four immunochromatographic assays	SARS-CoV-2 4 serological tests compared: Biotime, Autobio, ISIA Biotechnology and Biolidics	22 RT-PCR positive patients Demographics not described	Study was designed to evaluate four serological tests but reports timing of conversion and so was included in this evidence summary. **Rate and timing of seroconversion:** Mean antibody detection time was 8 days since onset of symptoms (for Autobio and Biotime (IgG or IgM)), 9 days for Biolidics (IgG or IgM) and 9 and 10 days for ISIA for IgM and IgG respectively. IgG was detected in all patients on day 15 since onset of symptoms, while IgM was not detected in 3 patients with Autobio and ISIA. IgM was detected before IgG in 1,1, 7 and 0 patients with the Biotime, Autobio, ISIA and Biolidics assay respectively. In other cases, IgM was detected at the same time as IgG. **Duration of immunity:** Not reported	Peer-reviewed; The Journal of infection

Dittadi 2020[22] 10.1101/2020.05.19.20099317 Italy Case series	SARS-CoV-2 Two step chemilumisecence immunoassay (CLIA) Maglumi 800, Snibe, China)	46 symptomatic subjects with suggestive symptoms and positive PCR except 4 included with negative PCR but 'almost certain' clinical diagnosis. 35 controls. Samples were analysed before 15 days of illness (Group 1) and after 15 days (Group 2)	**Rate and timing of seroconversion:** IgG positivity was 100% at day 15 after disease onset. IgM did not exceed 77% of cases by day 15. None of the controls tested positive for IGM or IgG. Overall, 61% of cases were positive for IgM and 85.7% were positive for IgG. • Group1, 71.1% were positive for IgG, with 44.7% positive for IgM. • Group 2 100% were positive for IgG, with 76.9% positive for IgM. In 9 cases with at least 3 samples each, IgG tended to increase and plateau after 15 days **Duration of immunity:** Not reported.	Not peer-reviewed
Du 2020[26] China Case series/follow-up study DOI: 10.1002/jmv.25820	SARS-CoV-2 Testing details not reported	N=60 patients N=10 had repeat samples No further patient demographics reported	**IgM** Approx. 6-7 weeks after symptom onset: 47/60 were positive (78%) IgG Approx. 6-7 weeks after symptom onset: 60/60 were positive (100%) IgG titres higher than IgM titres Serial samples (approx. 6-7 and 7-8 weeks after symptom onset): 10 patients were tested twice (1 week apart); both titres showed a decrease, with the IgG titre being greater than the IgM titre.	Peer-reviewed; Letter to the editor (Medical Journal of Virology)
Fafi-Kremer 2020[27] France Case series	SARS-CoV-2 2 tests used: a rapid immunodiagnostic	162 hospital staff who had recovered from mild forms of PCR-confirmed SARS-CoV-2 – 160 had not required	**Rate and timing of seroconversion:** • Rapid immunodiagnostic test detected antibodies (Abs) in 95.6%. • S-Flow detected ABs in 99.4% (The one patient the S-Flow did not detect did not have ABs detected by the rapid test either).	Not peer-reviewed

DOI: 10.1101/2020.05.19.20101832	test (Biosynex) and the S-Flow assay Blood samples Median time from symptom onset to testing 24 days (IQR, 21-28, range 13-39)	hospitalisation and were included in the analyses. Median age 32 years (IQR 26-44), 31.2% male.	• Neutralising ABs were detected in 79%, 92% and 98% of samples collected on day 13-20, 21-27 and 28-41 after symptom onset respectively. • At 21-27 days IgM the highest seropositivity rate by rapid testing was obtained (N=75/83; 90.4%); after 28 days highest IgG seropositivity was obtained (N=41/48; 85.4%); S-flow 83/83 (100%)	
Fu 2020[29] 10.1101/2020.04.03.20051763 China Retrospective case series	SARS-CoV-2 Immunogold ICT device (INNOVITA Biotechnology Co. Ltd. Tangshan, China) 41 patients tested month after admission; 14 tested a second time (timing not stated)	50 severe patients; 27 male, 23 female; median age 64 years (IQR, 37-87); more than half had underlying disorders (hypertension 20%; diabetes 24%, CHD 22%;COPD 6%) 41 of 50 patients divided into 'good' n=12 (29.3%) or 'poor' n=29 (70.7%) recovery according to their clinical outcome and those with lung lesions were divided into 'partial resolution patient group' and 'significant resolution patient group' 14 patients were tested a 2nd time and 1 (7.1%) was in good recovery group and 13 (92.8%) were in poor recovery group	**IgM/IgG:** IgM/IgG positive rates differed between mild/severe groups and varied with day after onset of disease Day 53-55: 100% (N=5/5) positive for IgG	Not peer-reviewed

		Severity defined according to Chinese management guideline for SARS-CoV-2 (version 5.0)		
Gao 2020[33] China Case series DOI: 10.1097/CM9.0000000000000820	SARS-CoV-2 Chemiluminescent immunoassay (CLIA), Gold immunochromatographic assay (GICA), and Enzyme-linked immunosorbent assay (ELISA)	N=22 Median age: 40 years (4-72) Female n=8; Male n=14	**Number of serum samples and time of sampling** N=37 (note: some missing) days 1-7 after onset: n=10 days 8-14 after onset: n=13 days 14-24 after onset: n=14 **IgM (at least 1 positive by CLIA/GICA/ELISA)** Seroconversion rate and timing: Early (1-7 days): 60% (6/10) Middle (8-14 days): 54% (7/13) Late (14-24 days):79% (11/14) **IgG (at least 1 positive by CLIA/GICA/ELISA)** Seroconversion rate and timing: Early (1-7 days): 50% (5/10) Middle (8-14 days): 77% (10/13) Late (14-24 days): 100% (14/14)	Accepted to Chinese Medical Journal (publish before print)
Grzelak 2020[34] France Case series	SARS-CoV-2 2 in-house ELISA assays: ELISA-N; ELISA triS. Flow cytometry S-flow assay; LIPS assay.	N=51 hospitalised patients Cases were severe/critical N=161 samples (taken at different time points)	Antibody prevalence was 61% (65-72%). Results from 5 patients with more than 5 available samples over time, suggest that seroconversion developed between day 5 and day 14 after disease onset	Not peer-reviewed
Guo 2020a[35] DOI: 10.1093/cid/ciaa310 China	**SARS-CoV-2** Deep sequencing or a qPCR assay for diagnosis of cases Antibody testing by ELISA-based assay on the recombinant	N=101 Two cohorts: confirmed positives (N=43) [deep sequencing or a qPCR assay] and probable positive (N=58) [suspected to be infected with SARS-CoV-2 based	**Timing of samples (confirmed or probably positive):** Total samples=208 Day 1-7: N=41 Day 8-14: N=84 After day 14: N=83 The appearance of IgM, IgA, and IgG antibodies against SARS-CoV-2 was positive as early as day 1 after the symptom onset	Peer-reviewed; Clinical Infectious Diseases Corrected proof

Case series/follow up	viral nucleocapsid protein ELISA cut-off values: Authors determined the mean values and SDs of plasma from healthy individuals. The optimal coating concentration of antigen and optimal plasma dilutions were 0.1 μg/mL and 1:200, respectively. The cutoff values were determined by calculating the mean absorbance at 450 nm (A450) of the negative sera plus 3-fold the SD values, which were 0.13, 0.1, and 0.30 for IgM, IgA, and IgG, respectively	on clinical manifestation, chest radiography imaging, and epidemiology but no virus were detected by deep sequencing or a qPCR assay] 208 plasma samples collected	The times of detection of IgM, IgA, and IgG against SARS-CoV-2 ranged from day 1 to 39 post-symptom onset Seroconversion rate & timing: **IgM** and **IgA**: 188/208 (90.4 %) and 194/208 (93.3%) Of acute phase samples, IgM (35/41, 85.4%) and IgA (38/41, 92.7&) antibodies were both detectable at a median of 5 days (IQR, 3–6 days) **IgM titres** Days 0-7: GMT 400 Days 8–14: GMT 535 (significant increase p=0.000) Days 15-21: GMT 536.31 (no significant increase p=0.992) Day >21: GMT 565.69 (no significant increase p=0.719) **IgA titres** Days 0–7: GMT 400 Days 8–14: GMT 597.24 (significant increase p=0.000) Day 15-21: GMT 723.28, no significant increase p=0.156) Day > 21: GMT 831.41 (no significant increase p=0.538) **IgG seroconversion rate and timing**: 162/208 (77.9 %) Median seroconversion timing post-symptom onset: Day 14 (IQR, 10–18 days) The times of detection of IgM, IgA, and IgG ranged from day 1 to 39 post-symptom onset **IgG titres** Day 0–7: GMT 490.45 Days 8–14: GMT 1325.6 (significant increase p=0.000) Days 15-21: GMT 2690.87 (significant increase p=0.000) Day 21: GMT 2974.83, (plateaued p=0.72)	
Han 2020[37] China Case series	The SARS-COV2 nucleic acid test was conducted via real-time RT-PCR	3 cases who were all from the same family	Case 1 • 47-year-old female	Peer-reviewed: Clin Immunol

DOI: 10.1016/j.clim.2020.108413	according to the protocol of the nucleic acid kit (Kangwei Century Biotechnology Company, China). The SARS-CoV2 antibody kit was used to test for specific IgM and IgG antibodies (Guangzhou Wonfo Biological Technology Co, Ltd., China) via colloidal gold immunochromatography		• PMHx: Systemic lupus erythematosus and had been taking oral prednisone (7.5 mg/d) since her diagnosis • Admitted for testing due to close contact testing positive for SARS-CoV-2 • SARS-CoV2 nuclei acid test from nasopharyngeal swabs was negative, but IgM and IgG antibodies were positive • She was given antiviral treatment, including 0.2 g BID of Abidol orally and 5 million IU of interferon nebulisation. • Ground-glass opacity changes were found in the right upper lung. She was given extra piperacillin sodium tazobactam sodium (4.5 TID), and then glycyrrhizin (150 mg QD). CT showed improvements and she was discharged Case 2 • 81-year-old male • Symptomatic • SARS-CoV-2 nucleic acid test was positive by both nasopharyngeal swabs and sputum on 27 February • IgM and IgG specific antibodies were positive 10 days post-symptom onset Case 3 • 44-year-old female • Symptomatic • SARS-CoV-2 nucleic acids and specific IgG and IgM antibodies positive 10 days post-symptom onset	
Haveri 2020[114] Finland Case study	SARS-CoV-2/Finland/1/2020 virus strain Immunofluorescence assays (IFA)	Female Chinese tourist in her 30s	While the antibodies were undetectable on Day 4 after onset of symptoms, IgG titres rose to 80 and 1,280 and IgM titres to 80 and 320 on Days 9 and 20, respectively.	Peer-reviewed; Eurosurveillance

DOI: 10.1016/j.clim.2020.108413				
Hou 2020[40] China Case series DOI: 10.1002/cti2.1136	SARS-CoV-2 IgM and IgG antibody levels were assessed via chemiluminescence immunoassay (YHLO-CLIA-IgG, YHLO-CLIAIgM kits supplied by YHLO Biotech Co. Ltd Shenzhen, China) Confirmed diagnosis of SARS-COV-2 was defined as a positive result using real-time RT-PCR detection from routine nasal and pharyngeal swab specimens.	N=338 patients N=171 (50.6%) males N=167 (49.4%) females. Mean age = 62 (SD: 16) Patients were classified into 3 groups: mild (64 cases, 18.9%), severe (199 cases, 58.9%) and critical (75 cases, 22.2%). The mild cases are those with fever, typical symptoms and pneumonia on chest radiography. Severe cases need to meet one of the following criteria: (1) respiratory distress (respiration rate ≥ 30 times/min); (2) blood oxygen saturation (SpO2) ≤ 93% in resting state; and (3) arterial partial pressure of O2 to fraction of inspired oxygen (PaO2/ FiO2) ratio ≤ 300 mmHg. Critical cases meet one of the following criteria: (1) respiratory failure requiring mechanical ventilation; (2) shock; and (3) multiple organ dysfunction needing	**IgM seroconversion rate** IgM was detected in 81.3% (mild), 82.9% (severe) and 82.7% (critical) **IgG seroconversion rate** IgG was detected in 90.6% (mild), 92.7% (severe) and 88% (critical) **Timing** • 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) • IgM levels increased during the first week after SARS-CoV-2 infection, peaked 2 weeks and then reduced to near-background levels in most patients. • IgG was detectable after 1 week and was maintained at a high level for a long period (>48 days). **Severity of infection** The positive rates of IgM and/or IgG antibody detections were not significantly different among the mild, severe and critical disease groups. Severe and critical cases had higher IgM levels than mild cases, whereas the IgG level in critical cases was lower than those in both mild and severe cases. **Titres** • The levels of IgM in the severe and critical groups were higher than those in the mild group (severe vs. mild, P = 0.0084; critical vs. mild, P = 0.031).	Clinical & Translational Immunology

		intensive care unit (ICU) treatment.	• In contrast, the levels of IgG in the critical group were lower than those in either the mild or severe groups (critical vs. mild, P = 0.0397; critical vs. severe, P = 0.026)	
Hu 2020[42] China Case series DOI: 10.1101/2020.04.20.20065953	SARS-CoV-2 IgM and IgG antibody levels were assessed via Magnetic Chemiluminescence Enzyme Immunoassay (MCLIA) kit supplied by Bioscience Co., Ltd (Chongqing, China) Testing of SARS-CoV-2 IgG and IgM antibodies was performed every 3 days post-symptom onset Discharge criteria: categorised into mild, moderate, severe and critical types by clinical manifestations. Discharge criteria included: 1) normal temperature lasting over 3 days; 2) significant improvement of respiratory	N=221 patients N=86 female and N=135 male patients Average age: 47.8 (47.8±15.1) years N=181 mild and moderate cases (the mild group); N=40 severe and critical cases (the severe group).	**IgM seroconversion rate** 73.6% detection rate IgM at day 13-15 (39/53) **IgG seroconversion rate** • Detection rates reached highest on days 22-24 for IgG which was 100% (25/25) • IgG 100% at end of follow-up (day 46-51) (11/11). **Timing** Median seroconversion time of 17.38 days (IQR 4.39-36.4) for IgM and 5.59 days (IQR 0.73-13.65) for IgG. **Titres** Significantly higher concentration of IgG in critically ill patients than in those with mild to moderate disease (P=0.027). **Association antibody levels and disease progression** • The IgG and IgM levels on day 16-21 after symptom onset was not correlated with the length hospital stay, the duration of positive virus detection, the duration of fever or the changes in pulmonary inflammation. Similarly, there were no correlation between the outcome (exacerbation or improvement) and the IgG/IgM levels. **Re-detected positive** • There were 74 recovered patients who met the discharge criteria and were discharged to isolation with medical observation for 14 days, and 39 (53%) of them presented with re-detected 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. • Within 7 days post-discharge, 40 recovered patients demonstrated a median decrease of 21.2% in IgG regardless of	Not peer-reviewed

	symptoms; 3) significant improvement of chest radiology; 4) negative nucleic acid testing in 2 consecutive respiratory specimens collected with an interval of at least 1 day.		re-detectable positive nucleic acid, indicating instant decrease of IgG after recovery. Long-term protection provided by IgG requires further study.	
Huang 2020b[43] China Case series DOI: 10.1101/2020.04.22.20071258	SARS-CoV-2 RT-PCR for confirmation of cases Details on testing platform for antibodies not reported	**Population setting:** 33 SARS-COV-2 confirmed hospitalised patients **Demographics:** *Mix of adults and children* *Sex:* Male, 17 (51.5%) Female, 16 (48.5%) *Age:* Median: 47 years (range, 2-84) **Clinical characteristics:** *Presentation* Fever, 19 (57.6%) Cough, 17 (51.5%) Sputum production (expectoration), 4 (12.1%)	The median (IQR) seroconversion time of anti-S IgM, anti-RBD IgM, and anti-N IgM was 10.5 (7.75-15.5) days, 14 (9-24) days, and 10 (7-14) days, respectively. The median (IQR) seroconversion time of anti-S IgG, anti-RBD IgG, and anti-N IgG was 10 (7.25-16.5) days, 13 (9-17) days, and 10 (7-14) days, respectively.	Not peer-reviewed

