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

9 June 2020

Version history

Version	Date	Specific updates
V1.0	13 May 2020	
V2.0	9 June 2020	Updated search with 36 new studies

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

Key points

- In total, 102 studies were identified that investigated the immune response following coronavirus infections, including SARS-CoV-2 (n=74), SARS-CoV-1 (n=25) and MERS-CoV (n=3).
- Six separate research questions were identified that focussed on the 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.
- The detection rate and or timing of antibodies following acute SARS-CoV-2 infection was assessed in 43 studies. Immunoglobulin M (IgM) was typically the first antibody to rise in acute infection, followed by immunoglobulin G (IgG), with IgG tending to persist for much longer in the body. The median time to antibody detection following symptom onset ranged from 5 to 17 days for IgM and 6 to 14 days for IgG. While the rate and timing of IgM and IgG detection were inconsistent across studies due to differences in the timing and sampling methods used, SARS-CoV-2-specific IgG antibodies were detected in over 90% of individuals at two weeks and 100% at four weeks.
- The adequacy or duration of the immune response is not yet known. Twelve studies were identified that reported the duration of the immune response following SARS-CoV-2 infection beyond four weeks. IgG was detected in all patients at the end of follow-up, including in four studies that followed individuals for eight weeks. Neutralising antibodies were detected in over 90% of all patients who were sampled at the end of follow-up (4-7 weeks).
- Due to the lack of long-term follow-up data relating to SARS-CoV-2, evidence on other coronaviruses was retrieved, although the applicability of these to SARS-CoV-2 is unknown. Twenty-five studies reported on the duration of SARS-CoV-1-specific immunity. In general, SARS-CoV-1-specific IgG antibody levels were sustained for one to two years post-infection, declining thereafter. Anti-SARS-CoV-1 neutralising antibodies may be detected up to 17 years post-infection. Three studies on MERS-CoV suggest the immune response is less consistent than for SARS-CoV-1; two studies reported sustained responses in cases of severe infection only while another reported a sustained response in all cases.
- Thirteen studies were retrieved that report re-detection of SARS-CoV-2 following recovery. An agreed definition for reinfection (as opposed to re-detection) was

not identified. These re-detection cases may be 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. Nearly all patients who were re-detected positive did not show obvious clinical symptoms or disease progression. Thus, it is not yet possible to conclude that reinfection following recovery from SARS-CoV-2 occurs.

- No study was found that directly addressed whether individuals re-detected with SARS-CoV-2 or other human coronaviruses are infectious to others. Four 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 of the four studies explicitly conducted contact tracing or follow-up.
- Data relating disease severity to immune responses were inconsistent across studies. While eight studies found that those with severe illness had higher antibody levels than those with moderate or mild illness, six found no or an inverse association.
- Thirty per cent of studies have not yet been peer reviewed (n=31/102) and the overall quality of evidence was low. Limitations of studies reviewed included the variability in the accuracy of tests used, use of tests that have not yet been validated, poor reporting of levels of detection employed, small sample sizes (both number of participants and number of samples taken), and short follow-up periods.

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

1 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 is 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 https://www.hiqa.ie/reports-and-publications/health-technology-assessment/protocol-evidence-synthesis-support-covid-19) were followed. Relevant databases of published literature and pre-print servers were searched. Below is the summary of all relevant evidence from 1 January 2000 until 26 May 2020. Data published by national agencies were not included. As the focus of the review is SARS-CoV-2, evidence was only considered for other coronaviruses where there was limited SARS-CoV-2 evidence available.

Results

The database search retrieved 4,744 citations. Following removal of duplicates, 4,119 unique citations were screened for relevance. In total, 102 studies were identified that met our inclusion criteria. These included 87 case series,[1-87] eight case reports,[88-95] five cohort studies[96-100] and two cross-sectional studies.[101, 102]

Seventy-four studies were conducted in China, five in France, four in Italy, three each in Germany, South Korea, and Taiwan, two each in Saudi Arabia, Singapore and the US, and one each in Finland, the Philippines, Switzerland and the UK.

SARS-CoV-2 was investigated in 74 studies, SARS-CoV-1 in 25 and MERS-CoV in three. Tables 1 to 6 provides the full details of the included studies.

2.1 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.[103] This response is followed by the generation of virus-specific immunoglobulin G (IgG), the most abundant antibody class in humans.[104] IgG responses are crucial for immunological memory and long-term immunity.[103]

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.

2.1.1 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,[3, 5-7, 14, 17, 19, 21, 22, 26-28, 30, 33, 35, 36, 39, 40, 42, 56-58, 63, 64, 67, 69, 78, 82, 83, 86, 105] five case reports,[45, 88, 89, 92, 95] two cohort studies[96, 98] and two cross-sectional studies.[101, 102] 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[33] and the largest number of samples taken was 535.[86] The median age ranged from 37[102] to 68 years,[51] 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).[22, 89]

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

2.1.2 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.[17] 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.[26, 58, 60, 64, 78, 82, 96, 102] 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 1 and 2, below, illustrate these findings.

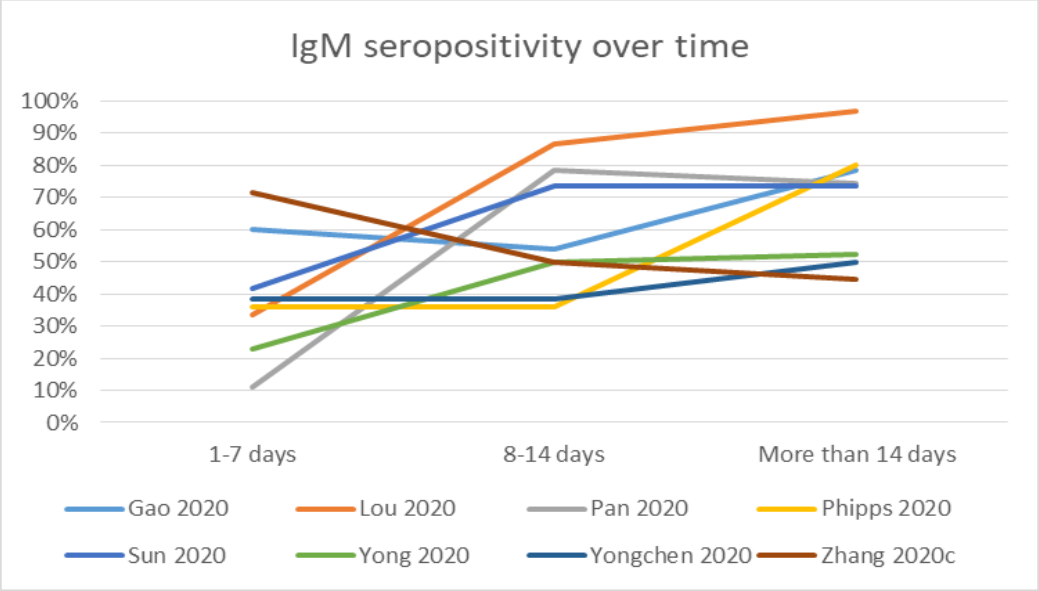
One study (n=34) evaluated antibody detection at two points in time;[14] at week three all patients tested positive for IgG and IgM, whereas at week five, all tested positive for IgG and 83% for IgM.

Seventeen studies reported the antibody detection rate at one point in time.[21, 39, 40, 56, 98, 106] 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.[22] Another case study found the patient tested positive for IgG on the seventh day.[89]

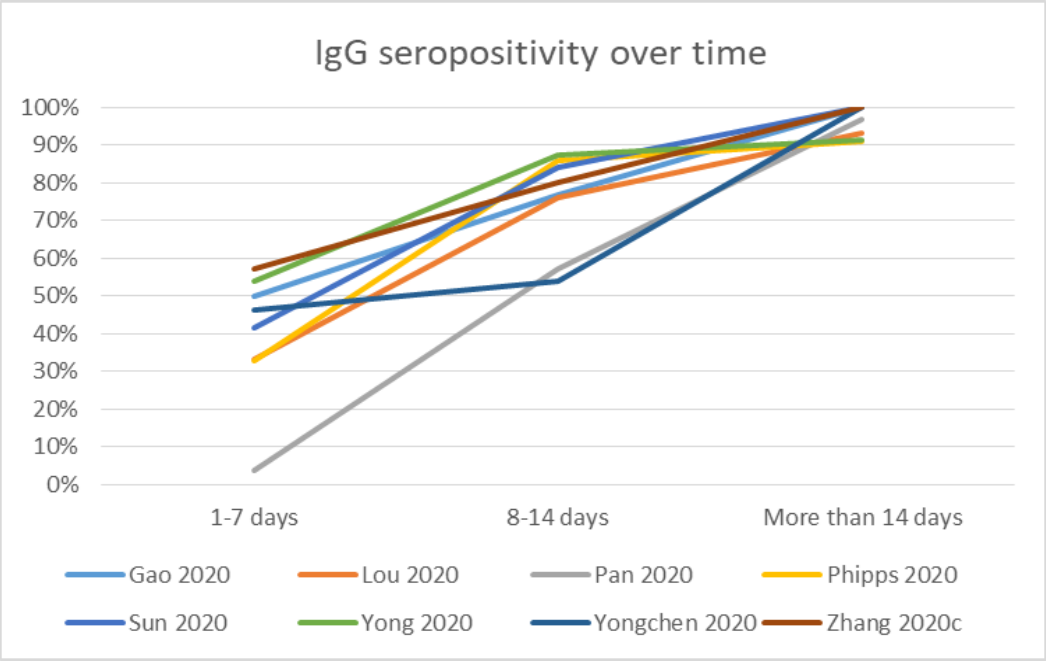
Two studies also reported IgA antibody detection; seroconversion rates were 93% at a median time of five days[28] and 74% at a median time of 22 days.[6]

Figure 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 2 IgG detection rate over time



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

2.1.3 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[28] to 17 days[35] for IgM and from six days[35] to 14 days[28] for IgG. Antibody detection timing was typically shorter for IgM than for IgG, while one study found IgG seroconversion before IgM.[106] 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.[21, 35, 102, 105]

Of the two studies that reported IgA antibody detection, the median seroconversion times were between five days[28] and 22 days.[6]

Four studies reported neutralising antibody data (sample sizes ranged from nine patients[69] to 162[22]). The first found that all patients tested positive for neutralising antibodies by day 14,[69] 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).[68] 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.[107] 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.[22]

Finally, a case series involving nine COVID-19 cases measured antibody titres (by immunofluorescence), viral load (by RT-PCR) and infectivity (live virus isolation).[69] 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

2.2 Research question 3: Duration of immune response

As SARS-CoV-2 was first identified in December 2019, there is a lack of evidence on the long-term duration of antibody responses following infection. Section 2.2.1 describes studies that report the duration of antibody detection beyond two weeks post-symptom onset.

