

memo

COVID-19-EPIDEMIC :

Immunity after
SARS-CoV-2 infection
– a rapid review

Title Immunity after SARS-CoV-2 infection
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Key messages

The findings in this memo are based on rapid searches in PubMed, EMBASE and two pre-print databases. One researcher went through all search records, selected and summarised the findings. In the current situation, there is an urgent need for identifying the most important evidence quickly. Hence, we opted for this rapid approach despite an inherent risk of overlooking key evidence or making misguided judgements.

We identified 16 original papers from the database search and by manual searching of reference lists that were relevant to our research questions.

Does primary infection with SARS CoV-2 result in immunity, and if so, how long does the immunity last?

We found very limited evidence on immunity after infection with SARS-CoV-2. One study on rhesus macaque monkeys suggests that primary infection with SARS-CoV-2 may protect against reinfection. The study was small and did not provide any information on the duration of immunity. Two studies showed sustainable IgG levels one to two years after SARS-CoV infection, but it is uncertain whether this finding is generalisable to SARS-CoV-2, and also whether sustained levels of antibodies provide full protection against reinfection.

How quickly does one develop SARS-CoV-2 specific antibodies, and what is the proportion of patients presenting seroconversion?

Seroconversion rate and timing varied across studies and between IgM and IgG antibodies. We believe this variation is largely due to differences in the test sensitivity. A problem that probably will dissolve when larger studies using validated tests are published.

Does the rate of seroconversion and/or the timing depend on the severity of SARS-CoV-2 infection?

Seroconversion rate and timing do not appear to differ between patients with mild to severe/critical COVID 19 infection. Studies of asymptomatic cases are however lacking.

Can antibodies be transmitted from women infected with SARS-CoV-2 to the fetus via placenta and thus confer immunity in the newborn?

Results from one small study suggest that antibodies from SARS-CoV-2 infected women may be transmitted to the foetus during pregnancy, but the evidence is uncertain.

Hovedfunn (Norwegian)

Funnene i denne hurtigoversikten baserer seg på raske søk i PubMed, EMBASE og to pre-print databaser. Én forsker gikk gjennom søketreff, valgte ut og oppsummerte resultatene. Ettersom det har vært viktig å få fram forskningsresultatene raskt, valgte vi denne framgangsmåten selv om det innebærer risiko for at vi kan ha oversett viktig dokumentasjon og kan ha gjort feilvurderinger underveis.

Etter søk i databaser og manuelle søk i referanselister identifiserte og inkluderte vi 16 originalpublikasjoner som vi anså å være relevante for våre forskningsspørsmål.

Gir førstegangssmitte av SARS-CoV-2 immunitet, og hvor lenge varer denne immuniteten?

Vi fant svært begrenset dokumentasjon om immunitet etter infeksjon med SARS-CoV-2. Én studie på rhesus macaque aper kan tyde på at førstegangsinfeksjon med SARS-CoV-2 kan beskytte mot reinfeksjon, men studien var liten og ga ingen informasjon om varigheten av en eventuell immunitet. To studier viste vedvarende høye IgG-nivåer ett til to år etter infeksjon med SARS-CoV, men det er usikkert om resultater fra SARS-CoV kan overføres til SARS-CoV-2, og om høye nivåer av antistoffer gir full beskyttelse mot reinfeksjon.

Hvor raskt utvikler man SARS-CoV-2-spesifikke antistoffer, og hvor stor andel av pasientene gjennomgår serokonversjon?

Serokonversjonsrate og -tid varierte mellom studiene og mellom IgM og IgG. Vi antar at denne forskjellene i stor grad skyldes varierende testsensitivitet, og at variasjonen vil bli mindre etter hvert som det publiseres større studier som benytter validerte tester.

Er det en sammenheng mellom serokonversjonrate eller- tid og infeksjonens alvorlighetsgrad?

Serokonversjonshastighet og -tid synes ikke å være forskjellig mellom pasienter med ulik alvorlighetsgrad av covid-19. Vi har ikke funnet studier som inkluderer asymptomatiske individer.

Kan mødre som smittes med SARS-CoV-2 overføre antistoffer til fosteret via morkake og dermed gi immunitet hos det nyfødte?