		Fatigue, 3 (9.1%) Diarrhoea, 3 (9.1%) **SARS-COV-2 Clinical syndromes (National Health Commission of the People's Republic of China definition)** Moderate: 31 (93.9%) Severe: 2 (6.1%)		
Jia 2020[46] China Case series/follow-up study DOI: 10.1101/2020.02.28.20029025.t	SARS-CoV-2 Primary screening of pharyngeal swab nucleic acid amplification was performed by 2 kits of 6 companies (DAAN, Sansure Biotech, BGI, ShangHai ZJ Biotech, Geneodx, Biogerm) IgM/IgG antibodies kit were detected on Time-Resolved Immunofluorescence Analyzer by Fluorescence immunochromatographic assay method (Beijing Diagreat Biotechnologies	N=24 patients tested positive for SARS-CoV-2 Other demographic details not provided	From the time of the first exposure to SARS-COV-2 infection to the nucleic acid test, the time ranged from 1 day to 34 days **IgM** Positivity rate = 79% (19/24) (once-off, time range: 1 to 34 days) **IgG** Positivity rate = 67% (16/24) (once-off, time range: 1 to 34 days)	Not peer-reviewed

	Co., Ltd, Lot: 20200214) Cutoff of IgM and IgG were 0.88 and 1.02 fluorescence intensity (Flu) units			
Jiang 2020[47] China Case series DOI: 10.1101/2020.03.20.20039495.	SARS-CoV-2 Proteome microarrays	N=29 (and 21 controls) Mean age: 42.3 (SD: 13.8) Female: 16; Male: 13. Severity: 3 mild cases; 26 'common cases'	**Samples:** N=29 (patient group); Collected mean 22 days after onset. **Results:** 100% seroconversion for IgG and IgM. The level of S1 IgG positively correlates to age and level of lactate dehydrogenase, especially for women. The level of S1 IgG negatively correlates to lymphocyte percentage.	Not peer-reviewed
Ju B 2020[50] China Prospective Case series DOI: 10.1101/2020.03.21.990770	SARS-CoV-2 ELISA	N=8 patients infected with SARS-CoV-2 in January 2020 Age range: 10 to 66 years	• The isolation and characterisation of 206 viral Spike protein receptor-binding domain (RBD)-specific monoclonal antibodies (mAbs) derived from single B cells of eight SARS-CoV-2 infected individuals was performed • Both clone types demonstrated impressive binding and neutralising activity against pseudovirus and live SARS-CoV-2 • No cross-reactivity with SARS-CoV or MERS was found.	Not peer-reviewed
Lee 2020[115] Taiwan Case study DOI: 10.1016/j.jmii.2020.03.003	SARS-CoV-2 ALLTEST 2019-nCoV IgG/IgM Rapid Test Cassette, Hangzhou ALLTEST Biotech Co., Ltd. Hangzhou, China	One 46-year old woman after returning from Macau to Taiwan	IgG antibody was measured in seven serum samples (obtained on the hospital day 2, 3, 7, 9, 13, 20, and 23) from the patient. The SARS-CoV-2 IgG antibody was detected in five serum samples since the hospital day 7 (illness day 11) IgM not reported/not tested	Journal of Microbiology, Immunology and Infection Short communication
Liu 2020a[59]	SARS-CoV-2	N= 238 admitted hospital patients with confirmed or	IgM and or IgG seropositivity rate in confirmed patients = 83.0% (127/153)	Published

China Case series/follow-up study DOI: 10.1101/2020.03.06.20031856	SARS-CoV-2 RNA was detected by real time RT-PCR on pharyngeal swab specimens ELISA assay for IgM and IgG antibodies against N protein of SARS-CoV-2 using ELISA kit (Lizhu, Zhuhai, China)	suspected SARS-CoV-2 infection Among the 238 recruited patients, 153 patients were laboratory-confirmed cases. The median age was 55 years (IQR, 38.3-65), and 138 (58.0%) of the patients were men	Seroconversion timing: After 10 days, seroconversion rate rose to >80% (IgM and or IgG)	Microbes and infection
Liu 2020b[60] China Case series DOI: https://DOI.org/10.1101/2020.03.28.20045765	SARS-CoV-2 SARS-CoV2 antibody detection kit	N=133 Median age: 68 Female: 63; Male: 70 44 moderate cases (22 males 22 females, median age 67.5 [IQR 64-71.75]), 52 severe cases (28 males 24 females, median age 68 [IQR 61.25-74]), and 37 critical cases (20 males 17 females, median age 70 [IQR 60-76.5])	**IgM** Seroconversion rate by severity of disease: Moderate: 79.55% Severe: 82.69% Critical:72.97% **IgG** Seroconversion rate by severity of disease: Moderate: 93.18% Severe:100% Critical: 97.30%	Not peer-reviewed
Long 2020[147] China Multi-centre cross-sectional study and a single-centre follow-up study	RT-PCR assay for nasal and pharyngeal swab specimens IgG and IgM antibody against SARS-CoV-2 in plasma samples were tested using	N=285 patients in multi-centre cross sectional study including N=63 patients in single-centre follow-up study Median age: 47 years (IQR, 34-56 years) 55% were males	**Seroconversion rate & timing** Of 262 cases with clear records on symptom onset: • IgG seroconversion rate reached 100% at around 17-19 days after symptoms onset • IgM seroconversion rate reached its peak of 94.1% approx. 20-22 days after symptoms onset **Titres:**	Not peer-reviewed

DOI: 10.1101/2020.03.18.20038018	Magnetic Chemiluminescence Enzyme Immunoassay (MCLIA) kit supplied by Bioscience (Chongqing) Co., Ltd, China	262/285 patients had clear records of time of symptom onset 39/285 cases were classified as severe or critical illness condition	▪ During the first 3 weeks of symptoms onset, there was an increase in the titre of IgG and IgM antibodies. However, the antibody level IgM showed a slight decrease after 3 weeks ▪ Severe cases (N=20) had higher antibody titres than non-severe Follow-up study (N=63 patients) Median day of seroconversion for both lgG and IgM was 13 days (after symptom onset)	
Lou 2020[146] China Cohort study DOI: 10.1183/13993003.00763-2020	SARS-CoV-2 ELISA, LFIA, and CMIA assays	N=80 cases and N=300 controls Median age: 55 (range: 45-64) Female proportion: 38.7%	**IgM** Seroconversion rate & timing: 0-7 days: 33.3% 8-14 days: 86.7% 15-24 days: 96.7% Median seroconversion time: 18 days post exposure; 10 days post onset **IgG** Seroconversion rate & timing: 0-7 days: 33.3% 8-14 days: 76.0% 15-24 days: 93.3% Median seroconversion time: 20 days post exposure; 12 days post onset	Published European respiratory journal
Nicastri 2020[118] Italy Case report DOI: 10.2807/1560-	2 real-time RT-PCR on a nasopharyngeal swab confirmed SARS-Cov-2 In house-prepared immunofluorescence (IF) slides and	Italian man in his late 20s Patient isolated for clinical assessment after travel to Wuhan, China. He was in Wuhan from 20 Jan to 3 Feb and isolated in Italy on 6 Feb.	**Seroconversion** Patient was asymptomatic. Exposure could be as early as 20 January. Retrospective analysis of admission sample (17 days after first travel to Wuhan): IF results showed positivity for both IgG and IgM (≥ 1:640 and 1:80, respectively) at the same time point of the first viral RNA positive result. **Re-detectable positive**	Peer-reviewed Eurosurveillance

7917.ES.2020.25.11.2000230	neutralisation test as confirmatory test for antibodies	Patient was asymptomatic (or paucisymptomatic, only had transient mild conjunctivitis and a body temperature of 37.3).	Nasopharyngeal swab was positive every day until day 11, negative day 12 and 13, positive day 14 to 16 and negative day 17 and 18.	
Okba 2020[69] Multisite (Samples from France & Germany) Case series DOI: 10.3201/eid2607.200841	Anti-SARS-CoV-2 S1 IgG and IgA: ELISAs by using β-versions of 2 commercial kits (EUROIMMUN Medizinische Labordiagnostika AG, https://www.euroimmun.comExternal Link) Optical density (OD) detected at 450 nm Virus-neutralising antibodies were tested by using a PRNT50	Serum samples (n=10) collected from 3 PCR-confirmed patients: 2 with mild SARS-COV-2 and 1 with severe SARS-COV-2 in France. For validation testing, samples from Wolfel 2020[87] included (n=31)	• SARS-CoV-2–specific antibody responses in severe and mild cases was detected by using serum samples collected at different times post-onset of disease from 3 PCR-confirmed SARS-COV-2 patients from France • After infection, all 3 patients seroconverted between days 13 and 21 after onset of disease (IgG/IgA) • When tested in a PRNT, serum samples from all 3 patients neutralised SARS-CoV-2 infection. Antibody responses detected by different assays correlated strongly with neutralising antibody response	In press Emerging Infectious Diseases
Padoan 2020a[71] Italy Case series DOI: 10.1016/j.cca.2020.04.026	SARS-CoV-2 Chemiluminescent (CLIA) assay (MAGLUMI 2000 Plus), measuring SARS-CoV-2 specific IgM and IgG and an ELISA measuring specific IgG and IgA antibodies against	The kinetics of IgA-Abs were longitudinally tested in 19 patients (15 males, mean age 65.4 years, SD 14.5, range 22–81 y; 4 females, mean age 63.7 years, SD 7.8, range 53–70 y) for an average follow-up time of 7.5 days (SD 4.9).	• Average levels of IgM and IgA antibodies increased since 6–8 days from the onset of SARS-COV-2. 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. • The values of IgG measured by the 2 assays was comparable and similar. Levels or detection time not reported.	Peer-reviewed Clinica Chimica Acta

	SARS-CoV-2 (Euroimmun Medizinische Laboradiagnostika, Luebeck, Germany)	IgM-Abs kinetics was tested in 51 patients (37 males, mean age 69.1 years, SD 13.5, range 22–89 y; 14 females, mean age 62.6 years, SD 11.0, range 41–82 y) for 4.6 days (SD 4.0)		
Pan 2020[110] China Case series DOI: https://DOI.org/10.1101/2020.03.13.20035428	SARS-CoV-2 ICG strip assay	N=105 patients 48 male, 57 female) Median age: 58 years (range 20-96 years) 134 samples from 105 patients taken	Samples taken at early stage (1-7 days from onset), intermediate stage (8-14 days) and late stage (more than 14 days). **IgM** Seroconversion rate & timing: 1-7 days: 11.1% 8-14 days: 78.6% ≥15 days: 74.2% In total: 55.8% **IgG** Seroconversion rate & timing: 1-7 days: 3.6% 8-14 days: 57.1% >15 days: 96.8% In total: 54.7%	Peer-reviewed Journal of Infection
Solodky 2020[78] France Case series DOI: 10.1016/j.annonc.2020.04.475	SARS-CoV-2 Toda Cornoadiag (TODA Pharma, Strasbourg, France) – rapid lateral flow immunoassay (LFIA) Blood sample	85 cancer patients suspected of having SARS-CoV-2 compared with 244 health care workers (HCW) 10 (12%) of cancer patients tested PCR positive for SARS-CoV-2 and 14 (5.4%) of HCW tested PCR positive.	**Rate and timing of seroconversion:** Of 10 cancer patients who tested positive for SARS-CoV-2, 5 had positive antibody tests. 3/10 positive cancer patients (30%) had detectable antibodies 15 days after clinical start of the infection. 2 of the 75 remaining cancer patients screening negative for PCR had detectable SARS-Cov-2 IgG. 6 of the 7 sero-negative cancer patients had received cytotoxic therapy or major surgical intervention in the previous weeks. 14 of 244 HCW tested positive with PCR. 10 of these (71%) had detectable antibodies 15 days or later than clinical symptoms. 3 of	Letter to the editor

			the remaining 230 HCWs had detectable antibodies but negative PCR. 2 of these reported possible SARS-CoV-2 symptoms in the previous weeks. **Duration of immunity:** Not reported. **Other:** Cancer patients had a lower detection rate of SARS-CoV-2 antibodies 15 days or later after symptoms and PCR positive testing. Anti-SARS-CoV-2 antibodies were more often undetectable in patients receiving cancer treatments in the month prior to testing.	
Sun 2020[80] China Case series DOI: 10.1080/22221751.2020.1762515	SARS-CoV-2 ELISA Between 3 and 28 days after symptom onset Blood samples	38 (27 non-ICU patients and 11 ICU patients) (131 blood samples and 16 samples from healthy volunteers) Non-ICU patients median age 44 years (IQR 32 – 56 years; 48% female ICU patients median age 58 years (IQR 49=69.5); 9% female	**Rate and timing of seroconversion:** *N-IgM (non-ICU patients)* Week 1: 41.7% Week 2: 73.7% Week 3: 73.7% *S-IgM (non-ICU patients)* Week 1: 41.7% Week 2: 68.4% Week 3: 73.7% *N-IgG (non-ICU patients)* Week 1: 41.7% Week 2: 84.2% Week 3: 100% *S-IgG (non-ICU patients)* Week 1: 58.3% Week 2: 78.9% Week 3: 100% *N-IgM + S-IgM + N-IgG + S-IgG (non-ICU patients)* Week 1: 75%	Emerging microbes & infections