SARS-CoV-1 and MERS-CoV, share similar clinical genetic and epidemiological features with SARS-CoV-2.[108, 109] As the process of generating SARS-CoV-1-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.

2.2.1 SARS-CoV-2

Twelve studies were identified that examined the duration of the immune response in SARS-CoV-2 infection beyond two weeks post-infection.[1, 20-22, 24, 35, 41, 56, 68, 82, 102] Maximum follow-up was between 60 and 65 days in one study.[1] Eight studies were conducted in China and one each was conducted in Germany, France and the UK. A number of different methods were used to determine immune response, including ELISA,[1, 20, 56] neutralising assay,[20, 28, 69] plaque reduction neutralisation test (PRNT),[56] ELISpot,[20] chemiluminescence immunoassay kits (CLIA),[41] as well as rapid tests such as lateral flow immunoassay devices (LFIA).[1] All studies were either case series or case reports. Four of these studies were published as pre-prints and have not yet undergone peer review.[1, 20, 28, 110] Details of study characteristics can be found in Table 2.

Eight studies reported on the duration of immunoglobulin antibody responses following infection (follow-up ranged from 4 to ≥8 weeks post-infection).[1, 20, 21, 24, 35, 41, 82, 102] Four of these studies were not peer-reviewed.[1, 20, 35] In three studies that followed patients for more than seven weeks (49-60 days), all (n=24) patients had IgG detected at the end of follow-up.[1, 21, 24]

In the first study, nine patients had serology data 50-60 days post-symptom onset.[1] IgM and IgG were detected in five (56%) and nine (100%) patients, respectively, at the end of follow-up. While IgG titres fell during the second month after symptom onset, they remained above the optical density threshold at 60 days. The second case series comprised 12 patients discharged from hospital (length of stay 11-37 days) following acute infection with SARS-CoV-2.[20] Serology testing was undertaken at discharge or two weeks after discharge.[20] An IgM and IgG response was detected in 100% patients and the IgG response was maintained for at least two weeks post discharge (the end of the study). The third study reported serology

results for a case series of 60 patients who were tested at 6-7 weeks from symptom onset.[21] IgM and IgG were detected in 47 (78%) and 60 (100%) patients, respectively. Serology was repeated in ten patients one week later (week 7-8) with a decline in titres noted for both antibodies, which was greater for IgG than IgM. In the fourth study, 98 serology measurements from 43 patients indicted that the positivity rate for IgG reached 100% by 11-15 days after onset of symptoms and remained at this level 31-55 days after symptom onset.[41] The fifth study reported serology results for eight patients at 40-50 days post-symptom onset.[82] 100% of cases were positive for IgG at this time, compared with 50% positive for IgM. The sixth study reported 100% seropositivity for IgG at 51 days (number of patients enrolled was 221, however the number followed for the entire duration of the study was not reported).[35] In the seventh study, at 49-56 days post-symptom onset, IgG positive was positive in all sampled cases (n =5).[102]

Four case series (range: 3-162 patients) reported neutralising antibody serology data, with the longest follow-up 41-53 days post-symptom onset. The first case series comprised 12 patients discharged from hospital following acute infection with SARS-CoV-2.[20] Serology testing was undertaken at discharge (n=6, length of stay 17-37 days) or within two weeks of discharge (n=6, length of stay 11 to 19 days). Four out of the six recently discharged patients had high neutralising antibody titres; the titres in five out of the six patients who were two weeks post discharge were positive, for four of these the titres were lower than in the recently discharged patients. Overall, 11/12 patients were positive for neutralising antibodies. In the second case series which included 117 samples from 70 patients, a 100% seropositivity rate was reported at 41-53 days after symptom onset (based on 29 samples). The highest antibody titres were reported to occur between days 31-40; titres then decreased slightly between days 41-53.[28] In a small case series comprising two mild and one severe case, the authors reported detection of neutralising antibodies in all three cases 20-30 days after symptom onset.[56] In the fourth case series, 162 healthcare staff infected with SARS-CoV-2 were followed and neutralising antibodies were detected in 79%, 92% and 98% of samples collected on day 13-20, 21-27 and 28-41 after symptom onset, respectively.[22]

Only one study reported on T-cell responses.[20] The authors found that compared with healthy donors, the number of IFN-gamma secreting NP specific T-cells in four (out of 6) recently discharged patients suggested that they had developed a SARS-CoV-2 specific T cell response.[20] Only one of the six patients who had serology testing two weeks after discharge had a high number of IFN-gamma secreting T cells, suggesting anti-viral T cells may not be maintained at high numbers in recovered patients. Table 3 summarises the duration of immune responses following SARS-CoV-2 infection.

Table 3 Summary of studies on maximum* duration of SARS-CoV-2 immune response

IgG positivity	**Adams 2020[1]**	50-60+ days post-symptom onset: N=9/9 patients positive for IgG; including N=2/2 positive at ≥60 days.**
	Dong 2020[20]	25–33 days post-admission to hospital: N=6/6 patients positive for IgG
	Du 2020[21]	49-56 days post-symptom onset: IgG positive in N=10/10 but titres declining
	Fu 2020[24]	53-55 days post-symptom onset: IgG positive in N=5/5
	Hu 2020[35]	46-51 days post-symptom onset: N=11/11 patients positive for IgG
	Jin 2020[41]	31-55 days post-symptom onset: N=8/8 serology measurements IgG positive
	Yongchen 2020[102]	44-50 days post-symptom onset: IgG positive in N=5/5
	Zhang 2020[82]	40-50 days post-symptom onset: N=8/8 serology measurements IgG positive
Neutralising antibodies	**Dong 2020[20]**	25-33 days post-admission to hospital: N=11/12 positive for neutralising antibodies
	Fafi-Kremer 2020[22]	28-41 days post-symptom onset: N=47/48 positive for neutralising antibodies
	Okba 2020[56]	20-30 days post-symptom onset: N=3/3 patients positive for neutralising antibodies
	Wang 2020[68]	41-53 days post-symptom onset: N=29/29 samples positive for neutralising antibodies
T-cells	**Dong 2020[20]**	4/6 recently discharged positive for T-cells. N=1/6 tested 14 days post discharge positive for T-cells

Note – *duration denotes longest follow-up in included studies. Duration of immune response inconsistently reported as either duration from symptom onset, post-admission or post-discharge. **Data derived from graph (Figure 1 in Adams 2020)

2.2.2 SARS-CoV-1

Twenty-five studies provided data on the duration of the immune response to SARS-CoV-1; maximum follow-up was up to seventeen years in one study,[4] up to twelve years in two studies,[29, 55] between one and six years in twelve studies,[8, 9, 12, 47, 49, 52, 54, 59, 65, 70, 76, 100] and up to one year in ten studies.[10, 11, 32, 34, 38, 46, 62, 74, 99, 111]

All studies were conducted in China apart from two in Taiwan,[11, 34] one in the Philippines [49] and two in Singapore.[4, 55] All studies were case series or prospective cohort studies, with sample sizes ranging from two[49] to 311[23] 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, 32, 34, 38, 112] and had disappeared by three to twelve months after infection.[11, 34, 46] In all studies IgG antibodies were detectable at the end of follow-up, which ranged from 12 weeks to one year.[10, 11, 23, 32, 34, 38, 46, 112] Two studies reported on the magnitude and duration of T cell immunity one year after the onset of symptoms.[38, 74] T cell populations were said to be decreased in convalescent patients compared with healthy controls in the early post-infection period in both studies.[38, 74] 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.[74]

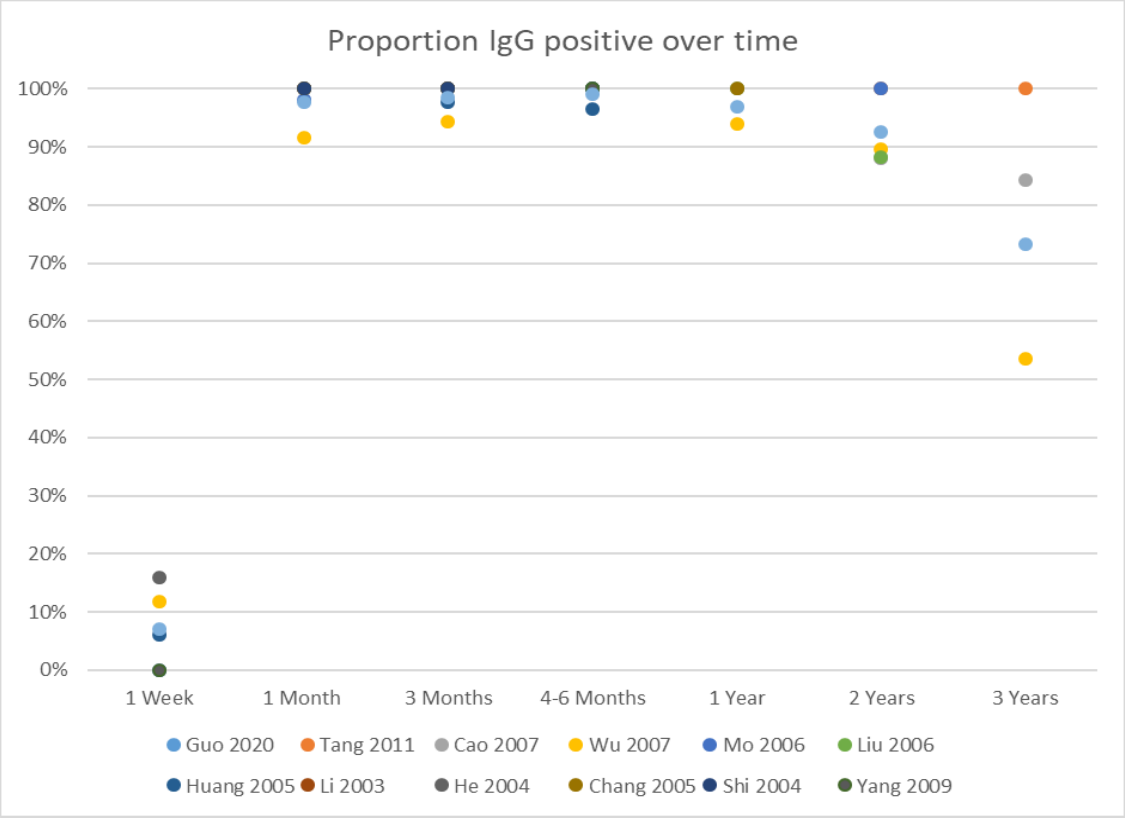
For studies with 1-2 years follow-up, IgG antibodies were still detectable at the study end point.[76, 100] Additionally, SARS-CoV-1 infection was reported to induce a strong memory T-cell response approximately one year after infection in both studies.[12, 76] Furthermore, cross-reactive memory T cells to SARS-CoV-1 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.[47, 52, 54, 59] In the first study, SARS-specific IgG and neutralising antibodies were detectable at the study end-point in all 30 patients.[47] High and sustainable levels of immune responses were found to be strongly correlated with disease outcome.[47] In a second study, IgG antibody and neutralising antibody titres were found to be highly correlated.[52] Neutralising antibodies were detectable in all patients at 24 months, however 11.8% of serum samples were negative for SARS-CoV-1-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.[54] 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,[47] in line with findings previously

