NIPH
Norwegian Institute of Public Health

memo

COVID-19-EPIDEMIC :

Immunity after SARS-CoV-2 infection, 1st update – a rapid review

Title	Immunity after SARS-CoV-2 infection, 1st update – a rapid review
Norwegian title	Immunitet etter SARS-CoV-2 infeksjon, første oppdatering – en hurtigoversikt
Institution	Norwegian Institute of Public Health
Responsible	Camilla Stoltenberg, Director General
Authors	*Flodgren GM,* seniorforsker, *Norwegian Institute of Public Health*
Memo	April – 2020
ISBN	978-82-8406-090-3
Publication type	Rapid Review, Covid-19 rapid response
Number of pages	21 (33 including appendices)
Commisioner	Norwegian Institute of Public Health
Citation	Flodgren GM. Immunity after SARS-CoV-2 infection, 1st update – a rapid review 2020. Oslo: Norwegian Institute of Public Health, 2020.

Key messages

This memo is an update of an earlier version, and the findings are based on rapid searches in PubMed, EMBASE, and supplementary searches for pre-prints. 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 20 new original papers from the database search and by manual searching of reference lists that were relevant to our research questions. This rapid review now includes 36 studies. Half of the included studies were pre-prints that had not been through peer review, and many studies had very small sample sizes.

Does primary infection with SARS CoV-2 result in immunity, and if so, how long does the immunity last?
We found 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-Cove infection, but whether this finding is generalizable to SARS-CoV-2 has still to be determined, also whether sustained levels of antibodies provide full or partial protection against reinfection.

Is there cross-protection from SARS-CoV-2 infection after infection with seasonal corona viruses (sCoVs)?
There is no direct evidence for cross-protection from SARS-CoV-2 infection after infection with sCoVs.

How long does it take to 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. Results from some of the studies suggest a median seroconversion timing around 10-14 days after disease onset, while some studies suggest a longer time (28 to 30 days or longer) for all patients to seroconvert. We believe that much of this variation is due to differences in the test sensitivity, but may also be due to differences in the immune response between different patient groups.

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

The results for this question was mixed. While some studies reported no relationship between seroconversion and severity of COVID-19 disease, evidence from other studies suggest that a more rapid and higher antibody response may be related to the severity of disease. Also, seroconversion may not be a prerequisite for virus clearance, since asymptomatic patients, and people with undetectable levels of antibodies still manage to clear the virus.

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

Results from two small studies (including in total 7 neonates) suggest that antibodies from SARS-CoV-2 infected women may be transmitted to the foetus during pregnancy, but the evidence is uncertain.

Hovedfunn (Norwegian)

Dette notatet er en oppdatering av en tidligere versjon, og 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 vi 20 nye originalpublikasjoner som vi anså at var relevante for våre forskningsspørsmål. Etter oppdatering inkluderer denne hurtigoversikten 35 studier. Halvparten av de inkluderte studiene var pre-prints som ikke har vært gjennom peer-review, og mange studier hadde veldig få deltakere.

Gir førstegangssmitte av SARS-CoV-2 immunitet , og hvor lenge varer denne immuniteten?
Vi fant begrenset dokumentasjon om immunitet etter infeksjon med SARS-CoV-2. Én studie på rhesusaper 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. Det er usikkert om disse resultatene fra SARS-CoV kan overføres til SARS-CoV-2, og om høye nivåer av antistoffer gir full eller delvis beskyttelse mot reinfeksjon.

Kan infeksjon med andre koronavirus (sCoV) beskytte mot SARS-CoV-2 infeksjon?
Det foreligger foreløpig ingen dokumentasjon for at infeksjon med sCoV kan gi kryssbeskyttelse mot SARS-CoV-2 infeksjon.

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. Mange av de inkluderte studiene antyder at median tid for serokonversjon er omkring 10-14 dager etter sykdomsdebut, men noen studier antyder lenger serokonversjonstid (28 til 30 dager eller lenger). Vi antar at den observerte variasjonen i serokonversjonstid i stor grad skyldes varierende testsensitivitet, og kan også skyldes forskjeller i immunresponsen hos ulike pasientgrupper.

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

De inkluderte studiene rapporterte varierende resultater. Noen studier rapporterte at de ikke fant noen sammenheng mellom serokonversjon og alvorlighetsgraden av covid-19, mens andre studier knyttet alvorlig sykdom til raskere og kraftigere antistoffrespons. Serokonversjon ser ikke ut til å være en forutsetning for virusklarering, ettersom asymptomatiske pasienter og personer med svært lave antistoffnivåer også blir virusfrie.

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

To små studier som inkluderte 7 spedbarn tyder på at gravide med SARS-CoV-2 infeksjon kan overføre antistoffer til fosteret, men dokumentasjonen er usikker.

Content

Introduction

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

The novel coronavirus SARS-CoV-2 that causes the disease COVID -19, bears the transmembrane 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 enables 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 neutralises the virus (1).This process may be associated with some level of immunity and protection against reinfection, for some period of time (2). Both cellular and humoral (adaptive) immunity are important in the immunological response to viral infections. This rapid review however, focuses on antibody-mediated immunity and seroconversion. 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, IgG, and IgA antibodies has recently been made possible through the development of new test s 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 update 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?
- Is there cross-protection against SARS-CoV-2 infection after infection with other coronaviruses?
- How long after symptom onset do people (adults and children) with COVID-19 develop SARS-CoV-2 specific antibodies (seroconversion timing)?
- What is the proportion of people (adults, and children) that develop these antibodies (seroconversion rate)?
- Is the severity of COVID-19 disease associated with seroconversion rate and/or timing?
- Can women infected with SARS-CoV-2 transmit antibodies to the foetus via placenta and thus confer immunity in the newborn?