			Week 2: 94.7% Week 3: 100% N-IgG/S-IgG ratio was significantly higher in ICU patients that non-ICU patients throughout the disease course. **Duration of immunity:** Reported up to 3 weeks **Conclusions** • Combined detection of N and S specific IgM and IgG can be useful for detection of SARS-CoV-2 infection in non-ICU patients. • Monitoring the kinetics of S-IgG should help to predict prognosis.	
To 2020[124] Hong Kong, China Cohort study DOI: 10.1016/S1473-3099(20)30196-1.	SARS-CoV-2 Antibody levels detected by Enzyme Immunofluorescence Assay (EIA)	N=23 Median age: 62 years (range 37–75)	For 16 patients with serum samples available 14 days or longer after symptom onset, rates of seropositivity were: • 94% for anti-NP IgG (n=15) • 88% for anti-NP IgM (n=14) • 100% for anti-RBD IgG (n=16) • 94% for anti-RBD IgM (n=15)	Peer-reviewed Lancet J Infectious Disease
Wang 2020d[83] China Case series/follow-up study DOI: 10.1101/2020.04.13.20040980	SARS-CoV-2 SARS-CoV-2–specific antibodies were detected using "New Coronavirus 164 (2019-nCoV) Antibody Detection Kit" (INNOVITA, China)	N=26 15 Female, 11 Male Median age not reported; range was 5 to 72 years All cases mild/moderate	**IgG seroconversion timing:** Mean seroconversion timing: 15.7 days Earliest seroconversion was in 7 days Two patients remained IgG positive at 50 days One SARS-COV-2 patient who did not initially produce SARS-CoV-2-bound IgG successfully cleared SARS-CoV-2, indicating innate immunity may be powerful enough to eliminate SARS-CoV-2	Not peer-reviewed
Wang 2020b[86] China	SARS-CoV-2	N=70 patients N=117 serum samples	**Neutralising Antibodies:**	Not peer-reviewed

Follow-up study/case series DOI.org/10.1101/2020.04.15.20065623	The presence of neutralising antibody was determined with a modified cytopathogenic assay based on live SARS-CoV-2	Mean age: 45.1 years (range 16-84) Female proportion: 58.6% Of the 70 patients enrolled into this study, 58 were recovered and discharged from hospital 1 (1.4%) patient was asymptomatic infected, 22 (31.4%) had mild clinical manifestations, 43 (61.5%) were moderate, and the remaining 4 (5.7%) were in severe condition	• Seropositivity rate reached 100% within 20 days post onset, and remained 100% until day 41-53 • Antibody level was highest during days 31-40 post onset, and then decreased slightly • No difference in titres between males and females • Multivariate analysis: • Patients aged 31-84 had a higher antibody level than those at age of 16-30 • Patients with a worse clinical classification had a higher antibody titre	
Wölfel 2020[87] Munich, Germany Case series DOI: 10.1038/s41586-020-2196-x.	SARS-CoV-2 Seroconversion was detected by IgG and IgM immunofluorescence using cells expressing the spike protein of SARS-CoV-2 and a virus neutralisation assay using SARS-CoV-2 Testing for virus by RT-PCR	N=9 hospitalised patients Sex of participants not reported All cases had comparatively mild courses	**Seroconversion rate & timing: IgM and or IgG** Day 7: 50% of patients by day 7 Day 14: 100% of patients by day 14 • Seroconversion was not followed by a rapid decline in viral load • No viruses were isolated after day 7 • All patients showed detectable neutralising antibodies, the titres of which did not suggest close correlation with clinical courses • Of note, case #4, with the lowest virus neutralisation titre at end of week 2, seemed to shed virus from stool over prolonged time • Results on differential recombinant immunofluorescence assay indicated cross-reactivity or cross-stimulation against the four endemic human coronaviruses in several patients	Peer-reviewed Nature

Xiao 2020b[91] China Case series DOI: 10.1016/j.jinf.2020.03.012	SARS-CoV-2 Chemiluminescent Immunoassay (CIA), Shenzhen Yahuilong Biotechnology Co., Ltd	N=34 Mean age: 55 (range: 25-87) Female: 12; Male: 22	**IgM** In week 3 after symptoms onset, all patients tested positive for IgM In week 5, 2 patients (16.7%) were negative **IgG** In week 3 and week 5 all patients were positive for IgG	Pre-proof Accepted to Journal of infection
Yong 2020[97] China Case series DOI: 10.1002/jmv.25919	SARS-CoV-2 Colloidal gold immunochromatographic assay (GICA) (Beijing Innovita Biological Technology Co. Ltd.)	**N=38** 38 cases with confirmed SARS-COV-2 in the Second People's Hospital of Fuyang 3 severe cases, 35 mild cases Median age (IQR): 40.5 years (31.0-49.5). 55.3% were males. Diagnosis of SARS-COV-2: the New Coronavirus Pneumonia Prevention and Control Program (5th edition) published by the National Health Commission of China Samples: 0-7 d: N=13 8-14d:N=8 >15d: N=23	**IgM** Seroconversion rate and timing: 0-7 d: 23% 8-14d: 50.0% >15d: 52.2% **IgG** Seroconversion rate and timing: 0-7 d: 53.8% 8-14d: 87.5% >15d: 91.3%	Accepted for publication J Med Virology

Yongchen 2020[131] China Retrospective cross sectional DOI: 10.1080/22221751.2020.1756699	SARS-CoV-2 Gold immuno-chromatography assay (Innovita Co. Ltd. China) Timing not stated but paper reports results from weeks 1,2,3 and up to 6 weeks, implying weekly tests. Serum samples	21 SARS-CoV-2 patients in 2 hospitals; non-severe n-11; severe n=5; asymptomatic carriers n=5. Median age overall 37 years (10-73); Median age non-severe 35 years(24-73); Median age severe 54 years (30-68); Median age asymptomatic 25 years (10-61) Female overall 38.1%; Female non-severe 45.5%; Female severe 20%; Female asymptomatic 40%; Illness severity defined according to the Chinese management guidelines for SARS-CoV-2 (version 6.0). Asymptomatic defined as individual who were positive for SARS-CoV-2 nucleic acid but without any symptoms during screening of close contacts.	**Rate and timing of seroconversion:** **IgM** 0-7 days: 31% (5/13) 7-14 days: 38% (5/13) 14 days+: 50% (8/16) **IgG** 0-7 days: 46% (6/13) 7-14 days: 54% (7/13) 14 days+: 100% (16/16) **Timing of seroconversion:** Non-severe 27.2% seroconverted within 1 week; 63.6% within 2 weeks; 81.8% within 3 weeks; 100% within 6 weeks For 72.7% of non-severe the first detection of antibody responses occurred during the period when their swab samples converted to RNA negative, suggesting that antibody reposes might facilitate the viral clearance especially for non-severe patients. All severe patients seroconverted within 2 weeks. 3 out of 5 severe patients generated viral specific IgG responses prior to viral clearance. It is possible that significantly high level of SARS-CoV-2 viral load observed in severe cases drives early antibody response produced by immediate activation of extrafolllicular B cell during acute infection. Only 1 (20%) out of 5 asymptomatic cases generated SARS-CoV-2 specific antibody responses, and this patient was not seroconverted until week 3 of her diagnosis. Consistent with her delayed antibody response, the throat swab converted negative as late as week 3. For the remaining 4 asymptomatic patients, 2 were not seroconverted within week 2 and 3 respectively, while 2 remained negative during week 4. It is not known if they seroconverted later. (False positive nucleic acid tests cannot be ruled out) **Duration of immunity:** Duration: All (5/5) positive for IgG in week 7 post-symptom onset **Other:**	Peer-reviewed; Emerging microbes & infections

			We did not identify a strong association of seroconversion and disease severity, in both severe and non-severe, viral specific antibody responses were detected. Our study revealed an early induction of antibody responses in severe cases. We can also speculate that high level of initial viral load may lead to severe SARS-COV-2 cases (Paper then describes the possible mechanism of this … strong B cell responses leading to rapid AB responses *not* following the sequence of IgG/IgM development stages… and promoting monocyte/macrophage accumulation and massive cytokine storm, which might be responsible for fatal acute lung injury)	
Zhang 2020b[103] China Case series DOI: 10.18632/aging.103102	SARS-CoV-2 Viral detection: RT-PCR Antibody testing: ELISA Positivity threshold (National Health Commission): ≥1:160	N=6 4 male, 2 female Age range: 30-50 years Plasma samples were collected at times ranging from 29 to 46 days after symptom onset, and 13 to 27 days after their discharge All patients were asymptomatic when samples taken	**IgM** 100% seroconversion **IgG** 100% seroconversion **Titres** All donors but one had high IgG titres (≥1:320) The time from onset of symptoms to clearance of virus, defined as two consecutive negative nucleic acid tests from throat swab samples, were varied from 8 to 18 days.	Peer-reviewed; Age
Zhao 2020a[106] China Case series DOI: 10.1093/cid/ciaa344	SARS-CoV-2 Enzyme Linked Immunosorbent Assay (ELISA) kits supplied by Beijing Wantai Biological Pharmacy Enterprise Co.,Ltd	N=173 patients; n=535 samples Median age: 48 (IQR: 35-61) Female proportion: 51.4%	**IgM** In week 3 after symptoms onset, all patients tested positive for IgM In week 5, 2 patients (16.7%) were negative **IgG** In week 3 and week 5 all patients were positive for IgG Note: The reason for the negative antibody findings in 12 patients might due to the lack of blood samples at the later stage of illness.	Peer-reviewed; Infectious Disease Society of America

Zhang 2020c[102] China Retrospective case series DOI: 10.1093/infdis/jiaa229	SARS-CoV-2 An IgM and IgG antibody detection kit was developed (Yahuilong Biotechnology, Shenzhen, China)	112 PCR positive patients; 70.5% female); median age 38.6 years +/- 14.9 years (range 25-78 years); 8.9% asymptomatic; all others with mild symptoms	**Rate & Timing of seroconversion** **IgM** 5/7; 71%; <10 days 5/10 50% at 10-20 days 17/38; 45%; at 20-30 days **IgG** 4/7; 57%; <10 days 8/10; 80%; at 10-20 days 38/38 (100%) at 20-30 days 8/8 100% at 40-50 days **Rate of seroconversion:** 93.75% overall • 51.79% positive for IgM and IgG • 6.25% positive for both, 0.89% positive for IgM and negative for IgG • 41.07% positive for IgG and negative for IgM **Timing of seroconversion:** IgM antibody appeared within a week post-disease onset, lasted for one month and gradually decreased, whereas IgG antibody was produced 10 days after infection and lasted longer. • Compared to the IgG titres tested within10 days after onset, IgG titres tested at 20-29 days, 30-39 days and 40-49 days after onset were significantly higher • Of 7 patients tested within 10 days of onset, 4 were positive for both IgG and IgM (6-8 days post onset), 1 positive for only IgM (4 days post onset), and 2 negative for both • Of 10 patients tested 10-20 days post onset, 5 were positive for both, 3 positive for IgG and 2 negative for both. Only initial PCR tests positive for these 2 patients, subsequent tests were negative.	Peer-reviewed

			• Of 38 patients tested 20-30 days post onset, 17 were positive for both, 21 were positive for IgG • Of 49 patients tested 30-40 days post onset, 27 were positive for both, 19 were positive for IgG, and 3 negative for both • Of 8 patients tested 40-50 days post onset, 4 were positive for both, the rest were positive for IgG **Duration of immunity:** • 26 patients underwent 2 successive antibody and nucleic acid tests, 11 were positive on second nucleic acid testing and 15 negative. Initial positivity rates of IgM and IgG were 50% and 100% respectively. Of the 11 positive on the second test, positivity rates for IgM and IgG were 45% and 100% respectively. Of 15 who were negative, positivity rates of IgM and IgG were 87% and 100% respectively (Study does not state when second test took place)	
Zhao 2020b[121] China Case study DOI: 10.1093/cid/ciaa408	SARS-CoV-2 Total antibody and IgM specific for SARS-CoV-2 was measured with chemiluminescence kits supplied by Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., China	38-year-old man Co-infected with HIV and HCV • Patient had 3 serial negative tests for SARS-CoV-2 RNA from nasopharyngeal swabs • Patient had pneumonia on CT • 42 days from the onset of his illness, his immune response was evaluated	<u>At 42 days post-symptom onset:</u> **IgM**: 49.5 cut-off index (COI) **Total antibody**: 13.2 COI • These were significantly lower and higher, respectively, than those in patients with SARS-COV-2 who had recovered from the illness who are not HIV/HCV positive. • At this time, SARS-CoV-2 RNA was still negative from nasopharyngeal and anal swabs. <u>At 49 days post-symptom onset</u>**:** IgM remained at similar levels with 54 COI Total antibody rose to 523.8 COI Note: • Patient was taking lamivudine, tenofovir and efavirenz daily since 2016	*Accepted manuscript to Clinical Infectious Diseases*

			• In 2017, he took antiviral agents (DAA) against HCV for 3 months by himself, and HCV became persistently negative • On admission his CD4 and CD8 T cell counts in peripheral blood were 216 and 584	

Table 6: Duration of immune response: SARS-CoV

Author DOI Country Study design	Virus type Test performed Location of sample Timing of sample	Population Patient demographics	Primary outcome results	Comments
SARS-CoV				
Anderson 2020[4] Singapore Case series DOI: 10.1080/22221751.2020.1761267	SARS-CoV ELISA and virus neutralisation test.	12 SARS cases <1year to 17 years post-symptom onset Patients 8 and 9 were 9 years post-infection; Patient 9 also described as 14 years post-infection patients 10, 11, 12 were 17 years post infection Study compares these with 4 negative controls and 7 SARS-COV-2 cases	Duration of immunity: Neutralising antibodies (NAs) detected in recovered SARS patients 9-17 years after initial infection. Cross-neutralisation: No evidence for cross-neutralisation of patient sera for SARS-CoV-2 was found	Published as letter to: Emerging microbes & infections
Cao 2010[9] DOI: 10.1186/1743-422x-7-299 China Case series	SARS-CoV Clinical case definition: WHO criteria **Testing:** ELISA (BJI-GBI Biotechnology, Beijing, China) and micro-neutralisation assays **Sample:** Serum **Timing:** 3 year follow-up; sampling at month	N = 19 recovered SARS patients. Control: N = 25 healthy blood donors	**Duration of detection of serum immunoglobulin levels:** 3 years **Duration of detection of neutralising antibodies:** *RBD-based ELISA:* Year2/3 = 1 sample became undetectable. Positive rate of 94.74%. *Lysate-based ELISA kit:* Year 2/3 = OD values for all samples dropped dramatically. Positive percentage of the year 3 samples was 42.11% (8/19) **Other outcome:**	Peer-reviewed BMC Virology journal

	3, 12, 18, 24, and 36 after the onset of clinical symptom		Viral lysate-based ELISA kit had much low sensitivity than the RBD-based ELISA	
Cao 2007[8] DOI: 10.1056/NEJMc070348 China Case series	SARS-CoV **Testing:** ELISA, Neutralising antibodies: conventional neutralisation assay. Reference value for positive result: 1:10 **Sampling:** Serum **Follow-up:** 3 years after disease onset (samples taken at 1, 4, 7, 10, 16, 24, 30, 36 months)	N = 56 positive for serum IgG and neutralising antibodies at recovery.	**Duration of detection of serum immunoglobulin levels:** 36 months **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** GMTs: 244 at month 4; 34 at month 30; 28 at month 36. IgG antibodies were undetectable in 19.4% of serum samples at month 30, and in 25.8% at month 36. **Duration of detection of neutralising antibodies:** 36 months **Serum titres of neutralising antibodies over time:** GMTs: 1,232 at month 4; 32 at month 30; 32 at month 36. Neutralising antibodies were undetectable in 11.1% of serum samples at month 30 and in 16.1% at month 36. **Other outcome:** The titres of IgG and neutralising antibodies were significantly correlated during the 3-year follow-up period (Spearman's correlation coefficient, 0.905; P = 0.002). Femoral neck necrosis: patients with femoral neck necrosis had significantly lower neutralising antibody levels (P<0.001, from mixed-linear random-effects models. No significant differences in the kinetics of specific antibodies according to disease severity, duration of hospitalisation, type and number of coexisting conditions, or use or non-use of corticosteroids. Treatment: Not reported.	Peer-reviewed; N Engl J Medicine