reported at one year follow-up. A second study reported that SARS-CoV-1 N-protein-specific memory CD4+ and CD8+ T cells were maintained for two years after SARS-CoV-1 infection,[59] 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.[49]

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

Figure 3 Proportion IgG positive over time following SARS-CoV-1 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-1–specific IgG. IgM became undetectable at approximately 90 days.[70] In another study, only two of 23 patients maintained a low level of SARS-CoV-1-specific IgG antibodies at six years post-infection.[65] However, memory T cell responses to a pool of SARS-CoV-1 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.[65] No

SARS-CoV-1 antigen-specific memory B cell responses were detected. Of note, a fourth study reported that SARS-CoV-1-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,[29] neutralising antibodies[4] and T-cells[55] among SARS-CoV-1 survivors. SARS-CoV-1 specific IgG antibodies against the whole virus were detected for at least 12 years in one study.[113] 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).[113] The second study reported on the response of memory T cells, and found that SARS-CoV-1-specific memory T cells targeted against SARS-CoV-1 structural proteins persisted up to 11 years post-infection in all three recovered patients.[55] SARS-specific T cells were not activated by MERS-CoV peptides suggesting that T cell immunity against SARS-CoV-1 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-1 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.

2.2.3 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.[85] Two studies were conducted in Saudi Arabia[2, 85] and one in South Korea.[15] 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.[15] 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.[85] 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.

2.3 Research question 4: Reinfection rate

No agreed definition for what constitutes "reinfection" was identified in the literature, however 19 studies were retrieved that relate to re-detection of viral RNA following a negative RT-PCR sample.[3, 13, 18, 25, 37, 43, 44, 67, 71, 72, 75, 77, 80, 81, 84, 90, 91, 93, 114] All studies were case series apart from three case reports.[43, 90, 91] Six studies have not yet been peer-reviewed. The largest sample size across studies was 414 patients.[37] The age of included patients ranged from 12 months[80] to 92 years,[71] while the median age of patient cohorts ranged from 37[77] to 62 years.[98]

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. 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).[115] In addition to respiratory RT-PCR tests, three studies reported re-detected positive anal or faecal samples.[18, 67, 84]

Characteristics of included studies are provided in Table 6.

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), 10 studies provided a rate of re-detection via RT-PCR of respiratory samples.[13, 18, 37, 67, 71, 72, 75, 77, 80, 113] In these studies, the re-detection rate ranged from 3% (2/62 cases)[75] to 30.7% (4/13 cases).[114] The largest cohort reported a re-detection rate of 16.7% (95% CI: 13.0%-20.3%; n=69/414 cases).[37]

Re-detected positive patients were asymptomatic at the time of the positive re-detection test in all but two studies.[13, 37] The first study reported that the majority of those who re-detected positive had respiratory symptoms, including cough and increased sputum production on readmission.[37] However, while symptomatic, only two of the 69 re-detected cases were febrile with typical clinical manifestations that

satisfied the first admission criteria. The majority of cases retested positive within 5-25 days after the first negative test. The second study reported that, while most of the 11 re-detected patients were symptomatic on readmission, compared with their first admission, the second hospital stay was shorter, clinical symptoms were relieved, laboratory outcomes were improved, and CT manifestations were ameliorated, which suggests that these rehospitalised patients were more likely to be in a status of recovery.[13] Of note, all re-detected positive anal or faecal samples were in asymptomatic patients.[18, 67, 84]

An agreed definition for reinfection (as opposed to re-detection) with SARS-CoV-2 was not identified, possibly due to the limited number of such events described in the literature. The following two definitions for "possible reinfection" were developed internally by the review team; one was stringent and the other was less stringent.

For the stringent criterion, "probable reinfection" was defined as:

> "A positive viral respiratory RT-PCR sample for SARS-CoV-2 following recovery, defined as at least two negative upper respiratory tract samples for SARS-CoV-2, collected at ≥ 24-hour intervals at a minimum of 14 days after the initial positive test AND a minimum of 14 days between recovery (e.g., symptom resolution, afebrile) and onset of new symptoms."

For the less stringent criterion, "possible reinfection" was defined as:

> "A positive viral respiratory RT-PCR sample for SARS-CoV-2 following recovery, defined as at least two negative upper respiratory tract samples for SARS-CoV-2, collected at ≥ 24-hour intervals. For symptomatic patients, samples should be collected at least seven days after symptom onset or after three days without fever. For asymptomatic SARS-CoV-2-infected persons, the tests to document virus clearance should be taken at a minimum of 14 days after the initial positive test."

Using the stringent criterion, it is possible that two cases were re-infected in one study (out of 69 re-detected cases).[37] These cases were febrile on readmission and fulfilled the initial admission criteria. While the study reported median durations for different groups, the duration of time between the initial positive test and discharge, and the duration between recovery and re-test positive, were not reported specifically for these two cases. Using the less stringent criteria, the majority of patients with re-detected viral RNA would be defined as "possibly" reinfected, although not all studies provided sufficient information (for example, the duration of time between 'recovery' and re-detected positive for each case).

2.4 Research question 5: Are individuals reinfected with SARS-CoV-2 or other human coronaviruses infectious?

No study was identified that directly addressed this research question. However, four 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. These tests presumably used upper respiratory tract samples to determine whether patients satisfied discharge criteria; however, the sample site is not clearly reported in all of these studies.[3, 18, 44, 67] All four studies were case series studies conducted in China, examining the re-detection of SARS-CoV-2 in patients recovering from COVID-19.[3, 18, 44, 67] Three of these studies were pre-prints and are not yet peer-reviewed.[3, 18, 67] 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 7.

All four studies had small sample sizes, ranging from four[18, 44] 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, 67] 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.[115]

Wang et al. reported that 20 of the 182 patients (11%) that met the discharge criteria, tested positive again for SARS-CoV-2 RNA within 14 days of discharge.[67] 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.[67] Similarly, An et al. reported that 38 of the 262 patients (14.5%) that met the discharge criteria, tested positive again for SARS-CoV-2 RNA following discharge.[3] Nasopharyngeal and anal swabs were both used to test patients for re-detection of SARS-CoV-2. However, it is unclear what proportion tested positive from each sample site, or whether detection in both samples was required to classify as positive re-detection.

Notably, across all four studies, patients had mild or no symptoms upon re-detection of SARS-CoV-2.[3, 18, 44, 67] None of the cases where SARS-CoV-2 was re-detected related to a patient classified as having severe disease on their initial presentation. Wang et al. observed that patients that were re-detected for SARS-CoV-2 had significantly shorter lengths of stay during their initial admission than patients who were not re-detected.[67] However, other studies did not observe any significant difference. It is possible that the duration of the initial admission differed by disease severity; however, insufficient data were reported to assess potential confounding.

Post-discharge follow-up for re-detection of SARS-CoV-2 occurred for at least two weeks in one study,[3] for up to two weeks in two studies,[44, 67] and for three days in a fourth study,[18] with some individual cases reporting extensive follow-up due to continuous positive results from anal swabs.[18, 67] In the single study that followed patients beyond 14 days, it is not clear from the reporting, whether any patient re-tested positive for SARS-CoV-2 greater than 14 days after meeting the discharge

criteria.[3] Hence, it is likely that re-detection of the original virus occurred in these studies rather than reinfection. However, as genome sequencing or virus culturing was not conducted in any of the included studies, it is not possible to rule out the possibility that patients were reinfected with a second virus, though this appears unlikely. None of the included studies reported viral load.

None of the four included studies reported onward transmission to any close contacts of those who re-tested positive for SARS-CoV-2. However, there was very limited information on how contact tracing was conducted for those contacts, what testing was conducted and how long the contacts were followed up for. Only one of the four studies explicitly reported conducting contact tracing, but provided limited details.[3] The other three studies simply stated that there were no reports of onward transmission, without providing any information on how this was established.[18, 44, 67] 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.

2.5 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, 14, 16, 18, 24, 28, 31, 37, 45, 56, 60, 61, 64, 79, 97, 101, 102] 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.[24, 28, 45, 56, 61, 79, 97, 101] 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.[101] 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.[56] The third study reported on 70 Covid-19 patients, 12 of whom were inpatients and

58 'convalescent' patients.[28] 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.[61] 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.[79] 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.[24]

The seventh study compared six symptomatic patients with eight asymptomatic or 'mild' patients.[45] 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.[97] 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, 16, 31, 60, 64, 102] 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).[16] 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, 60] 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.[31] 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.[64] 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.[102] 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 SAR-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 resposes 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.[31, 53] 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.[31] 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.[14] 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.