Én liten studie tyder på at gravide med SARS-CoV-2 infeksjon kan overføre antistoffer til fosteret, men dokumentasjonen er usikker.

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Introduction

In relation to the Norwegian Institute of Public Health's role in handling the COVID-19 epidemic, we have been asked to prepare a rapid summary of the available research on immunity after SARS-CoV-2 infection.

The novel corona-virus SARS-CoV-2 that causes the disease COVID -19, bears the trans-membrane glycoprotein spikes (S protein), which are typical for this type of viruses. The spikes are important targets for the human immune response, and in particular the receptor-binding domain (RBD) of the S protein (1). The spikes enable the virus to enter the host cells through the human receptor angiotensin converting enzyme 2 (ACE2). Individuals who are infected with SARS-CoV-2 typically start producing virus specific antibodies (IgM, IgG, and IgA) that cover the spikes and neutralise the virus (1). This process may be associated with some level of immunity and protection against reinfection, for some period of time (2). Seroconversion is the transition from a seronegative condition; where no antibodies are in the serum, or they are present but below the limit of detection, to a seropositive condition, in which antibodies can be detected in serum samples.

Detection of SARS-CoV-2 specific IgM and IgG antibodies has recently been made possible through the development of new tests e.g. ELISA kits (2), thus allowing the study of seroconversion rate and seroconversion timing in patients with COVID-19.

Methods

The main objective of this rapid review was to summarise current evidence concerning immunity after SARS-CoV-2 infection. More specifically we wanted to address the following research questions:

Main question: Does one become immune after infection with SARS-CoV-2?

- If so how long does the immunity last?
- How quickly does one develop SARS-CoV-2 specific antibodies (seroconversion timing)?
- What is the proportion of people who develop these antibodies (seroconversion rate)?
- Does the seroconversion rate and/or timing depend on the severity of infection?
- Can mothers infected with SARS-CoV-2 transmit antibodies to the fetus via placenta and thus confer immunity in the newborn?

We carried out searches in PubMed, EMBASE, and in two pre-print databases (BioRxiv, MedRxiv). Searches were limited to the period from 2019 to 31 March 2020, as the novel SARS-CoV-2 virus emerged in late 2019 (3).

We selected studies focusing on (i) immunity after SARS CoV 2 infection; (ii) seroconversion rate after SARS-CoV-2 infection (iii) seroconversion timing after symptom onset, (iv) severity of disease and seroconversion and (v) transmission of antibodies from infected mothers to the foetus during pregnancy.

One researcher (Gerd Flodgren) assessed the relevance of each reference and summarized the findings. Three other researchers (Lene Juvet, Kjetil Brurberg, Lisbeth Meyer Næss, Norwegian Institute of Public Health,) read and provided feedback on drafts of the review before publication. Kjetil Brurberg wrote the Norwegian summary. Elisabet Hafstad (Information Specialist) prepared the literature searches

Results

The search resulted in 439 unique records, and we ended up including 16 primary studies. Nine of these were published in peer reviewed journals, and seven studies were unpublished pre-prints. As expected, no systematic review on immunity after SARS-Cov-2 infection was identified. Thirteen studies were conducted in China, one in Finland, Taiwan and Australia respectively.

Summary of included primary studies

Five cohort and four retrospective studies (4-12), and three case studies (13-15) reported on seroconversion rate and/or seroconversion timing after SARS-CoV-2 infection (see Table 1). Two of these studies also provided some information on the association between seroconversion rate and severity of COVID-19 disease (5, 9). One retrospective study reported on transmission of antibodies from mother to foetus during pregnancy (16). One prospective study of rhesus macaque monkeys reported on protection against reinfection after primary SARS-CoV-2 infection in animal model (17). Two cohort studies evaluated the antibody levels after SARS-CoV infection, a virus with similarities to SARS- CoV-2 (18, 19).