Chan 2005[10] China DOI: 10.1128/cdli.12.11.1317-1321.2005	SARS-CoV Serological and RT-PCR confirmation of SARS CoV infection with an epidemiological link and clinical features compatible with SARS. **Testing:** Neutralisation tests and subclass-specific IF tests. Neutralisation titre was determined as the highest dilution of serum which completely suppresses the cytopathic effect in at least half of the infected wells. **Samples:** Sera **Timing:** collected during illness and convalescence up to 7 months postinfection	N = 20 SARS patients. Age: mean age of 39.8 years (range, 20 to 65). Sex: male-to-female ratio was 11:9 Follow-up sera at 7 months available for 11 patients. N = 2 chronic hepatitis B carriers. Patients infected with other human coronaviruses: Acute- and convalescent-phase sera from patients with recent OC43 infection (N = 11) and patients with recent 229E infection (N = 3)	**Duration of detection of serum immunoglobulin levels:** IgG: Detectable at 7 months. IgM: Detectable 8/11 patients at 7 months (GMT at 7 months = 19). IgA: GMT at 7 months = 35 Total immunoglobulin (IgGAM) titres at 7 months decreased in 1 patient, increased in 2 patients and remained stable in 8 patients. **Serum titres of IgG over time:** Time to seroconversion - 17.2 days (range of 13 to 28). Month 1: GMT = 206 Month 7: GMT = 34 IgG antibody titres remained stable at 7 months in 7 patients. IgG continued to increase in 3 patients. 1 patient showed a fourfold or greater decrease in SARS-CoV IgG at 7 months. **Duration of detection of neutralising antibodies:** 7 months **Serum titres of neutralising antibodies over time:** The mean time to developing neutralizing antibody was 15.4 days (range of 11 to 21). Month 7: Titres decreased in 2 patients, increased in 2 patients, and there was no significant change in seven patients. Month 1 and 7: neutralisation titres remained unchanged at 124. **Other outcome:**	Peer-reviewed; Clin Diagn Lab Immunol

			Time to seroconversion: No difference in time to seroconversion between the patients who survived (n = 14) and those who died (n = 6). **Crossreactivity:** SARS-CoV antibody response was sometimes associated with an increase in pre-existing IgG antibody titres for human coronaviruses OC43, 229E, and NL63. N = 12 (60%) of SARS patients had fourfold rising titres to OC43, 229E, or both. **Mortality:** N = 6 patients had a fatal outcome.	
Chang 2005[11] DOI: 10.1128/CDLI.12.12.1455-1457.2005 Taiwan Prospective follow-up	SARS-CoV SARS was diagnosed based on a positive RT-PCR result for SARS-CoV on their initial throat swabs and/or the seroconversion of the IgG specific antibody to SARS-CoV IgM and IgG measured with indirect immunofluorescent assay (IFA) (Euroimmune, Lübeck, Germany)	Of 76 SARS patients hospitalised with pneumonia, 18 were followed for 1 Chang 2005[11] year. For the 18 patients who were examined for 1 year, male-to-female ratio of this group was 7:11. Their ages ranged from 24 to 71 years, with a median age of 45.5 years.	**IgM** 15 patients had detectable IgM to SARS-CoV in their sera collected at 1 month after disease onset With the exclusion of 1 patient, whose serum samples were not collected at 3, 6, and 9 months after the disease onset, IgM antibodies were undetectable in 2 patients at 1 month after the disease onset, in 10 patients at 3 months, in 16 patients at 6 months, and in all 17 patients at 12 months **IgG** All of the patients except 1, whose serum sample was not collected at 12 months after the disease onset, had detectable IgG antibodies in their sera 12 months after disease onset. **Disease severity:** Patients who developed respiratory failure during their SARS disease courses did not have significantly higher IgG titres than those who did not develop respiratory failure. There was no correlation between the IgG titre checked 1 month after disease onset and the patients' ages, initial CRP levels, peak CRP levels, or development of respiratory failure as determined by statistical analysis.	Peer-reviewed; lin Diagn Lab Immunol

Chen 2005[12] DOI: 10.4049/jimmunol.175.1.591 China Case series	SARS-CoV **Testing:** Flow cytometry, ELISPOT assays **Sample:** Blood **Timing:** 12-14 months after recovery	N = 13 HLA-A*0201 subtype positive recovered SARS patients. Sex: 8 females, 5 males. N = 12 HLA-A*0201 subtype negative recovered SARS patients. Sex: 5 females, 7 males. Controls: N = 36 healthy donors. Sex: 21 females, 15 males. All donors aged 18 to 61 years.	**Duration of detection of T-cells:** 12 – 14 months **Detection of CD8+ T-cells:** Inactivated SARS-CoV elicited an Ag-specific recall CTL response to spike protein-derived epitopes (SSp-1, S978, and S1202) in PBMCs of recovered SARS patients. **Other outcome:** **Cytokine production:** Cross-reactive memory T cells to SARS-CoV may exist in the T cell repertoire of a subset of healthy individuals and can be reactivated by SARS-CoV infection *in vitro*. SSp-1-specific CTLs derived from healthy donors demonstrated reduced cytotoxic activity and low levels of IFN-g production in comparison with those of CTLs from recovered SARS patients	Peer reviewed; J Immunol
Fan 2005[28] China Case series	SARS-CoV **Testing:** ELISA. Cut-off value = 0.11 + negative control A **Sample:** Sera. Each patient was tested at least twice (Total 912 sera) **Timing:** 12 months. Sampling every 2 - 4 weeks.	N = 311 SARS patients from hospitals in Beijing (N = 258 cases in Xiaotangshan Hospital; N = 21 cases in Armed Police General Hospital, N = 9 cases in the Civil Aviation General Hospital; N = 23 cases in the PLA General Hospital) Sex: 132 males, 179 females. Age: Males 18 to 67 years, mean 37 years ± 13. Females aged 18 to 74 years, mean 38 years ± 13	**Duration of detection of serum immunoglobulin levels:** 12 months **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Peak titre 35 days after discharge. Then levels began to decline. IgG antibody level showed a 35.8% decrease within one year.	Peer reviewed
Guo 2020b[134] DOI.org/10.1101/2020	SARS-CoV **Testing:** ELISA kit using whole virus (BGI-GBI Biotech Co. Ltd., Beijing, China) and an	34 SARS-CoV-infected healthcare workers during the 2002-2003 SARS outbreak were followed. The majority of the participants were aged between 20 and 30 in	Anti SARS-CoV IgG was found to persist for up to 12 years	Not yet peer reviewed, published as pre-print

.02.12.2002 1386. China Long-term prospective follow-up study	in-house recombinant SARS-CoV N199 antigen assay. Any result Higher than the cut-off value considered positive. **Sampling:** Sera (Total 362 samples) **Timing:** Sampling in 2003 at hospital admission. Yearly sample collection until 2015.	2003, and 94.11% (32/34) of them were females. Serum samples were collected annually from 2003-2015.	IgG titres typically peaked in 2004, declining rapidly from 2004-2006, and then continued to decline at a slower rate. Patients treated with corticosteroids at the time of infection were found to have lower IgG titres than those without. *ELISA commercial kit:* 2003: IgG titre against whole virus was 81.25% (26/32). 2007: Peaked at 100% (32/32). 2015: Decreased to 69.23% (18/26). *In-house recombinant SARS-CoV N199 antigen assay:* 2003: IgG antibody against N199, the initial positive was 59.38% (19/32). 2005: Peaked at 87.50% (28/32). 2015: Decreased to 19.23% (5/26). **Conclusion:** IgG antibodies against SARS-CoV can persist for at least 12 years	
He 2004[39] China DOI: 10.1128/CDLI.11.4.792-794.2004 Case series	SARS Clinical case definition: fever of ≥ 38°C, cough or shortness of breath, new pulmonary infiltrates on chest radiography, and close contact with a person with a suspected or probable case **Testing:** IFA (Euroimmun AG, Lu¨beck, Germany), ELISA (Wantai Biological	N=271 laboratory-confirmed (RT-PCR) SARS cases. Age: 36 ± 16 years	**Duration of detection of serum immunoglobulin levels:** SARS CoV IgG: 95 days. SARS CoV IgM: SARS-CoV-specific IgM levels dropped as early as 2 or 3 weeks after the onset of illness. Days 60-95 (study end-point) = 58/70 (83%). SARS CoV IgA: Days 60-95 = 54/70 (77%). **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Days 1-14 = 140 (59.1%); Days 15-29 = 182/188 (96.9%); Days >25 = 165/165 (100%); .Days 60 to 95 = 70/70 (100%) with 58/70 (83%) showing titres >100. **Other outcome:**	Peer-reviewed; Clin Diagn Lab Immunol

	Pharmacy Enterprise Company, Ltd., Beijing, China) **Sample:** Serum (total number, 530; 1 to 5 samples per patient) **Timing:** 1-95 days after the onset of illness.		Diagnostic test accuracy SARS CoV IgG detection: IFA: Sensitivity 98%, specificity 98%. ELISA: Sensitivity 81%, specificity 99%. Diagnostic test accuracy SARS-CoV-IgM detection: IFA: Sensitivity 79%, specificity 100%. ELISA: Sensitivity 90%, specificity 99%.	
Hsueh 2004[41] Taiwan DOI: 10.1111/j.1469-0691.2004.01009.x Case series	SARS-CoV positive RT-PCR and real-time RT-PCR assays from respiratory or serum samples **Testing:** IFA (In-house assay and commercial kit). The Cut-off values for a positive result were 1:25 for the in-house IFA and 1:10 for the commercial IFA kit. Indirect ELISA. Cut-off value for a positive IgG result by ELISA was 0.26. Neutralisation assay. **Sample:** serum samples (6–12 samples from each patient) **Timing:** <7 days to 2–3 months after the onset of illness.	N = 30 patients with SARS Age: 25–80 years (mean 43 years) 4 patients had underlying disease, namely diabetes mellitus (n = 2), hypertension (n = 1) and chronic hepatitis B virus carriage (n = 1). Controls: N = 200 paired sera from patients with community-acquired pneumonia, N = 70 sera from hospitalised patients with acute respiratory distress syndrome, N = 10 sera from ten pregnant women obtained during routine pre-labour check-ups.	**Duration of detection of serum immunoglobulin levels:** IgG: > 3 months. IgM and IgA: Started to decline after 3–4 weeks, and remained at low levels (1:40–1:80) at 12 weeks. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Tests for IgG were negative until at least 3 days after the onset of illness. All patients were positive for IgG for > 28 days (1:400–1:1600). Peak titre = 1:6400. N = 1 had a high level of IgG (1:800) at 100 days after the onset of illness. **Duration of detection of neutralising antibodies:** 2-3 months **Serum titres of neutralising antibodies over time:** Days 10–12 = appeared (mean 1:32), increased thereafter. Days 18-24 = peaked (1:128– 1:256). N = 4 titre remained at 1:32 or 1:64 at 2 months after onset, and was 1:64 on day 100 of the illness. **Other outcome:**	Peer-reviewed; Clin Microbiol Infect.

			Seroconversion of IgG (mean 10 days). **Treatment:** In addition to treatment with ribavirin (29/30 patients), N = 28 patients received IV methylprednisolone (1–11 days, mean 6 days, and 2–4 days before any IgG response), N = 21 received IV immunoglobulin (2–12 days, mean 6 days), and N = 9 were given mechanical ventilation (4–12 days, mean 8 days) following respiratory failure. No significant differences in the kinetics of the IgG, IgM and IgA response between patients with or without underlying medical disease, steroid or IV immunoglobulin therapy, or mechanical ventilation.	
Huang 2005[45] China DOI: 10.1016/j.micinf.2004.11.017 Case series	SARS-CoV Case definition of SARS-CoV based on the Chinese Ministry of Health on April 14, 2003. **Testing:** Lymphocyte analysis: Flow cytometry. Humoral response: ELISA. Reference OD = 0.030 **Sample:** Blood **Timing:** 5 months follow up. Sampled at 1, 2, 3 and 4 weeks, and 2, 3, 4 and 5 months	Exposed population: N = 95 healthcare workers with SARS; *Sex:* Male = 19 (20%), *f*emale = 76 (80%) Mean age: 28.7 ± 9.5 years Controls: N = 60 healthy adults. Sex: Male = 13 (21.6%), female = 47 (78.4%), Mean age: 29.5 years old	**Duration of detection of serum immunoglobulin levels:** Specific IgG positive rate remained stable at around 96.5% at days 121-140 (study end-point). Specific IgM positive rate dropped to 54.5% at days 121-140 (study end-point). **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** General IgG antibodies: Month 1 = significant increase (Peak at week 3); 2 months = Decreased gradually to normal levels. Specific IgG antibodies: Days 1-5 = OD 0.069; Days 41-60 = OD 1.477 (peak); Day >60 = decreasing titres; Day >101 = increase in titres. **Duration of detection of T-cells:** CD4+ and CD8+ T lymphocytes decreased significantly over the 5 months. CD3+CD8+ memory T lymphocytes were decreased by 36.78% (P = 0.040) and CD3+CD4+ memory T lymphocytes by 19.65% in convalescent patients.	Peer-reviewed; Microbes Infect

			Other outcome: **Cytokine production:** IL-10 and TGF-b were continuously overproduced for the entire course of SARS infection. **Treatment:** antiviral regimens, gamma globulin and/or corticosteroids	
Li 2006[56] China DOI: 10.1371/journal.pone.0000024 Case series	SARS-CoV Case definition of SARS-CoV: WHO clinical criteria **Test:** Lymphocyte analysis: Flow cytometry Humoral responses: ELISA (No S20030004, HuaDa Comp, Beijing, China), ELISPOT-based technique (Diaclone, France), neutralisation assay **Sample type:** Blood **Timing:** 2 years follow-up; Samples collected at 1, 3, 6, 12 and 24 months after symptom onset.	N = 30 recovered SARS patients; Sex: 13 male and 17 female. Age: 37 ± 11 years antibody and antigen negative for HIV-1, CMV, and EBV Controls: N = 70 normal healthy age matched individuals. Sex: 36 male and 34 female. Age: 39 ± 10 years.	**Duration of detection of serum immunoglobulin levels:** 24 months **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Months 1-3 = significant increase in Total IgG; Months 3-12 = gradual decrease; Months 12-18 = significant decrease; Months 18-24 = no significant decrease. **Duration of detection of neutralising antibodies:** N protein-specific Nab detectable at 24 months S protein-specific Nab detectable at 24 months. **Serum titres of neutralising antibodies over time:** Trend towards decrease Nab titres over time. N protein-specific Nab: <6 month = antibody remained relatively high. Months 6 -12 = significant decrease in titres; Months 12-24 = no significant decrease. S protein-specific Nab: No significant decrease between sample measurements. **Detection of T-cells/B memory cells or other:** Total lymphocytes, CD3, CD4, and CD8 T lymphocytes, B lymphocytes and NK cells: Months 1-3 = increase in cell populations; Months >3 = decline in rate of lymphocyte population recovery; Month 24 = mean absolute numbers of lymphocytes remained statistically different from that in normal healthy age-matched controls.	Peer-reviewed; *PLoS One*.