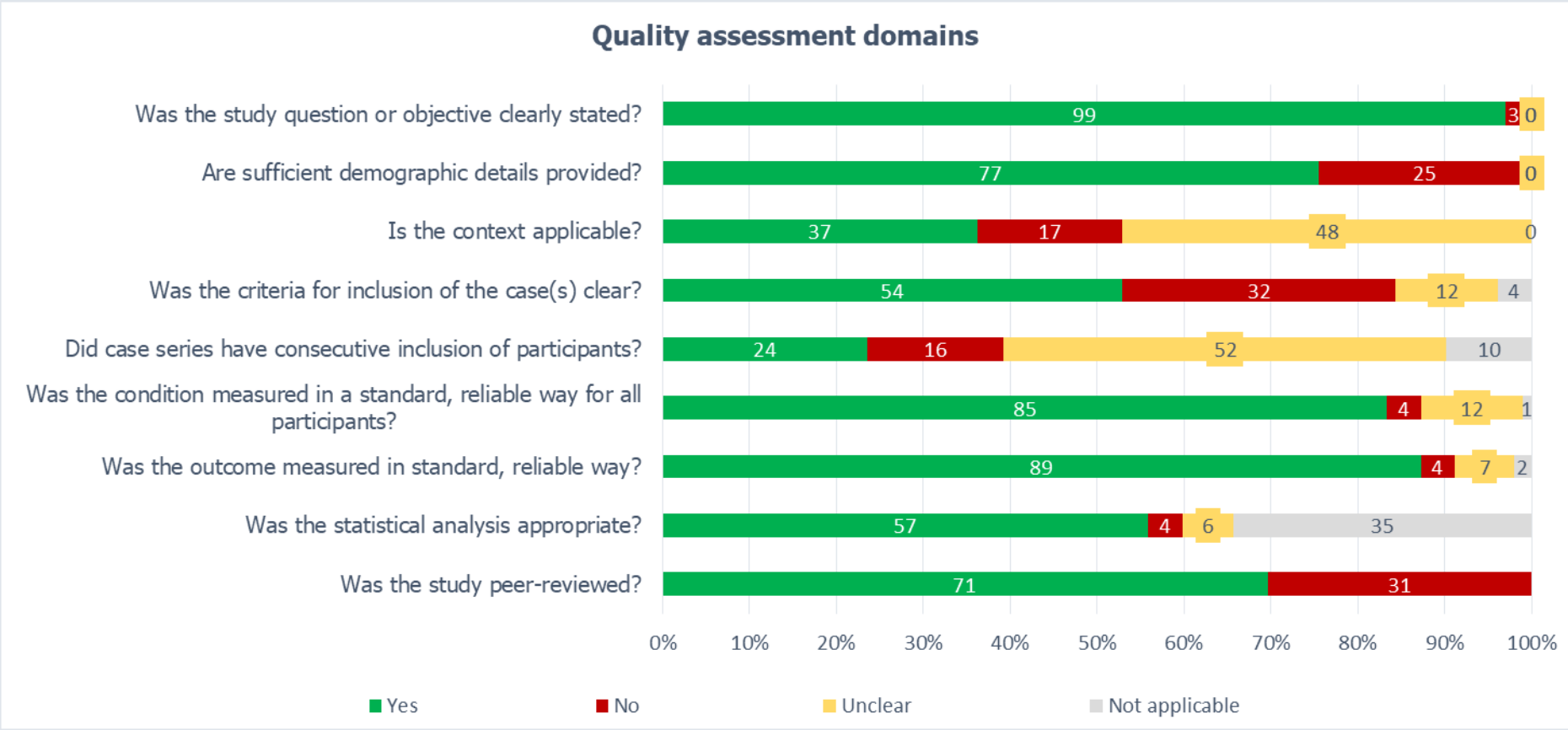
Finally, the association between re-detection positive and severity of initial disease was investigated in two studies.[18, 37] In the first study, authors found that 36.7% (11/38) of re-detected positive patients had a disease course characterised by mild initial symptoms. The percentage was significantly 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.[37] Through mathematical modelling, elevation of serum concentrations of cholinesterase, calcium and eGFR were found to be predictors of recurrence of RT-PCR positivity.

3 Methodological quality

Figure 4, below, provides details of the quality appraisal of all included studies, across nine critical domains. The overall quality of evidence is low due to the inherent biases in included the study designs. In general, study questions were clearly stated (n=99/102) and the reporting of the condition (n=85/102) and outcomes (n=89/102) were conducted in a standard, reliable way. Sufficient demographic details were provided in 77 of the 102 studies. Of concern was the applicablity 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=48 studies). Sixteen case series chose non-consecutive cases (n=16/93), while it was unclear in 52 (n=52/93). Thirty per cent of studies (n=31/102) were not peer-reviewed.

Figure 4 Quality assessment domains



Notes:
Data presented for all included studies (n=102); 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.

4 Discussion

In this review, the evidence on the immune response following coronavirus infections was summarised, including the rate and timing of antibody detection, the duration of immune responses following seroconversion, the reinfection rate among those recovered, and the association between these immune responses and the severity of initial infection. The focus of the review is SARS-CoV-2, evidence for other coronaviruses (SARS-CoV-1 and MERS-CoV) was considered where there was limited SARS-CoV-2 evidence available, however, the applicability of this to SARS-CoV-2 is unknown. Due to the recent emergence of SARS-CoV-2, the longest follow-up data on immune response currently available is eight weeks.

The overall quality of evidence was 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 was uncertain. Concerns also exist regarding the methodological quality of pre-print studies that have not undergone a formal peer review process (31 of the 102 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.

While studies consistently demonstrated anti-SARS-CoV-2 IgG and neutralising antibody detection beyond two weeks, limitations of this review included the variability in the accuracy of tests used across studies, the use of tests that have not yet been validated, poor reporting on the levels of detection employed, small sample sizes (both number of participants and number of samples taken), and limited duration of follow-up.

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.[116] 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.[117] Recently, however, two IgG tests have been validated by Public Health England (Roche Diagnostics and Abbott Laboratories).[118] 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 symptoms began.[119]

The levels of detection for SARS-CoV-2-specific antibodies were not uniform across studies, and frequently not reported. Differences in test accuracy, levels of detection, and the use of non-validated tests may partly explain differences observed in the early post-infection period, particularly for IgM and IgA. For IgG, however, studies in this review consistently identified nearly all patients after 2 weeks post-symptom onset, with 100% testing positive by eight weeks in three studies. Interim guidelines by the CDC has not identified an advantage of antibody tests whether they test for IgG, IgM and IgG, or total antibody.[120] Provided IgM or IgA are not the sole basis for detection of the immune response, and samples are taken a minimum of 2-3 weeks post-symptom onset, the testing platform used may not be a major issue.

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

4.1 Seroconversion rate and or timing following coronavirus infection

Forty-three studies were identified that described the initial immune response to SARS-CoV-2. Most studies used the first detection of IgM and or IgG as a proxy for seroconversion. The rate and timing of first detection of IgG or IgM antibodies differed across studies due to differences in the timing and sampling methods used. However, in general, a majority of patients tested positive for IgM within two weeks, and more than 90% of patients tested positive for IgG in studies that followed patients for at least two weeks. The median time to first detection of IgM and IgG ranged from 5 to 17 days and 6 to 14 days, respectively. In studies that measured serial titres in patients from the time of diagnosis, IgM was typically the first antibody to rise, followed by IgG; IgM titres then waned over time while IgG titres remained positive for up to seven weeks in four studies. Four studies reported on the response of neutralising antibodies; over 90% of participants developed antibodies within 2-3 weeks. IgA was detected in most participants in two studies that measured this immunoglobulin.[116]

4.2 Duration of immune response

As SARS-CoV-2 is a new virus, there are limited data on the duration of the immune response associated with infection and genetically similar coronaviruses, such as SARS-CoV-1 and MERS CoV, may provide some insight.

For SARS-CoV-2, the maximum follow-up was eight weeks in identified studies. While IgG and neutralising antibody titres appear to be maintained in most patients

over this time period, further studies will be needed to determine if these levels are maintained for longer periods of time. Unlike studies on seroconversion, less variability was observed, whereby IgG was detected in all samples at the end of the follow up period. However, these findings were based on studies with small sample sizes, and therefore must be confirmed with larger studies.

SARS-CoV-1-specific IgG antibodies were detectable for three years post-infection in five studies. However, there is considerable uncertainty regarding the duration of the immune response beyond this time-point. Of the four studies that followed patients for three to six years, in general, antibody levels were reported to decrease over time. Two studies that investigated the persistence of SARS-CoV-1 IgG antibody levels beyond six years post-infection presented discordant findings, with the positivity rate reported to be 8.7% at six years in one study, and 69.2% at 12 years in the second study. Differences in the positivity rate between studies may be attributable to IgG antibody levels falling below the limit of detection of the tests at follow-up, or cross reactivity with other common human respiratory pathogens. Two studies reported considerable differences in the positivity rate at follow-up using different diagnostic tests. Moreover, in the absence of data on reinfection, the levels of peptide-specific CD4+ memory T-cells or anti-SARS-CoV-1 IgG associated with effective SARS-CoV-1 immunity are unknown. One recent study reported on neutralising antibodies up to 17 years after SARS-CoV-1 infection. Authors report significant levels of anti-SARS CoV-1 neutralising antibodies in recovered patients from nine to 17 years post-infection. However, cross-neutralisation of SARS-CoV-1 sera against SARS-CoV-2 was not achieved.

Three studies were identified on the immune response to MERS-CoV. Two studies suggested that there is a greater and more sustained response in patients with severe disease compared with mild disease, however another reported sustained responses (up to 24 months) in all cases.

Based on data from SARS-CoV-1 and MERS CoV, it is possible that a specific immune response can be maintained for more than two years after infection. However, even if an immune response is maintained for this level of time, it is not known if it is sufficient to ensure full protection against reinfection by the same virus. It is possible that the antibody response would result in a less severe, or possibly asymptomatic infection, with the associated risk of transmission to others.

4.3 Reinfection

It is not yet possible to conclude that reinfection can occur following recovery from SARS-CoV-2. Nineteen 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 at the time of the positive re-detection

test in all studies, except two. The first study reported that two of the 69 re-detected cases were febrile with typical clinical manifestations that satisfied the first admission criteria. Using our stringent criterion for reinfection, it is possible that these two cases were re-infected. However, the duration of time between initial positive test and discharge, and the duration between recovery and re-test positive, were not reported specifically for these two cases. The second study reported that while most patients were symptomatic on re-admission, their clinical condition had improved compared with the initial presentation.