Characteristics of included studies

Studies of immunity after SARS-CoV-2 infection

We did not identify any human studies that could help answering whether people who have been infected with SARS-CoV-2 once, will be fully or partially protected from future re-infection by the same virus, and if so for how long. We found one relevant but unpublished study (pre-print). The study used an animal model including six adult rhesus macaque monkeys to investigate whether primary SARS-CoV-2 infection could have a protective effect against reinfection (17). We also found two studies that evaluated antibody levels after SARS-CoV infection (18, 19). One study by Guo et al. of healthcare workers (n=34) previously infected with SARS-CoV who's antibody levels were followed up for 13 years after the primary infection (19). A second study by Wu et al including 173 patients, who's antibody levels were followed up for three years after SARS-CoV infection (18). Even if these two latter studies do not study SARS-CoV-2 per

se, we judged that they might be of interest since SARS-CoV and SARS-CoV-2 have many similarities (1), and both viruses use the ACE2 receptor to enter the cell (20).

Studies of seroconversion rate and timing after SARS-CoV-2 infection

Nine studies (4-12) assessed the seroconversion timing and/or seroconversion rate in patients with SARS-CoV-2 infection. The sample sizes ranged from 22 to 173 patients (median sample size: 34), and median age ranged from 40 to 67 years. Four of the smaller studies included more men than women, while the large study by Zhao and colleagues (6), and most other studies, included a similar proportion of males and females. Four studies did not report the severity of disease of included patients (4, 7, 8, 11), while the remaining studies reported a mix of mild to severe or critically ill cases. Non-symptomatic patients were not included in any of the studies. See Table 1 for details on the severity of included patients. In one study 46% of included patients were reported to have chronic illnesses (5).

The number of serum samples analysed ranged from 29 to 535 across studies. The serological tests used in the included studies were as follows: EIA (5), CLIA (7), ELISA (6), proteomic microarrays (8), GICA (12), SARS-CoV-2 antibody detection kit (9), ICG strip assay (11). Two studies used three different serological test: CLIA, ELISA, and GICA (4), and ELISA, LFTA, and CMIA (10). For the full names of the tests see Table 1 footnotes.

Three case studies (13-15) also evaluated seroconversion timing in patients with SARS-CoV-2 infection. The three cases were all female, between 30 and 47 years old, and presenting with mild to moderate symptoms of SARS-CoV-2 infection. The number of analysed samples ranged from 4 to 7 across studies, and three different analysis methods were used for the analyses (see Table 1).

Studies of antibody transmission during pregnancy and SARS-CoV-2 infection

Zheng and colleagues reported a study of antibody transmission during pregnancy. Antibodies (IgM and IgG) in serum were assessed post-partum with a CLIA kit in six women with confirmed SARS-CoV-2 infection and their six infants. All infants were delivered by C-section, and mothers and personnel were all wearing protective masks during delivery. All six infants were isolated directly after delivery.

Table 1 Characteristics of included studies that reported on seroconversion rate and timing after SARS-CoV-2 infection (N=12)

Author Year	No of patients with COVID-19: age; gender	Severity of disease§	Test for detection of SARS-CoV-2 specific antibodies	No of serum samples and time of sampling	IgM	IgG	Publication type/ Journal/Impact factor (IF)
Gao 2020 Retrospective China	N=22 Median age: 40 years (4-73) F:8; M:14	Not reported (most patients received oxygen therapy and anti-viral medication)	CLIA, ELISA, GICA * *Considered positive if one of the tests was positive ³	N=37* d 1-7: n=10 d 8-14:n=13 d14 -24: n=14 (Some missing samples)	Seroconversion rate and timing: 1-7 d: 60% (6/10); 8-14 d: 53.8% (7/13); 14-24 d::78.6% (11/14)	Seroconversion rate and timing: 1-7 d: 50% (5/10); 8-14d: 76.9% (10/13); 14-24:d:100% (14/14)	Accepted for publication / Chinese Medical Journal/ IF: 1.053 in 2014
Jiang 2020 Cohort study China	N=29 (and 29 controls) Mean age: 42.3 (SD 13.8) F:16; M:13	3 mild cases; and 26 'common' cases	Proteome microarrays	N=29 Collected mean 22 days after onset	Seroconversion rate: 100%	Seroconversion rate: 100%	MedRxiv pre-print
Yong 2020 Retrospective China	N=34 Median age: 40.5 (IQR:31-49.5) M:53%	35 mild cases, 3 severe/critical cases	GICA	N= 76 Samples collected during hospitalisation.	Seroconversion rate: 50% (19/38)	Seroconversion rate: 92% (35/38)	MedRciv pre-print
Liu 2020 Retrospective China	N=133 Median age:68 F:63; M:70	44 moderate cases; 52 severe and 37 critical cases	SARS-CoV-2 antibody detection kit	Not reported	Seroconversion rate by severity of disease: Moderate:79.55% Severe: 82.69% Critical:72.97%	Seroconversion rate by severity of disease: Moderate: 93.18% Severe:100% Critical: 97.30%	MedRxiv pre-print
Lou 2020 Cohort study China	N=80 cases and N=300 controls Median age: 55 (45-64)	65 non-critical cases and 15 critical cases	ELISA, LFIA, and CMIA assays	N=304 Mean: 4 samples per/patient	Seroconversion rate & timing: 0-7d::33.3% 8-14d::86.7% 15-24d:96.7%	Seroconversion rate & timing: 0-7d: 33.3% 8-14d: 76.0% 15-24d: 93.3%	MedRxiv pre-print