			Other outcome: INF-g releasing cells detected at month 3, 12 and 18 after onset of symptom.	
Li 2003[55] China DOI: 10.1056/NEJM200307313490520 Case series	SARS-CoV **Testing:** Test not reported. Cut-off for a positive result 1:10 **Sample:** Serum **Timing:** Weeks 1-12. Measured at weeks 1, 2, 3, 4, 8, and 12.	Exposed group: N = 20 patients with SARS Controls: N = 103 healthy volunteers	**Duration of detection of serum immunoglobulin levels:** IgG peak titre at 12 weeks. IgM titres disappeared by the end of week 12. Controls tested negative for IgM and IgG. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Week 2 = mean titre 1:40; Week 3 = 1:256 (12/12 (100%) seropositive); Week 4 = 1:368; Week 8 = 1:640 (peak titre); Week 12 = 1:640. **Other outcome:** 20/20 100% seroconversion rate	Peer reviewed; N Engl J Med.
Libraty 2007[58] Philippines. DOI: 10.1016/j.virol.2007.07.015	SARS-CoV **Testing:** ELISA, IFN-γ ELISPOT assays **Sample:** Blood **Timing:** 6–30 months after infection	N = 2 recovered SARS healthcare workers. N = 16 healthy contacts.	**Duration of detection of serum immunoglobulin levels:** 12 months **Serum titres of IgG over time:** The waning of anti-SARS CoV IgG levels paralleled the waning of S protein-specific memory T-cells at 12 months (N = 1). Anti-SARS-CoV IgG levels were 4-fold lower in patient #2 than patient #1 at 6 months. **Duration of detection of T-cells:** 12 months **Detection of CD4+ T-cells:** S protein-specific memory CD4+ T-cells greatest 6 months after SARS-CoV infection (N=1), and decreased to near the limit of detection by 12 months onward.	Peer reviewed: Virology

			S protein-specific CTL activity could be detected after in vitro re-stimulation at 12 months, but not at 24 and 30 months (N=1). **Other outcome:** **Cytokine production:** IFN-γ+ production to peptide S729–745 was greatest 6 months after SARS-CoV infection, and decreased to near the limit of detection by 12 months onward (N=1). **Individual variation in immune responses:** CD4+ T-cell responses to any SARS-CoV structural protein epitopes were weaker or decreased more rapidly in SARS patient #2 compared to patient #1 suggesting that in some individuals humoral and CD4+ T-cell immunity to SARS-CoV may wane rapidly.	
Liu 2006[109] DOI: 10.1086/500469 China Prospective follow-up study	SARS-CoV Serum samples were collected from each patient at regular intervals (at 1, 4, 7, 10, 16, and 24 months after disease onset) Serum titres of IgG were measured using a commercially available ELISA kit Neutralising antibodies (NAbs) were measured by neutralisation assay	A total of 63 patients recruited; N=56 participants contributed at least 3 blood specimens during the follow-up. Mean age 29 years (range, 18–59 years); 27 patients were men. 9 patients had underlying disease and 7 patients had a severe clinical condition (such as oxygen ventilation and transfer of the patient to an ICU)	The number of study participants tested at each follow-up visit varied from 32 to 41 IgG serological findings remained positive throughout follow-up for all patients, except at the last visit (at month 24), when findings for 4 (11.8%) of 34 serum samples changed from positive to negative findings. Peak GMT occurred at month 4, before a significant decrease occurred over time until month 24 All samples tested positive for neutralising antibodies at all visits. GMTs peaked at month 4, decreased at month 7, and decreased again at month 24 Neutralising antibody and IgG antibody titres were strongly correlated	Peer reviewed; J Infect Dis
Mo 2006[66]	SARS-CoV	Exposed group:	**Duration of detection of serum immunoglobulin levels:**	Peer reviewed; Respirology

China DOI: 10.1111/j.1440-1843.2006.00783.x Case series	Case definition of SARS-CoV: WHO clinical criteria **Testing:** ELISA (GBI Biotech, Beijing China) and IFA. Reference value for positive result: OD 0.13 + A negative control. Neutralisation assay. **Sample type:** Blood sample **Timing:** 7 to 720 days after the onset of symptoms. Serial blood samples were taken on days 7, 15, 30, 60, 90, 180, 270, 360, 450, 540 and 720.	N = 98 patients with SARS (N = 18 completed follow-up), Sex: 43 men and 55 women, Age: 20–75 years (mean 37.8 ± 12.2 years), Average duration of hospitalisation was 23.1 ± 12.3 days. Control: N = 10 healthy volunteers, Sex: four men and six women, Age:17–58 years (mean 35.6 ± 12.2 year)	**Ratios of positive IgG/IgM:** 0/0, 45.4/39.4, 88.6/71.4, 96/88, 100/48.6, 100/30.9, 100/17.1, 100/0 per cent, respectively, on 1–7, 8–14, 15–21, 22–28, 29–60, 61–90, 91–180 and 181–720 days. IgM was undetectable on day 180. IgG was still detectable at day 720. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** IgG titres: Day 7 = not detected; Day 15 = increasing titres; Day 60 = 1:670 (peak); day 180 = 1:670 (plateaued); Day 540 = titres had rapidly declined; day 720 = average titre was close to the cut-off value for positivity (1:10). **Duration of detection of neutralising antibodies:** 17/18 detectable at 720 days **Serum titres of neutralising antibodies over time:** Day 15 = increasing titres; Day 30 = 1:590 (peak); Days 540 and 720 = 1/18 no detectable neutralising antibodies, 17/18 low titre (average of 1:10). Neutralising antibodies were not detectable in normal control sera. **Other outcome:** **Treatment:** Combination of antibiotics (cephalosporin and erythromycin) and antiviral agents (ribavirin or traditional Chinese medicine). Patients whose fever persisted for >3 days or who showed a progressive deterioration in their CXR (79.6%), received methylprednisonlone. **Seroconversion:** Earliest seroconversion occurred on day 10 after the onset of the disease.	

Ng 2016[68] DOI: 10.1016/j.vaccine.2016.02.063 Singapore Prospective follow-up study/case series	SARS-CoV (ELISpot) assays Intracellular cytokine staining (ICS) and degranulation assays and flow cytometry. Screening for the presence of SARS-specific T cells was performed by a number of different testing methods	N=3 SARS-recovered individuals Follow-up at 9 or 11 years post-infection	All memory T cell responses detected target the SARS-CoV structural proteins. 2 CD8+ T cell responses targeting the SARS-CoV membrane (M) and nucleocapsid (N) proteins were characterised by determining their HLA restriction and minimal T cell epitope regions. These responses were found to persist up to 11 years post-infection. An absence of cross-reactivity of these CD8+ T cell responses against MERS-CoV was also demonstrated. **Interpretation:** Persistence of SARS-specific cellular immunity targeting the viral structural proteins in SARS-recovered individuals was demonstrated up to 11 years post-infection. The persistence of T cell responses suggests that SARS-recovered patients could be protected from reinfection.	Peer-reviewed; Vaccine
Peng 2006[72] China DOI: 10.1016/j.virol.2006.03.036 Case-control study	SARS-CoV Diagnostic criteria for SARS-CoV infection: WHO clinical criteria **Testing:** Cytokine production: ELISA (R&D) and ELIspot assay (BD Biosciences) **Sample type:** venous blood **Timing:** 2 years	Exposed group: N = 14 recovered SARS Individuals Sex: 7 men and 7 women, Age: 20 to 37 Control: N = 3 subjects without any contact history with SARS patients.	**Duration of detection of T-cells:** 2 years SARS-CoV N-protein-specific memory CD4+ and CD8+ T cells were maintained for 2 years after SARS-CoV infection. **Other outcome:** **Cytokine production** PBMCs produced IFN-γ and IL-2 following stimulation with a pool of overlapping peptides from the SARS-CoV N protein sequence.	Peer reviewed; Virology
Shi 2004[77]	SARS-CoV probable SARS patients based on WHO criteria	N = 14 probable SARS patients.	**Duration of detection of serum immunoglobulin levels:** IgG antibody was detectable for 210 days.	Peer reviewed; Journal of

China DOI: 10.1016/j.jcv.2004.05.006 Case series	**Testing:** IFA, ELISA and viral neutralisation. ELISA cut-off value for a positive result = 0.15. Neutralisation titre = the highest dilution of the serum at which 50% of the wells were protected from viral cytopathic effect. **Sample:** Serum **Timing:** Samples for ELISA were collected at 7 to 210 days after the onset of the symptoms. Samples for neutralisation assays collected at 20, 30, 60, 120, and 210 days post disease onset.	Age: 22 to 73 years old (median of 45 years).	IgM was shown to be negative in 4, 8, 12 and all 14 patients by day 60,120,180 and 210 days post disease onset, respectively. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** anti-viral IgG peak titre = 120 days; 120-210 days = decreasing titres; 210 days = high antibody titres. Duration of detection of neutralising antibodies: 210 days (peak at 180 days) **Serum titres of neutralising antibodies over time:** The geometric means of the neutralisation titres on day 20, 30, 60, 120 and 210 was 1:150, 1:475, 1:400, 1:200 and 1:200, respectively. **Other outcome:** IgG seroconversion 13/14 patients IgM seroconversion 13/14 patients	Clinical Virology
Tang 2011[81] DOI: 10.4049/jimmunol.0903490 China	SARS-CoV The specific memory B cell and T cell responses to SARS-CoV were measured by means of ELISPOT assay. IgG was measured with commercially available ELISA kits	N=23 patients Mean age 31.7 ± 8.3 years (range, 20–51 years) 17 (73.9%) were females. 9 patients had underlying disease and 7 patients had a severe illness	6 years postinfection, specific IgG to SARS-CoV became undetectable in 21 of the 23 former patients. No SARS-CoV-specific memory B cell response was detected in either 23 former SARS patients or 22 close contacts of SARS patients and 20 health controls. Memory T cell responses to a pool of SARS-CoV S peptides were identified in 14 of 23 (60.9%) recovered SARS patients, whereas there was no such specific response in either close contacts or healthy controls.	Peer reviewed; J Immunol

Prospective follow-up study			Patients with more severe clinical manifestations seemed to present a higher level of Antigen-specific memory T cell response. **Interpretation:** SARS-specific IgG may eventually vanish and peripheral memory B cell responses are undetectable in recovered SARS patients. In contrast, specific T cell anamnestic responses can be maintained for at least 6 years.	
Tso 2004[125] China DOI: 10.1086/424573 Prospective cohort study	SARS-CoV **Testing:** IFA **Sample:** Serum **Timing:** 1 year. SARS survivors: Sampling on day of hospital admission, 15 days, 1 month, 3 months, 6 months, 9 months, and 12 months after the onset of SARS symptoms. HCW: samples collected 1, 3, 6, 9, and 12 months after the first day of deployment to the SARS ward	N= 62 survivors of SARS and N = 1 asymptomatic infected health-care worker. Sex: male:female ratio 0.82. Age: mean age 37.07 years (SD, 12.96). Baseline SARS CoV immunoglobulin titre <25 at hospital admission.	**Duration of detection of serum immunoglobulin levels:** 1 year **Serum titres of Ig over time (typically expressed as Geometric Mean Titres [GMTs]):** SARS survivors: SARS-CoV Ig mean titre at baseline = <25; Day 15 = 252.8; Months 1 = 613.3; Month 3 = 880.3; Months 3-12 = gradual decrease in the mean SARS CoV Ig titre; 12 months = 167.7 (i.e. 5.3-fold decrease in mean titre at 12 v 3 months). Asymptomatic HCW: 1 month mean SARS CoV Ig titre = 400; Month 3 and 6 = 50 (i.e., an 8-fold decrease). Month 9 and 12 = 25. **Other outcome:** 100% rate of seroconversion.	Peer-reviewed; J Infect Dis.
Wu 2007[88]	SARS-CoV Serum antibody titres measured by ELISA kit	A total of 176 cases that met the World Health Organization (WHO) SARS case definition Sex/age of cohort not reported	**IgG** 7 days after symptom onset, the percentage who were IgG positive was ≈11.8%.	Peer-reviewed; Emerg Infect Dis

DOI: 10.3201/eid1310.070576 China Prospective follow-up	(BJI-GBI Biotechnology, Beijing, China)		This percentage continued to increase, reached 100% at 90 days, and remained largely unchanged up to 200 days. After 1 and 2 years 93.88% and 89.58% of patients, respectively, were IgG positive, which suggests that the immune responses were maintained in >90% of patients for 2 years. 3 years later, ≈50% of the convalescent population had no SARS-CoV–specific IgG. **IgM** The percentage of patients who were IgM positive within the first 7 days was 21.4% and peaked at 76.2% after 21–30 days. For most samples the IgM readings had reached background levels on day 90. **Interpretation**: SARS-specific antibodies were maintained for an average of 2 years, and significant reduction of IgG positive percentage and titres occurred in the 3rd year. Thus, SARS patients might be susceptible to reinfection >3 years after initial exposure.	
Yang 2009(126) China DOI: 10.1080/00365540902919384. Retrospective sero-epidemiolo	SARS-CoV All recovered cases were post-hoc confirmed by SARS-CoV. A probable SARS case was a patient with SARS contact history, high fever (>38°C), and radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome. **Testing:**	N = 67 confirmed SARS patients with >9 serum measurements during follow-up. 37.3% were men. Age: 16 to 57 years; mean age: 35.5 years (SD = 10.59). N = 688 non-SARS controls: Low risk/non-exposed controls (n = 200); high risk healthcare workers (n = 488).	**Duration of detection of serum immunoglobulin levels:** IgG: 82 weeks after onset of illness (study endpoint) **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** OD = 0.7 at week 82 (approx) **Other outcome:** Low risk controls: No positive antibody test High risk controls: 3 people (0.61%) with a positive IgG using ELISA; 1 (0.21%) confirmed using IFA Treatment: Corticosteroid treatment	Peer reviewed; Scandinavian Journal of Infectious Diseases

gical cohort study.	IgG: ELISA (Beijing GBI company, patch no. 200305). Positive samples confirmed with IFA (Huada Diagnostics Ltd, Beijing, China) Reference value for positive test: OD > 0.18 or OD > 0.13 above negative controls. **Sample type:** Serum **Timing** Intervention: Blood sampling every 3 weeks; 16 month follow up. Controls: 2 serum samples were collected during the SARS outbreak and 6 months post-outbreak.			
Yang 2006[95] China DOI: 10.1016/j.clim.2006.05.002	SARS-CoV **Testing:** Cytokine production: ELISA (BD Pharmingen, San Diego, CA) and ELISpot (BD Pharmingen) assays. Lymphocyte analysis: Flow cytometry **Sample type:** peripheral blood	Exposed group: N = 8 recovered SARS patients Sex: 5 male and 3 female, Age: 25 to 34 years Control: N = 5 healthy donors, Sex: 3 male and 2 female, Age: 27 to 33 years,	**Duration of detection of T-cells:** >1 year after infection. SARS-CoV S-specific memory T cells were persistent in peripheral blood of recovered SARS individuals. **Other outcome:** **Cytokine production** Antigen-specific memory T cells of secreted high levels of IFN-g upon stimulation in vitro with a pool of SARS-CoV S peptides.	Peer reviewed; Clin Immunol.