Using the less stringent criteria, the majority of patients with re-detected viral RNA would be defined as "possibly" reinfected, although not all studies provided sufficient information (for example, the duration of time between 'recovery' and re-detected positive for each case).

As nearly all re-detected cases were asymptomatic across all studies, they are unlikely to be clinically or epidemiologically important, unless evidence emerges that these re-detected cases are themselves infectious to others. None of the included studies sequenced and compared the genomes of the first and second infections, or attempted culture of viable virus in addition to RT-PCR testing. Therefore re-detection could reflect detection of non-viable viral material (which is being inconsistently shed) rather than viable virus.

It is 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.[121] 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.[122] Molecular diagnostic tests (such as RT-PCR) detect viral RNA, but do not confirm presence of live virus. Intermittently positive test results may therefore reflect inconsistent shedding of non-viable virus, later in the course of an infection. A rapid review conducted by Alberta Health Services similarly concluded that *"reports of reinfection may relate to the reliability of the testing instead of these being cases of reinfection. In particular, clinical cases that test negative and then positive later by RT-PCR when followed post infection may have declining amounts of non-viable virus which is inconsistently detected by RT-PCR testing."*[123]

Another rapid research report led by the Australian Chief Scientist, similarly concluded that the evidence for reinfection with SARS-CoV-2 is thus far, not compelling.[124] The authors of the review suggested that there are three key questions to ask when considering whether a patient is definitively reinfected with SARS-CoV-2:

1. Does the patient have symptoms?
2. Is the patient shedding live virus?
3. Does the patient have neutralising antibodies to SARS-CoV-2?

It is also noteworthy that previous evidence summaries conducted by HIQA's research team found substantial discordance between different sample sites used for SARS-CoV-2 testing,[125] along with differences in viral kinetics.[126] In particular, viral RNA from faecal samples has been found to be detected for a prolonged period after symptom resolution,[127] and hence may not be the most appropriate sample for determining reinfection. It is not entirely clear what specimens were used to determine discharge criteria in some of these studies, so the potential for false negative test results upon discharge cannot be ruled out. The World Health Organization (WHO) recommends that *"if a negative result is obtained from a patient with a high index of suspicion for COVID-19 virus infection, particularly when only upper respiratory tract specimens were collected, additional specimens, including from the lower respiratory tract if possible, should be collected and tested."*[128] Hence, it may be appropriate if there is suspicion of ongoing infection, for clinicians to consider additionally testing lower respiratory tract specimens prior to discharge in order to reduce the potential for a false negative.

4.4 Infectiousness of re-detected cases

No evidence was found to determine whether patients re-detected positive with SARS-CoV-2 or any other coronavirus are infectious. Although none of the four 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.[129] 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.

4.5 The association between severity of initial disease and immune response

Data relating disease severity to immune responses were inconsistent across studies. While eight studies found that those with severe illness had higher antibody levels than those with moderate or mild illness, six found no or an inverse association. One study found that CD4+l and CD8+ T cell counts were inversely related to disease severity. The association between the detection rate of viral RNA in blood was investigated in another study; authors noted that detectable SARS-CoV-2 viral RNA in blood is a strong indicator for the further clinical severity. Finally, two studies reported on cases that re-detected RT-PCR, and found that a higher proportion of re-detected cases were characterised by mild or moderate symptoms. Small sample sizes and short follow-up periods limit the conclusions that can be drawn, and further research is needed to assess the associations between disease severity and immunologic responses.

5 Conclusion

Seroconversion studies on SARS-CoV-2 found that while the rate and timing of IgM and IgG detection varied across studies, most individuals displayed an IgG SARS-CoV-2-specific antibody response within two weeks.

The adequacy or duration of this response is not yet known, although all patients included in studies maintained an IgG response at the longest follow-up (eight weeks). While long-term immunological data relating to SARS-CoV-2 are not yet available, evidence from studies of SARS-CoV-1 suggested that SARS-CoV-1-specific IgG antibody levels are sustained for one to two years post-infection and decline thereafter. One study reported that antibody levels were still detected up to 17 years after initial SARS-CoV-1 infection.

The applicability from SARS-CoV-1 to SARS-CoV-2 is unknown. It is unclear if reinfection can occur following recovery from SARS-CoV-2. Noting that as yet there does not appear to be an agreed definition for reinfection (as opposed to re-detection), the limited data to date are more suggestive of re-detection.

Due to the relatively short testing period, and the lack of symptoms or disease progression in these cases, re-detection could reflect detection of non-viable viral material (which is being inconsistently shed) rather than viable virus. Limited evidence would appear to suggest that these cases are not infectious to others, as no evidence of onward transmission was identified.

Tables of study characteristics and primary outcomes

Table 1 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				
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 collection in the SARS-CoV-2 PCR positive patients.	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 controls. 87% confirmed cases male: median age 44 years (range 32-50 years) Subgroup analysis of 6	**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) 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.	Peer-reviewed; The Journal of infectious diseases

		patients, 3 immunocompromised and 3 immunocompetent.	**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: 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.	Peer-reviewed; Pediatric allergy and immunology

Du 2020[21] 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)
Demey 2020[17] 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 Four 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 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[19] 10.1101/2020.05.19.20099317 Italy	SARS-CoV-2 Two step chemilumisecence immunoassay (CLIA) Maglumi	46 (46 also stated?) symptomatic subjects wih suggestive symptoms and positive PCR except 4 included with negative PCR but 'almost certain'	**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.	Not peer-reviewed

Case series	800, Snibe, China)	clinical diagnosis. 35 controls. Samples were analysed before 15 days of illness (Group 1) and after 15 days (Group 2)	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.	
Du 2020[21] China Case series DOI: 10.1002/jmv.25820	SARS-CoV-2 Unclear which test kit used 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 the onset of symptoms)	**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
Fafi-Kremer 2020[22] France Case series	SARS-CoV-2 2 tests used: a rapid immunodiagnostic test (Biosynex) and the S-Flow assay	162 hospital staff who had recovered from mild forms of PCR-confirmed SARS-CoV-2 – 160 had not required hospitalisation and were included in the analyses.	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). • Neutralising ABs were detected in 79%, 92% and 98% of samples collected on day 13-20, 21-27 and 28-41 after	Not peer-reviewed

DOI: 10.1101/2020.05.19.20101832	Blood samples Median time from symptom onset to testing 24 days (IQR, 21-28, range 13-39)	Median age 32 years (IQR 26-44), 31.2% male.	symptom onset respectively. • At 21-27 days IgM the highest seropositivity rate was obtained (N=75/83; 90.4%); after 28 days highest IgG seropositivity was obtained (N=41/48; 85.4%)	
Gao 2020[26] 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[27] France Case series	SARS-CoV-2 Two 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[28]	**SARS-CoV-2**	N=101 Two cohorts: confirmed	**Timing of samples (confirmed or probably positive):** Total samples=208	Peer-reviewed;

DOI: 10.1093/cid/ciaa310 China Case series/follow up	Deep sequencing or a qPCR assay for diagnosis of cases Antibody testing by ELISA-based assay on the recombinant 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	positives (N=43) [deep sequencing or a qPCR assay] and probable positive (N=58) [suspected to be infected with SARS-CoV-2 based on clinical manifestation, chest radiography imaging, and epidemiology but no virus were detected by deep sequencing or a qPCR assay] 208 plasma samples collected	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 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 (interquartile range [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) **IgG titres** Day 0–7: GMT 490.45	Clinical Infectious Diseases Corrected proof

			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[30] China Case series DOI: 10.1016/j.clim.2020.108413	The SARS-COV2 nucleic acid test was conducted via real-time RT-PCR 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	3 cases who were all from the same family	**Case 1** ■ 47-year-old female ■ 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	Peer-reviewed: Clin Immunol

Haveri 2020[88] Finland Case study DOI: 10.1016/j.clim.2020.108413	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
Hou 2020[33] 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 three 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)	**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.	Clinical & Translational Immunology

		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 intensive care unit (ICU) treatment.	**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). • 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[35] 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	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 peer-reviewed

	days post-symptom onset Discharge criteria: categorized 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 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.		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 re-detectable positive nucleic acid, indicating instant decrease of IgG after recovery. Long-term protection provided by IgG requires further study.	
Huang 2020b[36] China Case series DOI:	SARS-CoV-2 RT-PCR for confirmation of cases Details on testing	**Population setting:** 33 SARS-COV-2 confirmed hospitalised patients **Demographics:** *Mix of adults and children* *Sex:*	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

10.1101/2020.04.22.20071258	platform for antibodies not reported	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%) 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[39] 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,	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

	ShangHai ZJ Biotech, Geneodx, Biogerm) IgM/IgG antibodies kit were detected on Time-Resolved Immunofluorescence Analyzer by Fluorescence immunochromatographic assay method (Beijing Diagreat Biotechnologies Co., Ltd, Lot: 20200214) Cutoff of IgM and IgG were 0.88 and 1.02 fluorescence intensity (Flu) units			
Jiang 2020[40] 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[42] China	SARS-CoV-2 ELISA	N=8 patients infected with SARS-CoV-2 in January 2020	▪ 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	Not peer-reviewed

Prospective Case series DOI: 10.1101/2020.03.21.990770		Age range: 10 to 66 years	▪ Both clone types demonstrated impressive binding and neutralising activity against pseudovirus and live SARS-CoV-2 ▪ No cross-reactivity with SARS-Cov-1 or MERS was found.	
Lee 2020[89] 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[50] China Case series/follow up study DOI: 10.1101/2020.03.06.20031856	SARS-CoV-2 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)	N= 238 admitted hospital patients with confirmed or 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	IgM and or IgG seropositivity rate in confirmed patients = 83.0% (127/153) Seroconversion timing: After 10 days, seroconversion rate rose to >80% (IgM and or IgG)	Published Microbes and infection
Liu 2020b[51] China	SARS-CoV-2 SARS-CoV2 antibody detection	N=133 Median age: 68 Female: 63; Male: 70	**IgM** Seroconversion rate by severity of disease: Moderate: 79.55% Severe: 82.69%	Not peer-reviewed