	F:37%				Median seroconversion time: 10d	Median seroconversion time:12 d	
Pan 2020 Retrospective China	N=67	No information	ICG strip assay	N=86 1 (78 pat.) 2 (25 pat.) 3 (2 pat.)	Seroconversion rate&timing: 1-7 d: 11.1% 8-14 d:: 78.6% >15 d:74.2%	Seroconversion rate&timing: 1-7 d: 3.6% 8-14 d: 57.1% >15 d: 96.8%	MedRxiv pre-print
To 2020 Cohort study China	N=23 patients Median age:62 (37-75) M:10; F:13 46% had chronic illnesses	13 mild cases and 10 severe cases	EIA	N=108 Mean no of tests per patient: 4.7 (Only 16 patients had samples ≥14 days after onset)	Seroconversion rate: Anti-NP IgM: 85 % (14/16) Anti-RBD IgM: 94% (15/16) Seroconversion timing:10 days or later for most patients. No difference due to severity of disease.	Seroconversion rate: Anti-NP IgG: 94% (15/16) Anti-RBD IgG: 100% (16/16) Seroconversion timing:10 days or later for most patients. No difference due to severity of disease.	Lancet Infection/IF: 27.516
Xiao 2020 Cohort study China	N=34 Mean age: 55 (26-87) F:12; M:22	Not reported (all hospitalised)	CLIA	N=32 week 1: 2; week 3 :6; week4: 7; week 5: 12; week 6-7: 7	Seroconversion timing: (-) week 1 ² (+) week 3&4 (but declining), week 5&7: declining and 2 patients negative	Seroconversion timing: (-) week 1 ² (+) week 3, 4 (and increasing), and week 5&7 all patients still positive	Pre-proof /Journal of Infection/ IF: 4.603 (2017)
Zhao 2020 Cohort study China	N=173 Median age: 48 (IQR:35-61) F:51.4%;	141 non-critical and 32 critical cases	ELISA	N=535 Median no of tests per patient: 3 (IQR:2-4)	Seroconversion rate: 82.7% (143/173) Median seroconversion time: 12d	Seroconversion rate: 64.7% (112/173) Median seroconversion time: 14d	Published by Oxford university press for the Infectious Disease Society of America.
Haveli 2020 Case study Finland	One woman in her thirties	Mild/Non-severe	IFA	N=4	Seroconversion timing: (-) day 4 ; (+) d 9, 10 and 20	Seroconversion timing: (-) day 4; (+) d 9, 10 and 20	Rapid communication / Euro-surveillance/ IF: 5.983 in 2015
Lee 2020 Case study Australia	One 46-year old woman	Not reported	ALLTEST 2019-nCoV	N=7	Not reported ¹	Seroconversion timing: (-) d 2, 5 ; (+) d 7, 9, 13, 20, 23	Short communication/J of Microbiology, immunology, and infection/ IF:2.455
Thevarajan 2020 Case study Taiwan	One 47-year old woman	Mild –moderate /non-severe	IF	N=4	Seroconversion timing: (-) d 7, 8; (2+) d 9, and (3+) d 20	Seroconversion timing: (1+) d 7; (2+) d 8; (3+) d 9 and d 20	Correspondence/Nature Medicine/IF: 30.641 in 2018

§ Asymptomatic -mild –moderate-severe-critical

Results

Protection against reinfection

Results from Bao and colleagues 's study of rhesus macaque apes suggest a protective effect of primary infection against reinfection with SARS-CoV-2 virus (17). The study included only four monkeys, and since there was no time gap between the time of recovery from the primary infection and the point in time when the monkeys were re-challenged with the virus, this study provide no insight into the duration of the potential immunity.