Case-control study	**Timing:** >1 year after SARS-CoV infection			
Xie 2006[92] China Case control study	SARS-CoV **Testing:** Flow cytometry **Sample:** Blood **Timing:** 1 year follow-up. Sample collection at 1 week, 2 weeks, 1 month, 2-3 month and 1 year.	N = 62 seropositive SARS cases Sex: 21 males and 41 females, Age: average age 38 ± 1 years Controls: N = 56 healthy individuals Sex: 30 males, 26 females. Age: average age 36 ± 10 years	**Duration of detection of T-cells:** *Total lymphocytes and T cells* Week 1: Total lymphocytes and T cells counts decreased significantly. Week 2: Numbers continued to decline. Months 1-3: Trend of rapid increase. Month 12: Significant differences between total lymphocyte and T cell count in SARS patients (Total lymphocyte 1,807 ± 473; T cell 1,285 ± 367) and normal controls (Total lymphocyte 2,254 ± 541; T cell 1,545 ± 394) at 1 year follow-up. *CD4 + T cells, CD8 + T cells, naïve and memory CD4 + T cells* Week 1: Numbers decreased significantly. Week 2: Numbers continued to decrease. Month 2/3: Increased rapidly. 1 year of follow-up: Memory CD4 + T cells recovered to normal levels (SARS patients 438 ± 140 v controls 495 ± 203). Average CD4 + T cells and naive CD4 + T cells were reduced compared to normal patients (SARS patients v controls: CD4 + T cells, 672 ± 192 v 870 ± 299; Naive CD4 + T cells, 200 ± 108 v 320 ± 121). CD8 + T cells recover significantly faster than CD4+ T cells. At 2-3 months the number of CD8 + T had returned to normal levels (SARS patients 578 ± 395 v controls 580 ± 174).	Peer reviewed; Acta Acad Med Sin

Table 7: Duration of immune response: MERS-CoV

Author DOI Country Study design	Virus type Test parameters	Population Patient demographics Clinical characteristics	Primary outcome results	Comments
Alshukairi 2016[2] DOI: 10.3201/eid2206.160010 Jeddah, Saudi Arabia Prospective follow-up	MERS-CoV ELISA for MERS-CoV S gene antibody; IFA (immunofluorescence assay) for MERS-CoV IgG	• N=9 healthcare workers who survived MERS. • Four of the 9 patients were women; 2 of them were 32 weeks and 20 weeks' pregnant. • Average patient age was 38 years (range 27–54 years). • Patients were classified into 4 categories according to their clinical presentation: asymptomatic, upper respiratory tract infection, pneumonia, or severe pneumonia. • Patients with severe pneumonia were those who required mechanical ventilation	**Duration of detection of antibodies:** • Of the 9 patients, 2 had severe pneumonia, 3 had milder pneumonia not requiring intensive care, 1 had upper respiratory tract disease, and 3 remained asymptomatic. All patients recovered without sequelae. • The 2 patients with severe pneumonia had the highest antibody titres detected among all patients and remained MERS-CoV-antibody–positive at 18 months after illness onset and had prolonged viral shedding documented by persistent positive rRT-PCR results for 13 days (patient 1) and 12 days (patient 2) • When tested at 18 months after illness onset both severe patients had positive antibodies. Asymptomatic/URT patients did not demonstrate positive ELISA for IgG at any point Conclusion: Results indicate that the longevity of the MERS-Cov antibody response correlated with disease severity. Accordingly, 2 patients with severe MERS-associated pneumonia had a persistent antibody response detected for >18 months after infection, whereas patients with disease confined to the upper respiratory tract or who had no clinical signs had no detectable MERS-CoV antibody response.	Peer reviewed *Emerging Infectious Diseases*
Choe 2017[16]	MERS-CoV	N=11 confirmed MERS-CoV patients	**Duration of detection of antibodies:** All 5 patients with severe disease, but only 2/6 (33%) with mild disease, had PRNT90 antibody titres ≥40 at 1-	Peer reviewed; CDC

DOI: 10.3201/eid2307.170310 Seoul, South Korea Case series	MERS confirmed by RT-PCR MERS S1 ELISA (commercially available EUROIMMUN, Germany) Neutralising antibody assay Plaque-reduction neutralisation tests (PRNTs) Serum samples collected at approx. 6 and 12 months	Samples collected at 21-50 days after disease onset and at 1 year follow-up. N=5 had severe disease, n=6 had mild disease	year follow-up. These patients also had positive microneutralisation assays, S1 ELISA assays and pseudoparticle neutralisation tests (ppNT), 1 year after illness onset. At 1 year after infection, the 4 patients who had mild disease (or who did not require supplemental oxygen or mechanical ventilation) all had negative results by micro-neutralisation assay and S1 ELISA, but 1 was positive by ppNT (titre of 10) and 2 by PRNT90 (titre 1:10). All bar 1 of these patients had chest infiltrates on x-ray. **Serum titres** All 5 patients with severe disease, but only 2 (33%) of 6 with mild disease, had PRNT90 antibody titres ≥40 at the 1-year follow-up. 2 of the severe patients who had acute-phase antibody titres of ≥320, declined ≥4-fold 1 year later. 4 patients with acute phase peak antibody titres in the range of 80–160 only had ≤2-fold declines in titre. MERS antibody titres waned during the first 6 months after disease onset, especially in patients who had had high antibody titres. The waning of antibody titres between 6 months and 1 year after disease onset was less steep. **Other outcome:** **Antibody titres in 4 of 6 patients who had mild illness were undetectable even though most had evidence of pneumonia** The kinetics of antibody production seen with the PRNT90, ppNT, microneutralisation test, and S1 ELISA were comparable, suggesting that any of these tests could be used for detection of MERS-CoV antibodies in patients with past infection. The authors found strong positive correlations between duration of virus detection and antibody titres	

			Because of the poor antibody response that resulted from symptomatic disease, persons with asymptomatic or mild infection without severe lung parenchymal disease are not expected to develop detectable MERS-CoV antibodies	
Zhao 2017[105] DOI:10.1126/sciimmunol.aan5393 Saudi Arabia Case series	MERS-CoV MERS confirmed by RT-PCR Anti-MERS-CoV antibody titres measured by ELISA and IFA Microneutralisation assay MERS-CoV PRNT50 assay	N=21 MERS patients (n=7 of these patients had sample taken at 24 months, while 14 had sample taken at 6 months post infection) N=4 controls 9/21 female, age range 25 to 59, and 7 had co-morbidities including diabetes mellitus, chronic heart disease, pregnancy, ESRD, organophosphate poisoning and pregnancy. Of 18 patients who provided PBMCs, 3 patients were asymptomatic, 6 patients had pneumonia, and 9 patients had severe pneumonia	**Duration of detection of antibodies:** Based on PRNT antibody responses tended to be present but lower (but not significantly different) in patients at 24 months compared to patients at six months after infection. **T-Cell response:** Both CD4+ and CD8+ T-cells responses were present but lower at 24 month post infection compared with 6 months post infection, however the difference was not statistically significant.	Peer-reviewed Published in Science Immunology

Table 8: Study characteristics: severity of initial disease

Author DOI Country Study design	Virus type Test performed Location of sample Timing of sample	Population Patient demographics	Primary outcome results	Comments
Adams 2020[1] UK Case series DOI: 10.1101/2020.04.15.20066407	SARS-CoV-2 ELISA and RT-PCR (used as reference test) Compared to 9 commercially available lateral flow immunoassay (LFIA) devices Plasma samples. RT-PCR from upper respiratory tract (nose/throat) swab Acute samples were collected from patients a median 10 (range 4-27) days from symptom onset (n=16), and from recovering healthcare workers median 13 [range 8-19]	N=40 adult positive for SARS-CoV-2 by RT-PCR. N=142 controls For SARS-CoV-2 patient: Age mean 60 (range 22-95) Severity: Mild 26(65%), Severe 4(10%), critical 9(22.5%), 1 asymptomatic (2.5%) N=18 convalescent cases (>28 days from symptom onset). N=16 case (≤ 28 days from symptom onset). N=6 convalescent health care worker (≤ 28 days from symptom onset)	**Duration of detection of serum immunoglobulin levels:** 40 SARS-CoV-2 samples and 50 controls tested by ELISA. 34/40 positive for IgG, other 6 where taken within 9 days of symptom onset. All samples taken >= 10 days after symptom onset positive for IgG. IgM positive in 28/40 samples (70%). No patient was IgM positive and IgG negative. N=9 patients had samples from between 50 and 60 days after onset of symptoms. In these 9 patients, 5/9 were IgM positive and 100% (9/9) were IgG positive. **Serum titres of IgG over time (typically expressed as Geometric Mean Titres [GMTs]):** Considering the relationship between IgM and IgG titres and time since symptom onset, univariable regression models showed IgG antibody titres rising over the first 3 weeks from symptom onset. The lower bound of the pointwise 95%CI for the mean expected titre crosses OD threshold between days 6-7. However, given sampling variation, test performance is likely to be optimal from several days later. IgG titres fell during the second month after symptom onset but remained above the OD threshold (at 60 days from symptom onset). No temporal association was observed between IgM titres and time since symptom onset.	Not peer reviewed

	days after first symptoms; (n=6). Convalescent samples were collected from adults a median 48 [range 31-62] days after symptom onset and/or date of positive throat swab (n=18)		**Other outcomes:** There was no evidence that SARS-2-CoV severity, need for hospital admission or patient age were associated with IgG or IgM titres in multivariable models	
An 2020[3] China Retrospective Case series DOI: 10.1101/2020.03.26.20044222.	SARS-CoV-2 The discharge criteria of the recovered patients included: temperature returned to normal for >3 days, respiratory symptoms significantly improved, and significant absorption of pulmonary lesions of chest CT imaging, and at least 2 consecutive negative RNA test results at least 24 hours apart.	N=262 confirmed SARS-COV-2 patients discharged from Shenzhen Third People's Hospital. Among them, mild, moderate and severe patients accounted for 11.4% (n=30), 81.0% (n=212) and 7.6% (n=20), respectively	Up to March 10, 14.5% of convalescent patients (n=38) were re-detected to be SARS-CoV-2 respiratory RNA positive during their followed-up period. **Rate of seroconversion** 36.7% (11/38) of RP patients were characterised by mild symptoms. The percentage was significantly higher than what was seen among non-RP patients (12.7%, 19/204, p<0.01). There were no re-detected positive cases in severe patients. **Timing of seroconversion** RNA negative conversion occurred mostly within 2-3 weeks since onset of illness among 63.6% of mild and within 1-2 weeks since onset among 22.2% moderate RP patients. By contrast, there were more NRP patients who displayed RNA negative conversion after 3 weeks since onset regardless of mild or moderate status. **Duration of immunity** Not reported **Other**	Not peer reviewed

	RT-PCR was performed using a China Food and Drug Administration (CFDA) approved commercial kit specific for 2019-nCoV detection (GeneoDX Co., Ltd., Shanghai, China) or Sherlock kit gifted from Feng Zhang lab. The redetectable positive (RP) patients were confirmed by digestive (anal swab) and respiratory positive RT-PCR tests. All patients followed for minimum of 14 days.			
Chen 2020d[15] https://www.tandfonline.com/DOI/pdf/10.1080/22221751.2020.1732837 China	SARS-CoV-2 Blood, pharyngeal and anal swabs Nucleic Acid Isolation Kit (Da'an Gene Corporation, Cat: DA 0630)	57 patients; 2 cohorts • blood detection cohort (n=57) • anal swab cohort (n=28) Patient diagnosed as severe if they had at least one of the following (1) respiratory distress; rate >= 30/min (2) oxygen	**Rate of seroconversion:** • In blood detection cohort, 6 cases had detectable virus in the blood (10.5%); 51 had no virus detectable in the blood (89.5%) • In anal swab cohort, 11 of 28 were anal swab positive (39%) **Timing of seroconversion:** Not reported.	Peer-reviewed; Emerging Microbes & Infections

Cross-sectional		saturation ≤ 93% in the rest state; (3) arterial oxygen tension over inspiratory oxygen fraction of less than 300mm Hg	**Duration of immunity:** Not reported **Other:** • In blood detection cohort, 6 cases had detectable virus in the blood, all of which were classified as severe; 51 had no virus detectable in the blood and only 12 (23.5%) were classified as severe. The ratio of severe symptoms between these 2 groups was statistically significant (p=0.0001) • In anal swab cohort, 11/28 were anal swab positive, 8 of them (72.7%) classified as severe, which was significantly higher than that 4 (23.5%) of the remaining 17 cases were classified as severe	
Dahlke 2020[17] 10.1101/2020.04.14.20059733 Germany Immunological case series	SARS-CoV-2 Peripheral Blood mononuclear Cell immunotyping (PBMC) IgG, IgM and IgA serum antibody interactions differentially detected with fluorescently labelled secondary antibodies **Day of serum collection after symptom onset:** Patient 1: 6, 10 and 22 Patient 2: 3,15 and 24	4 patients and 1 healthy control Patient 1: 64-year old male defined as a 'more severe' case than the others Patient 2: 62-year old female (mild) Patient 3: Female; age not reported (mild), included as control Patient 4: Male; age not reported (mild/moderate) included as control Patient 5: age and gender not reported, included as negative control	**Rate of seroconversion:** 100% **Timing of seroconversion:** Memory B-cell population (CD19+CD24+cd38-/low) increased after approx. 15 days post disease onset in patients 1 (more severe) and 2 (mild) and persisted in the severe case to day 32 Expansion of plasmablasts (CD19+CD27+CD38+) detected in the mild case day3 and in the severe case as symptoms began to resolve but early time points were not analysed by flow cytometry from this patient Patient 1 (more severe) showed few IgA and IgG reactive peptides (above control sample threshold) at day 6, which considerably increased towards day 22 after virus clearance. Mild case had higher number of IgA reactive peptides already at day 3 post onset of symptoms and showed a decreasing number of reactive peptides from day 3 to 24. At this early time point, defined IgA epitopes were detected in the spike protein, while patient 1 developed these only at day 22. The trend of early IgA	Not peer-reviewed MedRvix