Case series DOI: https://DOI.org/10.1101/2020.03.28.20045765	kit	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])	Critical:72.97% **IgG** Seroconversion rate by severity of disease: Moderate: 93.18% Severe:100% Critical: 97.30%	

Long 2020[106] China Multi-centre cross-sectional study and a single-centre follow-up study DOI: 10.1101/2020.03.18.20038018	RT-PCR assay for nasal and pharyngeal swab specimens IgG and IgM antibody against SARS-CoV-2 in plasma samples were tested using Magnetic Chemiluminescence Enzyme Immunoassay (MCLIA) kit supplied by Bioscience (Chongqing) Co., Ltd, China	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 262/285 patients had clear records of time of symptom onset 39/285 cases were classified as severe or critical illness condition	**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:** ▪ 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 <u>Follow-up study</u> (N=63 patients) Median day of seroconversion for both lgG and IgM was 13 days (after symptom onset)	Not peer-reviewed
Lou 2020[96] China Cohort study	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	Published European respiratory journal

DOI: 10.1183/13993003.00763-2020			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	
Nicastri 2020[92] Italy Case report DOI: 10.2807/1560-7917.ES.2020.25.11.2000230	Two real-time RT-PCR on a nasopharyngeal swab confirmed SARS-Cov-2 In house-prepared immunofluorescence (IF) slides and neutralisation test as confirmatory test for antibodies	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. Patient was asymptomatic (or paucisymptomatic, only had transient mild conjunctivitis and a body temperature of 37.3).	**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** 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.	Peer-reviewed Eurosurveillance
Okba 2020[56] 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)	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[69] 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

	Optical density (OD) detected at 450 nm Virus-neutralising antibodies were tested by using a PRNT50			
Padoan 2020[57] 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 SARS-CoV-2 (Euroimmun Medizinische Laboradiagnostika, Luebeck, Germany)	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). 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)	• 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 two assays was comparable and similar. Levels or detection time not reported.	Peer-reviewed Clinica Chimica Acta
Pan 2020[58] China Case series DOI: https://DOI.	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	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%	Peer-reviewed Journal of Infection

org/10.1101/2020.03.13.20035428		patients taken	≥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%	
Solodky 2020[63] 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 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.	Letter to the editor

Sun 2020[64] 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% 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	Emerging microbes & infections

			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[98] 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[66] 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[68] China Follow-up study/case series DOI.org/10.1101/2020.04.15.20065623	SARS-CoV-2 The presence of neutralising antibody was determined with a modified cytopathogenic assay based on live SARS-CoV-2	N=70 patients N=117 serum samples 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	**Neutralising Antibodies:** ▪ 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	Not peer-reviewed

		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	▪ Patients with a worse clinical classification had a higher antibody titre	
Wölfel 2020[69] 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[73] 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[78] 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[102] China Retrospective cross sectional DOI: 10.1080/2222175	SARS-CoV-2 Gold immuno-chromatography assay (Innovita Co. Ltd. China) Timing not stated but paper reports results from weeks	21 SARS-CoV-2 patients in two 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	**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)	Peer-reviewed; Emerging microbes & infections

1.2020.1756699	1,2,3 and up to 6 weeks, implying weekly tests. Serum samples	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.	**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 SAR-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:** 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[83] 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[86] 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[82]	SARS-CoV-2 An IgM and IgG	112 PCR positive patients; 70.5% female); median age 38.6 years +/- 14.9	**Rate & Timing of seroconversion** **IgM** 5/7; 71%; <10 days	Peer-reviewed

China Retrospective case series DOI: 10.1093/infdis/jiaa229	antibody detection kit was developed (Yahuilong Biotechnology, Shenzhen, China)	years (range 25-78 years); 8.9% asymptomatic; all others with mild symptoms	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. • 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[95] 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 ■ In 2017, he took antiviral agents (DAA) against HCV for 3 months by himself, and HCV became persistently negative	*Accepted manuscript to Clinical Infectious Diseases*

			▪ On admission his CD4 and CD8 T cell counts in peripheral blood were 216 and 584	

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

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	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, 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. **Other outcome:** There was no evidence that SARS-2-CoV severity, need for hospital	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)		admission or patient age were associated with IgG or IgM titres in multivariable models	
Dong 2020[20] 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)	**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 T cells among those two groups (discharged and follow-up) and the healthy donors. Compared to healthy donors, the number of IFN-gamma secreting NP specific t-cells in four of the recently discharged patients suggests that they had developed a SARS-CoV-	Not peer reviewed; medRxiv

			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[21] 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 the onset of symptoms)	**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[24] 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	**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 Odds of impaired lung lesion resolutions were higher in patients with elevated IL-4 (as well as hyperproteinemia, hyperlipidemia and ferritin)	Not peer-reviewed

		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)		
Jin 2020[41] 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	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	**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	Peer-reviewed; I Journal of infectious diseases

	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) and 18 days (IQR 11–23 days), respectively	(2, 4.7%). Fever was present in 62.8% of SARS-COV-2 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	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 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).	
Okba 2020[56] 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	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-1, 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 two 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

	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			
Wang 2020a[94] 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[68] 10.1101/2020.04.15.20065623	SARS-CoV-2 Neutralising antibody determined using	N=70 SARS-COV-2 inpatients (n=12) and convalescent patients (n=58). Patients for longitudinal changes in	**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	cytopathogenic assay. 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).	n= 8 convalescent 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).	
Wölfel 2020[(69)] 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	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	Peer-reviewed; Nature

	assay using SARS-CoV-2 Testing for virus by RT-PCR		▪ Results on differential recombinant immunofluorescence assay indicated cross-reactivity or cross-stimulation against the four endemic human coronaviruses in several patients	

Table 4 Duration of immune response: SARS-CoV-1

Author DOI Country Study design	Virus type Test performed Location of sample Timing of sample	Population Patient demographics	Primary outcome results	Comments
SARS-CoV-1				
Anderson 2020[4] Singapore Case series DOI: 10.1080/22221751.2020.1761267	SARS-CoV-1 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	SARS-CoV-1 Clinical case definition: WHO criteria **Testing:** ELISA (BJI-GBI Biotechnology, Beijing, China) and micro-neutralisation assays	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 = one sample became undetectable. Positive rate of 94.74%. *Lysate-based ELISA kit:* Year 2/3 = OD values for all samples dropped dramatically.	Peer-reviewed BMC Virology journal

Case series	**Sample:** Serum **Timing:** 3 year follow-up; sampling at month 3, 12, 18, 24, and 36 after the onset of clinical symptom		Positive percentage of the year 3 samples was 42.11% (8/19) **Other outcome:** 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-1 **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	Peer-reviewed; N Engl J Medicine

			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 hospitalization, type and number of coexisting conditions, or use or non-use of corticosteroids. Treatment: Not reported.	
Chan 2005[10] China DOI: 10.1128/cdli.12.11.1317-1321.2005	SARS-CoV-1 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	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-1 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 two patients, increased in two patients, and there was no significant change in seven	Peer-reviewed; Clin Diagn Lab Immunol

	months postinfection		patients. Month 1 and 7: neutralisation titres remained unchanged at 124. **Other outcome:** **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-1 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-1 SARS was diagnosed based on a positive RT-PCR result for SARS-CoV-1 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 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.	Peer-reviewed; Clin Diagn Lab Immunol

			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.	
Chen 2005[12] DOI: 10.4049/jimmunol.175.1.591 China Case series	SARS-CoV-1 **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-1 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-1 may exist in the T cell repertoire of a subset of healthy individuals and can be reactivated by SARS-CoV-1 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[23] China Case series	SARS-CoV-1 **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.	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

	Sampling every 2 - 4 weeks.			
Guo 2020b[113] DOI.org/10.1101/2020.02.12.20021386. China Long-term prospective follow-up study	SARS-CoV-1 **Testing:** ELISA kit using whole virus (BGI-GBI Biotech Co. Ltd., Beijing, China) and an in-house recombinant SARS-CoV-1 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.	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 2003, and 94.11% (32/34) of them were females. Serum samples were collected annually from 2003-2015.	Anti SARS-CoV IgG was found to persist for up to 12 years 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 100.00% (32/32). 2015: Decreased to 69.23% (18/26). *In-house recombinant SARS-CoV-1 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	**Not yet peer reviewed, published as pre-print**
He 2004[32] 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	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 =	Peer-reviewed; Clin Diagn Lab Immunol

	Testing: IFA (Euroimmun AG, Lu¨beck, Germany), ELISA (Wantai Biological 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.		70/70 (100%) with 58/70 (83%) showing titres >100. **Other outcome:** 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[34] Taiwan DOI: 10.1111/j.1469-0691.2004.01009.x Case series	SARS-CoV-1 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.	N = 30 patients with SARS Age: 25–80 years (mean 43 years) Four 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:**	Peer-reviewed; Clin Microbiol Infect.

	Sample: serum samples (6–12 samples from each patient) **Timing:** <7 days to 2–3 months after the onset of illness.		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:** 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[38] China DOI: 10.1016/j.micinf.2004.11.017 Case series	SARS-CoV-1 Case definition of SARS-CoV-1 based on the Chinese Ministry of Health on April 14, 2003. **Testing:** Lymphocyte analysis: Flow cytometry. Humoral response: ELISA. Reference OD = 0.030 **Sample:**	Exposed population: N = 95 healthcare workers with SARS; *Sex:* Male = 19 (20%), female = 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.	Peer-reviewed; Microbes Infect

	Blood **Timing:** 5 months follow up. Sampled at 1, 2, 3 and 4 weeks, and 2, 3, 4 and 5 months		**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. **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[47] China DOI: 10.1371/journal.pone.0000024 Case series	SARS-CoV-1 Case definition of SARS-CoV-1: WHO clinical criteria **Test:** Lymphocyte analysis: Flow cytometry Humoral responses: ELISA (No S20030004, HuaDa Comp, Beijing, China), ELISPOT-based technique (Diaclone, France), neutralisation assay	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.	Peer-reviewed; *PLoS One*.