Results from the study by Guo et al. of healthcare workers previously infected with SARS-CoV, showed sustained IgG levels one year after infection, but persisting levels up to 13 years after infection. (19). Results presented by Wu and colleagues suggest that IgG levels after SARS-CoV infection may be maintained for up to two years after infection, but that IgG levels are seen to decrease during the third year (18).

Seroconversion rate after SARS-CoV-2 infection

Seroconversion rate varied across studies, antibodies, and stage of Covid-19 disease. In three studies (4, 10, 11) that reported seroconversion rate for IgM and IgG at different stages of the disease the rate ranged between 11.1%-60% and 3.6%-50% at the early stage (d 1- 7 after symptom onset), between 53.8%-86.7% and 57.1%-76.9% at intermediate stage (d8-14), and between 74.2%-96.7% and 93.3-100% at late stage for IgM and IgG respectively. For four studies that reported seroconversion rate at only one point in time it ranged from 50% to 100% for IgM, and from 64.7% to 100% for IgG (5, 6, 8, 12). For details on the seroconversion rate in individual studies see table 1.

Seroconversion timing after SARS-CoV-2 infection

Seroconversion timing for IgM and IgG varied across studies and antibody class. Production of virus specific antibodies after infection were detected at an early stage after symptom onset in some cases, and in other cases at the intermediate or late stage. In two studies the seroconversion timing was reported to be shorter for IgM than for IgG (6, 10), while results from two other studies suggest earlier timing for IgG than for IgM (5, 15). Two studies reported median seroconversion timing ranging from 10-12 days for IgM and between 12 and 14 days for IgG (6, 10). In the three case studies seroconversion timing for IgM was reported to be 9 days after symptom onset in two studies (13, 15), and between 7 to 9 days for IgG in three studies (13-15). For details on the seroconversion timing for IgM and IgG see Table 1.

Seroconversion and severity of disease

One study reported no correlation between serum levels of IgM and IgG antibodies and severity of disease, but reported some evidence for a faster peak in antibody response

in people with COVID 19 disease who later died, than in those who recovered (5). One study reported no differences in seroconversion rate (or concentration) of IgM and IgG antibodies between groups of patients with different severity of disease(9).

Antibody transmission during pregnancy

Zheng and colleagues reported that all six infants delivered by SARS-CoV-2 infected mothers had increased levels of antibodies (five had increased IgG levels, two had increased IgM levels), and that none of the infants tested positive for SARS-CoV-2. All mothers also had increased levels of antibodies (16).

Discussion and conclusion

We included 16 original studies in this rapid review of research related to immunity after SARS-CoV-2 infection. Nine of these studies were published in international peer reviewed journals, while six were unpublished pre-prints that had not been subjected to peer review. Thirteen studies were conducted in China, and one study was from Finland, one from Taiwan and one from Australia. The latter three were case-studies.

Immunity and protection against reinfection

We did not identify any human studies directly addressing whether infection with SARS-CoV-2 results in immunity and protection against re-infection. Results from a study on rhesus macaque monkeys suggest protection against reinfection after primary infection, but the study was small and did not provide any information on the potential duration of immunity. Results from two studies of antibody levels after infection with SARS-CoV, a similar corona virus, suggest that high levels of IgG may last for up to 1-2 years after infection (18, 19). However, due to the recent identification of the SARS-CoV-2 virus, there are no studies available that can confirm or refute whether this is the case also for SARS-CoV-2. Even if it is likely that sustained levels of antibodies are related to some level of protection against reinfection, we do not at present know if they ensure full protection against reinfection by the same virus or may result in less severe infection at future exposure to the virus.