	Patient 3: day 12 Patient 4: days 4 and 11 Patient 5: N/A		and IgG antibody response was also observed in control patient 4 (moderate case, day4 and day12) Patient 1 on day 6, IgA only target the ORF1ab polyprotein, at day 10 IgA response still low and at day 22 it turns into a broad response targeting the spike (S), membrane (M), ORF8, and nucleocapsid (N) proteins. While most IgA ORF1ab signals increase over time in patient 1, three signals decrease considerably. In contrast, some IgG responses were already present on day 6, targeting the S and M protein. In patient 2 a stronger and more focused IgA response was observed at day 3 against the S,E, N and ORF1ab proteins compared to patient 1, whereas in the IgG response only one stronger response was observed in towards the S protein. **Duration of immunity:** Not reported	
He 2020[38] 10.1016/j.jcv.2020.104361 China Retrospective	SARS-CoV-2 fluorescence RT-PCR Clinical, laboratory, and radiological findings of patients obtained from electronic medical records.	204 patients classified as 'severe' (n=69; 33.82%) and 'non-severe' (n=135; 66.2%) *Sex* Male 38.7%; 31.1% non-severe were male; 53.62% of severe were male. *Age* There was significant difference in age between non-severe (43; IQR, 31-53) and severe (61, IQE, 52-74). 57 (27.94%) patients had comorbidities, including hypertension, diabetes, malignancy, chronic lung disease. The proportions of some	**Rate of seroconversion:** Not reported. **Timing of seroconversion:** Not reported. **Duration of immunity:** Not reported. **Lymphocyte counts:** Lymphocyte subset count were significantly lower in the severe group (p<0.001). The level of all lymphocyte subsets was within the normal range during hospitalisation in non-severe group. *CD3+ count* Non-severe: 1066 (804-1321); Severe: 305 (198-525). *CD4+ count* Non-severe: 645 (461-794); Severe: 184 (103-293). *CD8+ count*	Peer-reviewed; Journal of Clinical Virology

		comorbidities, including hypertension, CVD and cerebral aneurysm, were significantly higher in the severe group. Patients classified as severe and non-severe according to 'Pneumonia diagnosis and treatment program for novel coronavirus infection (trial version 5).	Non-severe: 366 (274-482); Severe: 121 (54-197). *CD19+ count (B cell)* Non-severe: 190 (139-268); Severe: 91 (54-139). *CD16+ 56+ count (NK cell)* Non-severe: 144 (93-231); Severe: 105 (66-168). **Humoral immune function** A significantly higher level of IgG and Complement C3 and lower IgM were detected in patients in the severe group. The level of IL-4 and TNF-α were significantly higher in the severe group. **Association of comorbidities and immune response** T cell counts, IgM, IgA and C4 were significantly lower in patients with comorbidities. **Immune status according to disease severity** Levels of TNF-α, IL-4, IgG and C3 were negatively correlated with the counts of T cell in severe patients but IgM showed a positive correlation. 15 patients in severe group were further divided into 'improved' (n-7) and 'dead' (n=8). T cell count in dead group continued to decrease till death. However, T cell count began to increase after 15 days treatment, finally returning to normal level after 25 days treatment in patients in improved group. The time of recovery of lymphocyte count was approximately consistent with the time point of improvement of clinical course. The levels of B cell and NK cells were close to normal range with no significant difference in the two groups. **AUC/ROC in severe patients:** CD3+, CD4+, CD8+ t cells had significantly high sensitivity and specificity and the AUC were 0.980 (95% CI, 0.966-0.995), 0.972 (95% CI, 0.954-0.990) and 0.933 (95% CI, 0.896-0.969) respectively in severe patients with SARS-COV-2 pneumonia.	

			The sensitivity and specificity of humoral immune parameters were lower (AUC ranged from 0.5 to 0.612. **Conclusion** The level of T lymphocyte could be used as an indicator for prediction of severity and prognosis.	
Huang 2020a[44] China Case series DOI: 10.1101/2020.05.06.20089573	SARS-CoV-2 Chemiluminescent microparticle immunoassay (CMIA) kit (Innodx, Xiamen, China, catalog no. Gxzz 20203400198)	417 SARS-COV-2 in-patients who were discharged; mild (n=16), moderate (n=309), severe (n=73), critical (n=19) 3 died and remaining 414 included in this study. Patients who had positive nasopharyngeal swab post-discharge were defined as 'case' patients. Controls 13.6% 0-29 years; 47.5% 30-54 years; 38.8% 55-86 years; 48.4% male; 3.8% mild; 71.9% moderate;19.7% severe; 4.6% critical. Cases 33% 0-29 years; 49% 30-54 years; 17% 55-86 years; 41% male; 4% mild; 88% moderate; 7% severe; 0% critical. Patients who had positive nasopharyngeal swab post-discharge were defined as 'case' patients. Case patients were generally younger than controls and 93% had mild or moderate illness.	**Definition of reinfection:** Positive qRT-PCR nasopharyngeal test. **Definition of recovery/Discharge criteria:** Being afebrile for at least 3 days; improvement of radiological abnormalities on CT or X-ray, 2 consecutive negative qRT-PCR tests sample >1 day apart. **Readmission criteria:** Positive qRT-PCR nasopharyngeal test. **Rate and timing of re-detection positive:** Of 414 patients, 69 re-test positive (53 with 1 readmission, 13 with 2 readmissions and 3 with 3 readmissions). Median time from new onset of symptoms either to first positive nasopharyngeal swab PCR test after admission or PCR test negative after treatment was 3 to 12 days respectively. 70% overall in the case group retested positive within 5-25 days after the first negative test, with a peak occurring at 10-15 days. Of the 16 who retested positive once again there was a median of 8.5 days from test negative to retest positive. Of the 3 patients who retested positive for the fourth time, median time from prior testing to retest positive was 5.5 days. 16.7% (95% CI 13.0=20.3%) retest positive 1 to 3 times after discharge despite being in strict quarantine.	Not peer-reviewed

		A subset of 154 patients had IgG/IgM antibody testing at initial discharge	A subset of 154 patients had IgG/IgM antibody testing at initial discharge. 85 and 153 were IgG and IgM positive respectively. 1/154 had repeated negative antibody tests (n=5) of both IgM and IgG. Of the 154 patients tested, 40 (100%) of the case group were IgG positive, and 30 (75%) of were IgM positive. **Symptomatic/Asymptomatic (overall and at time of re-detection)** Patients who had positive nasopharyngeal swab post-discharge were defined as 'case' patients. Case patients were generally younger than controls and 93% had mild or moderate illness and had respiratory symptoms including cough and increased sputum at the readmission of PCR positivity. **Other:** Multivariable model developed to predict the risk of recurrence	
Lee 2020b[54] Taiwan Cross sectional https://www.journalofinfection.com/article/S0163-4453(20)30230-9/abstract	SARS-CoV-2 Frequencies of antibody testing of the 14 patients were performed at the discretion of the attending physicians at each participating hospital ALLTEST 2019- nCoV IgM/IgG Rapid Test Cassette (Hangzhou	33 samples from 14 SARS-COV-2 patients from 6 hospitals between January and March 2020; 6 symptomatic, 8 asymptomatic/mild (see below for classification) Median age (range): Symptomatic 52 years (45-73); Asymptomatic/Mild 50 years (30-88) Males: 2 (33.33%) symptomatic; 5 (62.5%) asymptomatic/mild. 1 patient had diabetes, 1 HIV infection; all patients in symptomatic group had fever but only 1 in asymptomatic had fever.	**Rate of seroconversion:** • Of 6 symptomatic patients, all had positive IgG and 4 had positive IgM responses • Of 8 asymptomatic/mild patients, none had positive IgM responses and 3 had negative IgG responses. In 1 of these 3 cases, a false positive rRT-PCR was suspected. However, the presence of lower IgG titres may have contributed to the negative IgG results obtained. **Timing of seroconversion:** • Earliest detection of IgM was day 5 (symptomatic patient) and longest persistence was day 42 (symptomatic patient).	Peer-reviewed; Journal of Infection

	ALLLTEST Biotech Co.)	28 samples from 28 hospitalised with respiratory tract infections that tested negative (twice) for SARS-CoV-2) were evaluated to validate the performance of the assay SARS-COV-2 patients were classified as *symptomatic* (fever for more than 3 days, obvious pneumonia patches on chest radiographs, and respiratory distress defined as oxygen saturation less than 95% or needing oxygen supply during hospitalisation) and *asymptomatic/mild* (those who did not meet the criteria for severe)	• Earliest detection of IgG was day 5 (symptomatic patient) and most cases had persistently positive IgG after positive conversion. **Duration of immunity:** • Of 6 symptomatic patients, the duration of positive rRT-PCR results ranged from 12 to 46 days. Patients with positive IgM results seemed to have a short duration of viral shedding. • Of 8 asymptomatic/mild patients, none had positive IgM results and 3 had negative IgG results (The last day of the IgM/IgG testing after the notification of positive rRT-PCR for these 3 cases was >42 days in case 11, > 28 days in case 12 and 13 days in cases 13 (the latter showed a positive result only on 1 day but was negative on the 3 subsequent tests)) • Except for case 13, the duration of the presence of SARS-C0V-2 RNA was generally longer in the asymptomatic than the symptomatic group. **Other:** The duration of positive rRT-PCR persistence was associated with antibody response and clinical manifestation. Patients with prominent symptoms and development of anti-SARS-CoV-2 IgM antibodies had a shorter duration of positive results and no worsening of clinical conditions compared to those without IgM antibodies.	
Liu 2020c[62] https://www.journalofinfection.com/article/S0163-4453(20)30182-1/pdf China	SARS-CoV-2 Test type and location of sample not stated Tests undertaken on admission to hospital	39 hospitalised patients; mean age 53 (IQ, 41 to 61); 20 women, 19 men; median time from onset to admission 5 days (IQR, 3-7); 38.5% had co-morbidities. 21 (53.8%) mild and moderate infection	**Rate of seroconversion:** Not reported. **Timing of seroconversion:** Not reported **Duration of immunity:** Not reported **Other:** CD4+T cell and CD8+ T cell counts were closely related to disease severity and clinical outcome. The more serious the disease and the worse the prognosis, the	Letter to editor

Letter to editor describing retrospective cross-sectional		18 (46.2%) severe and critical infection (according to Guidelines for Diagnosis and Treatment of SARS-COV-2 (Trial version 6))	lower were the T cell, CD4+ T cell and CD8+ T cell counts on admission.
			• T cells (x10^6/L) *p*=0.004
			  ○ mild/moderate; 914.0 (468.0-1214.0)
			  ○ severe/critical; 343.5 (237.0-730.3)
			• CD4+ T cells (x10^6/L) *p*=0.006
			  ○ mild/moderate; 591.0 (266.0-718.5)
			  ○ severe/critical; 217.5 (112.8-324.5)
			• CD8+ T cells (x10^6/L) *p*=0.011
			  ○ mild/moderate; 288.0 (165.0-414.5)
			  ○ severe/critical; 122.5 (76.0-256.8)
			• CD4+/CD8+ *p*=0.447
			  ○ mild/moderate; 1.780 (1.305-2.330)
			  ○ severe/critical; 1.345 (0.930-2.413)
			• B cells(x10^6/L) *p*=0.360
			  ○ mild/moderate; 174.0 (69.5-306.5)
			  ○ severe/critical; 105.0 (55.8-235.5)
			• NK cells (x10^6/L) *p*=0.352
			  ○ mild/moderate; 149.0 (58.8-240.5)
			  ○ severe/critical; 123.5 (44.5-177.8)	

Liu 2020b[60] DOI: https://DOI.org/10.1101/2020.03.28.20045765 Case series China	SARS-CoV-2 SARS-CoV2 antibody detection kit	N=133 Median age: 68 Female: 63; Male: 70 44 moderate cases (22 males and 22 females, median age was 67.5 [IQR 64-71.75]), 52 severe cases (28 males and 24 females, median age was 68 [IQR 61.25-74]), and 37 critical cases (20 males and 17 females, median age was 70 [IQR 60-76.5])	**Rate of seroconversion** **IgM** Seroconversion rate by severity of disease: Moderate: 79.6% Severe: 82.7% Critical:73.0% **IgG** Seroconversion rate by severity of disease: Moderate: 93.2% Severe:100% Critical: 97.3%	Not peer-reviewed

			Timing of seroconversion Not reported **Duration of immunity** Not reported	
Long 2020[129] 10.1101/2020.03.18.20038018 China Multi-centre cross sectional study with single centre follow-up	SARS-CoV-2 Magnetic Chemiluminescence Enzyme Immunoassay (MCLIA) (Bioscience Chongqing Co. Ltd., China, CFDA approved) Serum samples taken at 3-day intervals from February 8th 2020 to hospital discharge.	285 patients in multi-centre cross sectional study and 63 patients in single-centre follow-up Median age 47 years old (IQR, 34-56 years): 55.4% males 39 of 285 classified as severe or critical condition according to the guidelines	**Rate of seroconversion:** Overall 96.8% (61/63). 2 patients, a mother and daughter, lost to follow-up maintained IgG and IgM negative status during hospitalisation Not reported stratified by severity of disease **Timing of seroconversion:** Not reported stratified by severity of disease **Duration of immunity:** Not reported **Other:** IgG and IgM titres in severe group was higher than those in the non-severe group, although significant statistical difference is only observed in IgG level of 2 weeks (p=0.001)	Not peer-reviewed medRVIX
Okba 2020[69] Samples collected from France, the Netherlands, Germany, 10.3201/eid2607.200841	SARS-CoV-2 PRNT was used as a reference for this study ELISA Serum samples taken between day6 and 27 in mild and severe cases, days not specified but noted samples	10 samples from France were stratified as 'mild infection' (6 samples from 2 patients at different time points) or severe infection' (4 samples from 1 patient at different time points)	**Rate of seroconversion:** 100% of 2 cases that are stratified by severity **Duration of immunity:** Not reported **Other:** Antibody levels were higher following severe infection compared to the mild ones	Not peer-reviewed MedRvix

	were taken 'at different time points' over this period			
Phipps 2020[74] 10.1101/2020.05.15.20103580 USA, Texas Case series	SARS-CoV-2 Qualitative detection of IgG tested using Abbott ARCHITECT i2000SR (CMIA). Positivity threshold: ≥1.4 IgM tested using 'a laboratory developed protein microarray described previously'* Positivity threshold: Normalized signal intensity (NSI) ≥25	968 subjects, including 656 healthy controls, 29 with lupus erythematosus, 20 with RA, 90 with previous positive respiratory viral PCR panel and 173 confirmed cases who were tested for IgG 'Severe' cases were those admitted to ICU A subgroup of 37 PCR-positive cases (17 IgG positive, 20 IgG negative) tested for nucleocapsid-specific IgM. For 15 PCR-positive cases, 2-6 serial measurements were performed using available residual plasma samples. IgG levels and seroconversion were tracked over time (n=13 with known date of symptom onset, n=2 indeterminate date of symptom onset.	**Rate and timing of seroconversion:** **IgG** Of 173 confirmed or suspected cases, 76 were confirmed positive by PCR. Of these, overall 38% tested positive for IgG. The time course of symptom onset revealed increasing IgG positivity rates: • <3days: 7% (1/15) • 3-7 days: 30% (8/27) • 5-15 days: 33% (5/15) • >14 days: 83% (5/6) • Patients with indeterminate time from symptom onset: 77% (10/13) 77% (10/13) of 13 patients with known date of symptom onset with samples available for serial monitoring became IgG positive: • 0% (0/8) less than 3 days post-symptom onset • 33% (3/9) 3-7 days post-symptom onset • 86% (6/7) 8-13 days post-symptom onset • 91% (10/11) more than 14 days post-symptom onset • For those where seroconversion was not observed, samples were only available for <7 days from symptom onset for 2 cases or patient was significantly immunosuppressed. **IgM**	Not peer-reviewed medrxiv