	Sample type: Blood **Timing:** 2 years follow-up; Samples collected at 1, 3, 6, 12 and 24 months after the onset of symptoms.		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. **Other outcome:** INF-g releasing cells detected at month 3, 12 and 18 after onset of symptom.	
Li 2003[46] China DOI: 10.1056/NEJM200307313490520 Case series	SARS-CoV-1 **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[49] Philippines.	SARS-CoV-1 **Testing:** ELISA, IFN-γ ELISPOT assays	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:**	Peer reviewed: Virology

DOI: 10.1016/j.virol.2007.07.015	**Sample:** Blood **Timing:** 6–30 months after infection		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-1 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-1 infection (N=1), and decreased to near the limit of detection by 12 months onward. 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-1 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-1 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-1 may wane rapidly.	
Liu 2006[52] DOI: 10.1086/500469	SARS-CoV-1 Serum samples were collected from each patient at regular	A total of 63 patients recruited; N=56 participants contributed at least 3 blood specimens during the follow-up.	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	Peer reviewed; J Infect Dis

China Prospective follow-up study	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	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)	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	
Mo 2006[54] China DOI: 10.1111/j.1440-1843.2006.00783.x Case series	SARS-CoV-1 Case definition of SARS-CoV-1: 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,	Exposed group: 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 hospitalization 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)	**Duration of detection of serum immunoglobulin levels:** **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,	Peer reviewed; Respirology

	360, 450, 540 and 720.		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[55] DOI: 10.1016/j.vaccine.2016.02.063 Singapore Prospective follow-up study/case series	SARS-CoV-1 (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. Two CD8+ T cell responses targeting the SARS-CoV membrane (M) and nucleocapsid (N) proteins were characterized 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[59]	SARS-CoV-1 Diagnostic criteria for	Exposed group: N = 14 recovered SARS Individuals	**Duration of detection of T-cells:** 2 years SARS-CoV N-protein-specific memory CD4+ and CD8+ T	Peer reviewed; Virology

China DOI: 10.1016/j.virol.2006.03.036 Case-control study	SARS-CoV-1 infection: WHO clinical criteria **Testing:** Cytokine production: ELISA (R&D) and ELIspot assay (BD Biosciences) **Sample type:** venous blood **Timing:** 2 years	Sex: 7 men and 7 women, Age: 20 to 37 Control: N = 3 subjects without any contact history with SARS patients.	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.	
Shi 2004[62] China DOI: 10.1016/j.jcv.2004.05.006 Case series	SARS-CoV-1 probable SARS patients based on WHO criteria **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	N = 14 probable SARS patients. Age: 22 to 73 years old (median of 45 years).	**Duration of detection of serum immunoglobulin levels:** IgG antibody was detectable for 210 days. 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.	Peer reviewed; Journal of Clinical Virology

	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.		**Other outcome:** IgG seroconverion 13/14 patients IgM seroconversion 13/14 patients	
Tang 2011[65] DOI: 10.4049/jimmunol.0903490 China Prospective follow-up study	SARS-CoV-1 The specific memory B cell and T cell responses to SARS-CoV-1 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-1 became undetectable in 21 of the 23 former patients. No SARS-CoV-1-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. 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.	Peer reviewed; J Immunol
Tso 2004[99] China DOI: 10.1086/424573	SARS-CoV-1 **Testing:** IFA **Sample:** Serum **Timing:**	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 =	Peer-reviewed; J Infect Dis.

Prospective cohort study	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		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.	
Wu 2007[70] DOI: 10.3201/eid1310.070576 China Prospective follow-up	SARS-CoV-1 Serum antibody titres measured by ELISA kit (BJI-GBI Biotechnology, Beijing, China)	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 the onset of symptoms, the percentage who were IgG positive was ≈11.8%. 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**:	Peer-reviewed; Emerg Infect Dis

			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[100] China DOI: 10.1080/00365540902919384. Retrospective sero-epidemiological cohort study.	SARS-CoV-1 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:** 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:**	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

	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[76] China DOI: 10.1016/j.clim.2006.05.002 Case-control study	SARS-CoV-1 **Testing:** Cytokine production: ELISA (BD Pharmingen, San Diego, CA) and ELISpot (BD Pharmingen) assays. Lymphocyte analysis: Flow cytometry **Sample type:** peripheral blood **Timing:** >1 year after SARS-CoV infection	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.
Xie 2006[74] China Case	SARS-CoV-1 **Testing:** Flow cytometry **Sample:** Blood	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.	**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.	Peer reviewed; Acta Acad Med Sin

control study	**Timing:** 1 year follow-up. Sample collection at 1 week, 2 weeks, 1 month, 2-3 month and 1 year.	Age: average age 36 ± 10 years	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).	

Table 5 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[15]	MERS-CoV	N=11 confirmed MERS-CoV patients	**Duration of detection of antibodies:** All 5 patients with severe disease, but only 2/6 (33%)	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	with mild disease, had PRNT90 antibody titres ≥40 at 1-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 one 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. Two of the severe patients who had acute-phase antibody titres of ≥320, declined ≥4-fold 1 year later. Four 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[85] DOI:10.1126/scii mmunol.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	**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

		severe pneumonia		

Table 6 Study characteristics: 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)	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)

	patients were confirmed by digestive (anal swab) and respiratory positive RT-PCR tests. All patients followed for minimum of 14 days.			
Chen 2020[13] 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 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	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. • 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,	Peer reviewed; Journal of medical virology

			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.	
Deng 2020[18] 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 Viral RNA was not consistently detected in subsequent tests in 3 of 4 patients.	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 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	**Redetectable Positive (RP)/Reinfection rate** 17.6% (3/17) patients were found to be re-detectable positive by viral RNA RT-PCR of nasophayngeal 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 one showed anal swab result positive after 3 days of discharge. ▪ No patient presented with symptoms upon re-detection ▪ 3 patients returned to the designated hospital for quarantine again. Two 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.	Not peer-reviewed (pre-print)

		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		
Fu 2020b[25] China Case series DOI: 10.1002/jmv.25968	SARS-CoV-2 SARS-CoV-2 RNA test (Type of test not stated) IgM and IgG antibody test (type of test not stated) Timing of test is unclear	3 confirmed cases; 2 female; Aged 36, 74 and 34 years; Case 2 had history of hypertension **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.	**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. 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	Published letter to the editor

			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.	
Loconsole 2020[91] 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
Huang 2020a[37] 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	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	**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	Not yet peer reviewed

	the hospitalization, 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.	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% mild; 88% moderate; 7% severe; 0% critical. **Definition of recovery/Discharge criteria:** Being afebrile for at least 3 days;	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:** Multivariable model developed to predict the risk of recurrence **Prediction of PCR re-detection using mathematical modelling**	

		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	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[43] 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: sore throat and intermittent myalgia SARS-COV-2 Clinical syndromes: Patient 1: Moderate Patient 2: Mild (not defined)	▪ 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
Li Y 2020[114]	**Test:** RT-PCR	**Population setting:** 13 discharged SARS-	**Duration of virus detection** *Days from onset of symptoms to the first of two consecutive*	Peer reviewed

China Case series DOI: 10.1002/jmv.25905	**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	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%)	*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.	(Zhongguo Wei Zhong Bing Ji Jiu Yi Xue)
Lim 2020[90] South Korea Case report DOI: 10.3346/jkms.2020.35.e79	SARS-CoV-2 RT-PCR (Quantstudio 1 Applied Biosystems, Foster 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	**Population setting:** 1 patient admitted to hospital **Demographics:** 54 year old man **Clinical characteristics:** Presentation: Chills and muscle pains **SARS-COV-2 Clinical syndromes**	▪ Patient experienced 2 consecutive days of undetectable virus RNA from sputum samples on days 11 and 12 since symptom onset, having had 2 previous days of positive test results. ▪ Patient subsequently had 4 more consecutive days of positive test results	Published J Korean Med Sc

	Re-detected using sputum samples	**(WHO definition):** Pneumonia		
Qu 2020[93] 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 hospitalization), 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[98] Hong Kong, China Cohort study DOI: 10.1016/s1473-3099(20)30196-1	SARS-CoV-2 qRT-PCR (QuantiNova Probe RT-PCR Kit (QIAGEN, Hilden, Germany)) using blood, urine, 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	**Population setting:** 23 patients at 2 hospitals in Hong Kong **Demographics:** 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	One 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

		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[67] 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; 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)	**Population setting:** 182 post-discharge patients recovering from SARS-COV-2 under medical isolation **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) **Clinical characteristics:** *Initial presentation:*	▪ 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)

		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[72] China Case series DOI:10.1002/jmv.25855	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 negative RT-PCR): median 36 days (IQR: 28-40)	▪ 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.
Xing 2020[75] China Case series	SARS-CoV-2 RT-PCR assay for SARS-CoV-2 SARS-CoV-2 nucleic acid in throat swab samples were	N=62 SARS-CoV-2 cases among medical personnel, of which 2 were repeat positive after discharge.	▪ 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,	Eurosurveillance Peer-reviewed

DOI: 10.2807/1560-7917.ES.2020.25.10.2000191	taken according to the manufacturer's protocol (Shanghai BioGerm Medical Technology, Shanghai, China).	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	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.	
Ye 2020[77] 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 **Demographics:** Adults Age: for n=55 Median 37 (range 22-67) The age range of the 5 SARS-CoV-2 reactivated patients	▪ 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): Four of the 5 patients presented withfever without chills and one was afebrile. Of the febrile patients, onene had a high fever (39.3 °C). Patients' body temperatures fluctuated within a range from 36.2 to 39.3 °C. One patient showed normal body temperature. Other symptoms of an upper respiratory tract infection were also observed: one patient had cough, one had sore throat and all patients reported fatigue. Additionally, one patient had constipation. ▪ Time from testing negative to testing positive again ranged from 4 to 17 days.	Peer reviewed; Journal of Infection

		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.		
Yuan 2020[80] 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 (median 49, range 1-81); 39 (21.4%) had severe symptoms, 143 (78.6%) mild and moderate **Discharge criteria:**	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** 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	Not peer-reviewed

		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	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[84] 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:** Presentation: Fever 20 (87%), cough 13 (57%), weakness 9 (39%), myalgia 5 (22%), pharyngalgia 5 (22%), headache 3 (13%) SARS-COV-2	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)

		Clinical syndromes (National Health Commission of the People's Republic of China definition): Severe, 2 (9%) Mild-to-moderate, 21 (91%)		

Table 7 Infectiousness of re-detected cases

Author Country Study design Study URL	Population setting	Primary outcome results	
An[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	**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)	**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

	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 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*	**Discharge criteria:** Temperature returned to normal for more than three days, respiratory symptoms significantly improved, and 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	**Method of contact tracing undertaken:** NR **Duration of follow-up of contacts:** 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.