Production of disease specific antibodies- seroconversion rate and timing

After infection IgM antibodies appear first and thereafter IgG (2). Further, that IgM levels are higher at early stages of disease and then decreases over time, while IgG levels increases during the intermediate and later stage after symptom onset (2). The results from this rapid review however were mixed, with some studies reporting earlier seroconversion for IgM, others for IgG, and yet other studies suggesting similar seroconversion time for both antibodies. One explanation to this may be due to different test sensitivity to the different antibodies for the, sometimes non-validated, serological tests used in the included studies. One study reported differences in detection rate of antibodies across the three (validated) tests used in the study (CLIA, GICA and ELISA), with GICA exhibiting higher positive rate in serum IgM detection, while ELISA had comparatively higher rates in serum IgG detection (4). Difference in the proportion of patients who presented seroconversion also differed across studies and antibodies. We believe

that the seroconversion rate will be higher and more coherent with more studies using validated tests, better study designs, and larger sample sizes being conducted.

Severity of disease and seroconversion

Few studies assessed whether seroconversion rate was associated with the severity of disease in patients (5, 9). Results from two studies, in which the severity of disease ranged from mild to severe or critical, suggest no correlation between severity of illness and seroconversion rate. One of the studies suggest a possible association between a fast early peak in serum antibodies after symptom onset and risk of death (5), but otherwise little information was provided. No study included asymptomatic non-hospitalised cases, and little is therefore known regarding whether or not seroconversion occur in these subjects, and if so, when.

Transmission of antibodies during pregnancy

Only one small retrospective study including 6 women and their babies supports transmission of protective antibodies from women with mild SARS-CoV-2 infection to the foetus through the umbilical cord. All infants, and their mothers, had increased levels of antibodies. None of the new-borns tested positive for SARS-CoV-2 (16). This study was limited by the lack of follow up of the infants after birth.

One retrospective study that included nine women with non-severe COVID-19 disease also reported that all new-borns who were tested (N=6) were negative for SARS-CoV-2 in analyses of amniotic fluid, cord blood, neonatal throat swab and breast milk (21). Another retrospective study, which included 28 women with mild to severe COVID-19 disease and their offspring, reported that 3.6% (1/28) of the infants tested positive for SARS-CoV-2 after birth (22). In this study cord and placental samples were negative to SARS-CoV-2, which may indicate that this was not a vertically transmitted infection, but maybe a false positive. The infant's symptoms were resolved in 2 days' time. None of the latter studies however assessed the IgM or IgG levels.

In conclusion, we identified 16 studies, of which a majority were from China, and many that were unpublished pre-prints. It is still early days, and answering the question regarding immunity after primary infection must await well-conducted studies with larger sample sizes, using validated methods. A large number of antibody tests have been made available after the SARS-CoV-2 outbreak in China in December 19, but many of these need further validation.

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Attachment

Search strategies

MEDLINE & Embase

Databaser: Embase 1974 to 2020 March 30; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to March 30, 2020		
Søkegrensesnitt: Advanced search		
1	(Severe Acute Respiratory Syndrome/ or SARS Virus/) use ppezv	5728
2	(Severe Acute Respiratory Syndrome/ or SARS Coronavirus/) use oomezd	10651
3	((("corona virus" or coronavirus* or coronovirus*) adj3 (novel or "2019" or Wuhan or Huanan)) or ((atypical or Wuhan) adj3 pneumonia) or "COVID-19" or COVID19 or CORVID-19 or CORVID19 or "coronavirus 2" or nCoV or 2019nCoV or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV19 or SARS-CoV19 or SARS-CoV-19 or HCoV-19 or WN-CoV or "severe acute respiratory syndrome" or SARS).tw,kw,kf.	26933
4	exp *Immunity/ use ppezv	141162
5	exp *Immunity/ use oomezd	493622
6	(immunity or IgM or IgA or IgG or IgG3 or IgG4 or seroconverters*).tw,kw,kf.	2802808
7	or/1-3	30885
8	or/4-6	3102327
9	7 and 8	3373
10	limit 10 to yr="2019-Current"	222

PrePrints

[bioRxiv](#) (91 treff – lastet opp til EndNote)

((covid-19 OR nCoV OR SARS-CoV2 OR SARS-CoV-2) AND (immunity OR seroconversion OR IgA OR IgG OR IgM))

[medRxiv](#) (207 treff – screenes på skjerm)

((covid-19 OR nCoV OR SARS-CoV2 OR SARS-CoV-2) AND (immunity OR seroconversion OR IgA OR IgG OR IgM))