			IgM testing was performed on 37 PCR positive specimens showed positivity in 53% (9/17) IgG positive patients and in 35% (7 /20) IgG negative samples. Compared to IgG positivity, IgM positivity occurred at: • larger proportion for <3days (3/6, 50%) • similar rates for 3-7 days (4/11, 36%) • similar rates for 8-13 days (4/11, 36%) • similar rates after 2 weeks (4/5, 80%) **Duration of immunity:** >14 days **Timing of sample collection and antibody response** Severely affected patients had higher IgG and IgM levels measured at a later time compared to mild cases. However, severely affected patients were tracked longer. Early increase in antibody titres was observed in mild/moderately affected patients when compared to severely affected patients **Disease severity and IgM/IgG value:** No association was observed between mild and severe disease course with respect to IgG and IgM cases.	
Qu 2020b[75] 10.1093/cid/ciaa489 China Case series	SARS-CoV-2 iFlash-SARS-CoV2 IgG/IgM immunoluminescent kit (C86095G/C86095M, YHLO BIOTECH, Shenzhen) 347 serum samples from 41 patients (5-31	394 patients admitted to hospital, 41 patients with preserved serum samples were included. Mild/moderate n = 15 Severe n = 16 Critical n = 10 Median age 62 years (IQR 42-66), 34.1% male, 22% had at least one comorbidity	The majority of patients developed robust antibody response between 17 and 23 days of illness onset. Delayed but stronger antibody response were observed in critical patients. **Rate of seroconversion:** 97.6% of patients (40/41) were positive with IgG and 87.8% (36/41) were positive with IgM. All controls tested negative. **Timing and duration of seroconversion:** As most early cases went to the hospital late (~8 days after symptom onset), their first serum specimens were already positive with IgG or IgM. Thus, seroconversion of	Peer-reviewed; Clinical Infectious Diseases

	samples from each patient) collected between 3 and 43 days of disease onset Control sera from 10 patients with influenza and 28 patients completing routine check-ups. These were tested for IgG and IgM simultaneously.	Patients classified as mild and moderate (n=15), severe (n=16) and critical (n=10) Mild=clinical symptoms were mild without manifestation of pneumonia on imaging. Moderate= fever, respiratory symptoms, and with radiological findings of pneumonia. Severe= any 1 of – respiratory distress/hypoxia/abnormal blood gas analysis. Critical = any 1 of -respiratory failure requiring mechanical ventilation/shock/other organ failure that requires ICU care.	IgG and IgM was only observed in 16 (39%) and 21 (51.2%) respectively. • Median time of seroconversion for IgG was 11 days (8-16) after onset. • Median time of seroconversion for IgM was 14 days (8-28) after onset. • IgG reached highest concentration on day 30. • IgM reached highest concentration on day18, but then began to decline. • 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)	
Tan 2020[123] China Prospective cohort study https://www.medrxiv.org/content/medrxiv/early/2020/03/26/2020.03.24.20042382.full.pdf	SARS-CoV-2 Serum ELISA kits (Livzon Diagnostics Inc. Zhuhai, China)	67 hospitalised SARS-CoV-2 infected patients with 342 sequential serum samples. Median age 49 years (range 10-77 years); 35 (52.2%) male; 25 (37.3%) had underlying diseases; 29 were classified as severe pneumonia (9 critical), including all 3 children,	**Rate of seroconversion:** • Of severe patients 53.6% were positive for IgM, 44.4% negative • Of non-severe patients, 41.9% were positive for IgM, 58.1% negative • Of severe patients 82.1% were positive for IgM, 17.9% negative • Of non-severe patients, 84.6% were positive for IgG, 15.4% negative **Timing of seroconversion:** Min required observation period for IgM 18 days and for IgG 21 days. • Days of antibody 1st detectable in positive severe patients IgM 11.6 +/-3 days	Not peer-reviewed MedRvix

			• Days of antibody 1st detectable in positive non-severe patients IgM 14 +/- 5.3 days • Days of antibody 1st detectable in positive severe patients IgG 13.4+/- 4 days • Days of antibody 1st detectable in positive non-severe patients IgG 15.3 +/- 5.7 days **Duration of immunity:** Not reported **Other:** Patients were classified as strong responders (peak titre >2-fold of cut-off value), weak responders (peak titre 1-2 fold of cut-off value) and non-responders (peak titre below cut-off value). • Proportion of strong responders is significantly higher and the proportion of weak responders is significantly lower in severe patients than in non-severe patients, IgM (p=0.017) and igg (p=0.032). • Titres of IgM and IgG were continuously significantly higher in severe patients than in those in non-severe patients along with time (IgM, p=0.008; igg p=0.009). • Proportion for viral clearance at day 7 after antibodies appearance was significantly higher in non-severe patients than in severe patients (for IgM, 81.8% vs. 7.7%, p=0.001; for igg, 60.0% vs. 26.3%, p=0.048). Furthermore, the weak responders for IgG antibodies had a significantly higher viral clearance rate (56.5%) than that (9.1%) of strong responders (p=0.011)	
Yongchen 2020[131] China	SARS-CoV-2 Gold immuno-chromatography assay (Innovita Co. Ltd. China)	21 SARS-CoV-2 patients in two hospitals; non-severe n-11; severe n=5; asymptomatic carriers n=5.	**Rate of seroconversion:** 100% overall **Timing of seroconversion:**	Peer-reviewed; Emerg Microbes Infect

Retrospective cross sectional DOI: 10.1080/22221751.2020.1756699	Timing not stated but paper reports results from weeks 1,2,3 and up to 6 weeks, implying weekly tests. Serum samples	Median age overall 37 years (10-73); Median age non-severe 35 years(24-73); Median age severe 54 years (30-68); Median age asymptomatic 25 years (10-61) Female overall 38.1%; Female non-severe 45.5%; Female severe 20%; Female asymptomatic 40%; Illness severity defined according to the Chinese management guidelines for SARS-CoV-2 (version 6.0). Asymptomatic defined as individual who were positive for SARS-CoV-2 nucleic acid but without any screening of close contacts.	Non-severe 27.2% seroconverted within 1 week; 63.6% within 2 weeks; 81.8% within 3 weeks; 100% within 6 weeks For 72.7% of non-severe the first detection of antibody responses occurred during the period when their swab samples converted to RNA negative, suggesting that antibody reposes might facilitate the viral clearance especially for non-severe patients. All severe patients seroconverted within 2 weeks. Of note, 3 out of 5 severe patients generated viral specific IgG responses prior to viral clearance. It is possible that significantly high level of SARS-C0V-2 viral load observed in severe cases drives early antibody response produced by immediate activation of extrafolllicular B cell during acute infection. Only 1 (20%) out of 5 asymptomatic cases generated SARS-CoV-2 specific antibody responses, and this patient was not seroconverted until week 3 of her diagnosis. Consistent with her delayed antibody response, the throat swab converted negative as late as week 3. For the remaining 4 asymptomatic patients, 2 were not seroconverted within week 2 and 3 respectively, while 2 remained negative during week 4. It is not known if they seroconverted later. (False positive nucleic acid tests cannot be ruled out) **Duration of immunity:** We observed well-maintained antibody responses for all seroconverted individuals for at least 6 weeks **Other:** We did not identify a strong association of seroconversion and disease severity, in both severe and non-severe, viral specific antibody responses were detected. Our study revealed an early induction of antibody responses in severe cases. We can also speculate that	

			high level of initial viral load may lead to severe SARS-COV-2 cases (Paper then describes the possible mechanism of this … strong B cell responses leading to rapid AB responses *not* following the sequence of IgG/IgM development stages… and promoting monocyte/macrophage accumulation and massive cytokine storm, which might be responsible for fatal acute lung injury)	
Wang 2020b[86] 10.1101/2020.04.15.20065623 China Case series	SARS-CoV-2 Modified cytopathogenic assay. Indicators for immunogenicity assessment included seropositivity rate and determination of GMT. Neutralising antibody titre calculated by Reed-Meunch method on day 5. Blood samples collected from 2, 3 and 4 time points in 19, 8 and 4 patients, respectively. 39 patients had 1 blood sample only. Total 117 blood samples were analysed.	70 SARS-CoV-2 Patients (12 inpatients and 58 convalescent patients). Mean age 45.1 years (range 16 to 84 years). 2 patients had history of CVD, 5 of diabetes, 9 of hypertension. • 1 patient asymptomatic • 22 mild • 43 moderate • 4 severe (1 inpatient and 3 convalescent) 117 blood samples	**Rate of seroconversion:** 100% **Timing of seroconversion:** Not reported stratified by severity **Duration of immunity:** Seropositivity reported up to day 53 of study, not stratified by severity **Other:** Compared to the patients with asymptomatic or mild manifestations (GMT 1:141.9, 95% CI, 79.5 to 235.2), the antibody levels were similar to patients with moderate or severe condition (GMT 1:199.5, 95% CI, 141.8 to 280.5). However, after adjusting other factors, patients with more severe symptoms tended to have a higher antibody titre (β=0.4639, (SE 0.2036; CI 95%, 0.0649 to 0.8630, P=0.0227)). The GMT of convalescent patients was 1:212.7 (95% CI, 157.5 to 287.3), and was higher than inpatients (1:76.1, 95% CI, 33.5 to 172.9; P=0.0055)	Not peer-reviewed MedRvix

	Mean neutralising antibody test of 1st sample since onset of this study was 33 days (range 10 to 53 days) and 'the time of convalescent patients (35 days) was longer than inpatients (13.5 days)'			
Yu 2020[98] 10.1183/13993003.01526-2020 China Case series	SARS-CoV-2 Chemiluminescent immunoassay (CLIA)	37 patients with SARS-CoV-2; average 52.3years +/-16.3 years: 25 (67.7%) male. 183 samples collected during hospitalisation 20 severe (includes severe and critically-ill cases) (54%) and 17 non-severe (includes mild and moderate) patients. Severe patients had at least 1 of: shortness of breath with respiratory rate >=30 times/min; oxygen saturation ≤ 93%; PaO2/FiO2 ≤300mmHg Critical patients had a least 1 of the following criteria: respiratory failure requiring mechanical ventilation; shock; or multiple organ failure requiring ICU.	**Rate of seroconversion:** Positive rate of IgA, IgM and IgG were 98.9%, 93.4% and 95.1% respectively. **Timing of seroconversion:** First seroconversion day of IgA was 2 days after onset of initial symptoms, and 1st seroconversion of IgM and IgG was 5 days after onset. Seroconversion for IgA, IgG and IgM was 100% by day 32. Median conversion time was 13, 14 and 14 days respectively. IgA and IgG were markedly increased around 2 weeks after symptom onset and remained continuously elevated for the following two weeks. In contrast, the levels and time dependent changes of IgM were minimal. **Duration of immunity:** IgG antibody levels increasing at week 8 since illness onset for all patients (positivity threshold not reported) **IgA** Severe: Levels start to decline at week 2/3 Non-severe: Levels increase at weeks 3/4-4/5(end-point) **IgG**	Letter to editor

			Severe: Levels decline weeks 2/3-5/6. Increase weeks 5/6-7/8. Non-severe: Levels decline between weeks 2/3 and 4/5 (end-point). **IgM** Severe: Levels decline between weeks 5/6-7/8. Non-severe: Levels decline between weeks 2/3-4/5 (end-point). **Other:** • The relative levels of IgA and IgG were markedly higher in severe patients compared to non-severe. • There were significant differences in relative levels of IgA and IgG between the severe and non-severe. • There were no statistically significant changes occurred in the levels of IgM between severe and non-severe patients after disease onset. • The levels of specific IgM were significantly lower than those of IgA in both severe and non-severe patients.	
Yuan 2020[99] DOI: 10.21203/rs.3.rs-22829/v1 China Case series ('cohort study')	SARS-CoV-2 **RT-PCR for viral load** Performed by nasopharyngeal swabs and anal swabs 7 and 14 days post-discharge RT-PCR test kits (Bio-Germ)	N=182 recovered patients under medical isolation observation Among all the recovered and isolated, there are 182 of them has been re-tested for at least one time, 84 (46.2%) of the 182 were males and 98 (53.8%) were females, the average age was 46.4±17.1	20 (10.99 %) patients out of the 182 were re-detected SARS-CoV-2 RNA positive Thirteen of them tested to be re-positive on the 7th day, and another 7 on the 14th day; 14 were tested as nasopharyngeal swabs positive, and 6 were anal swabs positive, none has found both swabs positive None became symptomatic on re-detection Females and young patients aged under 15 have higher re-positive rate than the average, and none of the severe patients turned re-positive.	Not peer-reviewed

	A cycle threshold value (Ct-value) < 37 was defined as positive, and Ct-value no less than 40 was defined as negative. A medium load, more than 37 and less than 40, will be defined as weak positive, which requires further confirmation by retesting Ig detection The total immunoglobulin, IgA, IgG and IgM of 14 re-positive patients were tested on the 7th day by a SARSCoV-2 testing kit (WANTAI BioPharm) based on Chemiluminescence method	(median 49, ranges 1-81); 39 (21.4%) had severe symptoms, 143 (78.6%) mild and moderate Discharge criteria: 1. Temperature below 37 degrees lasting at least 3 consecutive days; 2. Resolved respiratory symptoms; 3. Substantially improved in chest lesions computed tomography (CT) images; 4. 2 consecutively negative RT-PCR test results with at least 1 day interval	Notably, most of the re-positive cases turn negative in the followed tests **Antibodies** 14 out of the 20 re-positives were assessed. Total immunoglobulin, IgA and IgG were positive in 14/14 IgM positive in 10/14 The re-positives are transferred to designated infectious hospital for quarantine treatments, and again their RT-PCR testing results of blood, nasopharyngeal swabs and anal swabs were collected on the 1st, 4th and 7th day (some were taken on 2nd and 6th) N=5/14 still positive	
Zhou 2020[107] China Case series	SARS-CoV-2 Inflammation profiles measured with automatic biochemical	21 ICU patients; 13 males, 8 females; 8 severe, 13 critical; mean age 66.10 years (SD 13.94 years); 76.2% had at least one coexisting disorder on admission.	**Rate of seroconversion:** IgG 100% (19/19) IgM 89.5%;75% (6/8) severe, 100% (11/11) critical **Timing of seroconversion:**	Peer-reviewed; Clinical and Translational Science

DOI: 10.1111/cts.12805	analyser (Cobas 6000 c501 analysers Roche, Germany) SARS-CoV-2 IgG and IgM measured with immunoanalyser (iFlash 3000 immunoanalysers, YHLO Biotech, Shenzhen, China)	Fever was present in 81.0% of patients on admission. Most patients had at least one coexisting disorder on admission. Classification according to China's National Health Commission	Not reported **Duration of immunity:** Not reported **Other:** **Lymphocyte counts (mean ± SD)** Lymphocytopenia was present in 85.7% of patients. Severe: 0.79 ± 0.41 Critical: 0.66 ± 0.46 There were 18 patients (94.7%) with high CRP, 17 (89.5%) with high IL=6, 1 with elevated PCT. Autoimmune phenomena exist in SARS-CoV-2 subjects, and the results provide the rationale for a strategy of prevention of dysfunction of immune and optimal immunosuppressive therapy in future.	

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