	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%)		

Deng[18] China Case series https://europepmc.org/article/PPR/PPR122436	**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) 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*:	**Test parameters** **Virus:** SARS-CoV-2 **Test:** RT-PCR (device NR) **Thresholds:** NR **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	**Infectiousness outcomes** **Location of patients after discharge:** NR **Post-discharge follow-up for re-detection of** SARS-CoV-2**:** 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

	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	4 patients. **Genome testing:** Not conducted	

Lan L 2020[44] 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.	**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).	**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:**

	SARS-COV-2 ***Clinical syndromes (Definition not reported):*** Mild to moderate, 4 (100%) ***Length of stay:*** NR **Re-detection** *Clinical characteristics* No symptoms	**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		NR **Duration of follow-up of contacts:** NR
Yuan Y 2020[81] China Case series https://onlinelibrary.wiley.com/DOI/full/10.1002/jmv.25796	**Population setting:** 6 hospitalised SARS-COV-2 patients **Demographics:** *Adults* *Age median (range)* 64 years (36-71) *Sex* Males, 2 (33%) Females, 4 (67%) **Clinical characteristics:** Cough, 4 (67%), Fever 2 (33%) White phlegm 2 (33%) No symptoms, 1 (16.7%) SARS-COV-2 **Clinical syndromes:** NR	**Test parameters**	**Duration of virus detection* (Days)**	**Other relevant findings**
		Test: rRT-PCR **Thresholds:** Not defined **Gene Targets:** RdRP, E, and N **Sample site(s):** NP and faeces	**From first positive test to the first of two consecutive negative tests:** *Time to negative NP swab result (median (range))* Day 10.5 (7-18) after the onset of treatment (n=6). *Time to negative faeces swab result (median (range))* Day 10 (10-14) after the onset of treatment (n=3).	Faeces samples were persistently positive in some patients. All patients with 2 consecutive negative tests later retested positive for SARS-CoV-2 infection using NP samples. **Treatment:** Combination therapy including nutritional support.
Wang[67]	**Population setting:**	**Test parameters**		**Infectiousness outcomes**

China Case series https://europepmc.org/article/PPR/PPR150648	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). **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	**Virus:** SARS-CoV-2 **Test**: RT-PCR (BioGerm) Total Ig, IgA, IgG and IgM (WANTAI BioPharm) **Thresholds:** 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.	**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**:** 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

	Re-detection *Clinical characteristics* No symptoms, 20 (100%)	**Genome testing:** Not conducted		
Xiao 2020c[71] China Case series https://www.sciencedirect.com/science/article/pii/S1386653220300883?via%3Dihub	**Population setting:** 301 confirmed SARS-COV-2 patients hospitalised at Tongji Hospital **Demographics:** *Adults* *Age median (range)* 58 years (IQR, 44–68; range, 10–92 years) ≥65 years: 110 (36.5%) *Sex* Male, 154 (51.2%) Female, 147 (48.8%) **Clinical characteristics:** NR SARS-COV-2 **Clinical syndromes (Diagnosis and treatment of 2019-nCoV pneumonia in China. (Version 5)):** Mild to moderate, 301	**Test parameters**	**Duration of virus detection* (Days)**	**Other relevant findings**
		Test: rRT-PCR **Thresholds:** Positive: Ct-value < 35 Negative: Ct-value >39.2 Confirmatory retest: Ct-value 35 to <39.2 **Gene Targets:** ORF1ab and N protein **Sample site(s):** throat and/or nasal swabs (92.7 % throat swabs)	**From onset of symptoms to the first of two consecutive negative tests:** Available for 216 patients: 20 days (IQR 17–24; range, 7–44) *Patients <65 years* 19 days (IQR 17–23) *Patients ≥65 years* 22 days (IQR, 19–26) *Male* 21 days (IQR 17–25) *Female* 19 days (IQR 17–24) **Positive rate of RT-PCR:** Day 0-7: 97.9% (137/140) Day 8-14: 68.8% (152/221) Day 15-21: 36.3% (127/350) Day 22-28: 30.0 % (92/307) Day >28: 26.3% (25/95)	Authors reported that older patients had a longer duration of viral detection than younger patients (22 days vs 19 days, p = 0.015) 85 (28.2 %) patients still tested positive results at the last follow-up. **Re-detection positive rate:** Older (≥65 years) patients had a higher re-testing positive rate (32 %, 7/22) than younger (29 %, 14/48) patients had, although the difference is not significant (p = 0.82). The authors conclude that longer observation period and >2 consecutive negative viral test may be necessary for patients ≥65 years.

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 nine 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 adults a median 48 [range 31-62] days after symptom onset and/or date of positive	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	Not peer reviewed

	throat swab (n=18)		symptom onset. **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. 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	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

	patients followed for minimum of 14 days.			
Chen 2020[14] https://www.tandfonline.com/DOI/pdf/10.1080/22221751.2020.1732837 China Cross-sectional	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 saturation <= 93% in the rest state; (3) arterial oxygen tension over inspiratory oxygen fraction of less than 300mm Hg	**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. **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	Peer-reviewed; Emerging Microbes & Infections
Dahlke 2020[16] 10.1101/2020.04.14.20059733 Germany	SARS-CoV-2 Peripheral Blood mononuclear Cell immunotyping (PBMC)	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	**Rate of seroconversion:** 100% **Timing of seroconversion:** Memory B-cell population (CD19+CD24+cd38-/low) increased after approx. 15 days post disease onset in	Not peer-reviewed MedRvix

Immunological case series	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 Patient 3: day 12 Patient 4: days 4 and 11 Patient 5: N/A	(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	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 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[31] 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 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).	**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* 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**	Peer-reviewed; Journal of Clinical Virology

			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[37] 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'	**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	Not peer-reviewed

		patients. Case patients were generally younger than controls and 93% had mild or moderate illness. A subset of 154 patients had IgG/IgM antibody testing at initial discharge	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. 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[45] Taiwan	SARS-CoV-2 Frequencies of antibody	33 samples from 14 SARS-COV-2 patients from 6 hospitals between January and March	**Rate of seroconversion:** • Of 6 symptomatic patients, all had positive IgG and 4 had positive IgM responses	Peer-reviewed; Journal of Infection

Cross sectional https://www.journalofinfection.com/article/S0163-4453(20)30230-9/abstract	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 ALLLTEST Biotech Co.)	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. One patient had diabetes, one HIV infection; all patients in symptomatic group had fever but only one in asymptomatic had fever. 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	• 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). • 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))	

		did not meet the criteria for severe)	• 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[53]
 	
https://www.journalofinfection.com/article/S0163-4453(20)30182-1/pdf
 	
China
 	
Letter to editor describing retrospective cross-sectional
	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
		18 (46.2%) severe and critical infection (according to Guidelines for Diagnosis and Treatment of SARS-COV-2 (Trial version 6))
			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 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)
				Letter to editor

			○ 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[51] 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% **Timing of seroconversion** Not reported **Duration of immunity** Not reported	Not peer-reviewed
Long 2020[101] 10.1101/2020.03.18.20038018 China Multi-centre cross sectional study with single centre	SARS-CoV-2 Magnetic Chemiluminescence Enzyme Immunoassay (MCLIA) (Bioscience Chongqing Co. Ltd., China, CFDA approved) Serum samples taken at 3-day intervals from February	285 patients in mulit-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	Not peer-reviewed medRVIX

follow-up	8th 2020 to hospital discharge.		**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)	
Okba 2020(56) 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 were taken 'at different time points' over this period	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
Phipps 2020(60) 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:	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	**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	Not peer-reviewed medrxiv

	Normalized signal intensity (NSI) ≥25	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.	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** 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%) • at similar rates for 3-7 days (4/11, 36%) • at similar rates for 8-13 days (4/11, 36%) • at 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[61] 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 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.	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 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 one of – respiratory distress/hypoxia/abnormal blood gas analysis. Critical = any one of -respiratory failure requiring mechanical	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 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	Peer-reviewed; Clinical Infectious Diseases

		ventilation/shock/other organ failure that requires ICU care.	vs. 13.75±4.60 days, p=0.0019)	
Tan 2020[97] 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 with342 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 • 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).	Not peer-reviewed MedRvix

			▪ 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[102] 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 two 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%;	**Rate of seroconversion:** 100% overall **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. Of	Peer-reviewed; Emerg Microbes Infect

		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.	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 SAR-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[68] 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. 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)'	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
Yu 2020[79] 10.1183/13993003.01526-2020	SARS-CoV-2 Chemiluminescent immunoassay (CLIA)	37 patients with SARS-CoV-2; average 52.3years +/-16.3 years: 25 (67.7%) male.	**Rate of seroconversion:** Positive rate of IgA, IgM and IgG were 98.9%, 93.4% and 95.1% respectively.	Letter to editor

China Case series		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 one of: shortness of breath with respiratory rate >=30 times/min; oxygen saturation <= 93%; PaO2/FiO2 ≤300mmHg Critical patients had a least one of the following criteria: respiratory failure requiring mechanical ventilation; shock; or multiple organ failure requiring ICU.	**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** 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[80] 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) 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	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 (median 49, ranges 1-81); 39 (21.4%) had severe symptoms, 143 (78.6%) mild and moderate Discharge criteria: 1. Temperature below 37	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 **Antibodies**	Not peer-reviewed

	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	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	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[87] China Case series DOI: 10.1111/cts.12805	SARS-CoV-2 Inflammation profiles measured with automatic biochemical analyser (Cobas 6000 c501 analyzers Roche, Germany) SARS-CoV-2 IgG and IgM measured with immunoanalyser (iFlash 3000 immunoanalyzers, YHLO Biotech, Shenzhen, China)	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. 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	**Rate of seroconversion:** IgG 100% (19/19) IgM 89.5%;75% (6/8) severe, 100% (11/11) critical **Timing of seroconversion:** 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	Peer-reviewed; Clinical and Translational Science

			strategy of prevention of dysfunction of immune and optimal immunosuppressive therapy in future.	

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