We searched in PubMed, EMBASE, using the search strategy in Appendix 1. Searches were limited to the period from December 2019 to 23 April 2020, as SARS-CoV-2 was first identified in December 2019 (3). We also searched for pre-prints (bioRxiv, chemRxiv and medRxiv) using words / word stems such as immun; seropos; seroconv; IgG; cross-protect; reinfect (see line 4 in the Ovid search strategy) from within the EndNote-database containing all the references for Norwegian Institute of Public Health's systematic and living map on COVID-19 evidence, to which a reference file is daily downloaded from Stephen B. Thacker CDC Library's collection of COVID-19 research articles (CDC, Centres for Disease Control and Prevention). The search methods used by the CDC are detailed on their website.

We selected studies focusing on (i) immunity after SARS-CoV-2 infection; (ii) cross-protection against SARS CoV-2 infection after infection with other coronaviruses (iii) seroconversion timing after symptom onset (iv) seroconversion rate after SARS-CoV-2 infection, (v) severity of disease and seroconversion and (vi) transmission of antibodies from infected mothers to the foetus during pregnancy. We excluded studies that included both patients with confirmed and non-confirmed COVID-19 that did not report results for confirmed cases separately. We also excluded letters to the editor. This rapid

review does not include a formal quality assessment of included papers, nor does it include a grading of the certainty of evidence. The results should therefore be interpreted with caution.

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

Results

The update-search resulted in 391 unique records, and we ended up including 20 new primary studies, which together with the 16 previously included studies made a total of 36 included studies. A majority of included studies were conducted in China, two studies were conducted in Germany, two in the UK, and one in Finland, France, Italy, Taiwan, Australia and Peru respectively. Five of the latter were case-studies. Around half of the included studies were published or accepted for publication in peer reviewed journals, and the others were unpublished pre-prints.

Summary of included studies

The majority of included studies had a retrospective study design. Twenty-nine studies reported on seroconversion rate and/or seroconversion timing after SARS-CoV-2 infection. See Appendix 1 and 2. Ten of these studies also reported on associations between seroconversion rate or timing, antibody titres, age and severity of COVID-19 (4-13). One retrospective study, and two case studies reported on transmission of antibodies from SARS-CoV-2 infected women to the foetus during pregnancy (14-16). See Appendix 3. One prospective study of rhesus macaque monkeys reported on protection against reinfection after primary SARS-CoV-2 infection in animal model (17). One retrospective study reported on long-term co-existence of SARS-CoV-2 and SARS-CoV-2 specific antibodies (18). Two cohort studies evaluated the antibody levels after SARS-CoV infection, a virus with similarities to SARS-CoV-2 (19, 20). One study reported on the possibility of cross-protection from SARS-CoV-2 infection after infection with other coronaviruses (21).

Characteristics of included studies

Studies of immunity after SARS-CoV-2 infection

One relevant but unpublished study (pre-print) used an animal model including four 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 (19, 20). 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 (20). 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 (22).

One study (18) assessed co-existence of SARS-CoV-2 virus and SARS-CoV-2 specific antibodies in patients with mild COVID-19, following up patients for up to 53 days after disease onset. The study authors did not mention the role of T cells, MHC, etc., and did not attempt to cultivate the virus, which would have provided more information on whether the virus was actually co-existing with the antibodies, or was inactivated.

One Scottish epidemiological study (21) evaluated the possibility of co-infection of different seasonal coronaviruses (sCoVs), The study included diagnostic data for more than 70,000 episodes of respiratory illness that had been tested for a number of seasonal coronaviruses (data from 2017) against SARS-CoV-2 , but did not include any data on SARS-CoV-2.

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

Twenty-six studies and 3 case studies that are descried below assessed the seroconversion timing and/or seroconversion rate in patients with SARS-CoV-2 infection (See Appendix 1 and 2). The median sample size in included studies was 37(range: 2 to 285; N= 1,897 patients in total). Median age of included patients with confirmed COVID-19 disease was 55 years across studies (range: 36 to 66 years), but not all studies reported the age of patients. Children below the age of 18 (4-16 years) were included in four studies (9, 11, 12, 23). Seven studies did not report the severity of disease of included patients (8, 11, 24-28). The remaining studies typically reported a mix of mild to severe or critical cases. One study included only severe or critical cases (29), and three studies included only mild cases (12, 30, 31). One study included a small number of asymptomatic carriers (32). One study(4) used the WHO categorisation of severity of COVID-19 disease (33) to describe their study population (33),while other studies used other definitions/guidelines (6, 10, 11, 13, 32, 34-36). Three studies reported the proportion of patients with comorbidities which ranged from 37.3% to 46.5 % (8, 10, 35). Infection with SARS CoV-2 was in all studies confirmed with RT-PCR.

The number of serum samples analysed ranged from 29 to 535 across studies. A large number of different serological test were used to detect SARS CoV-2 specific antibodies in serum e.g. EIA, CLIA, ELISA, GICA, proteomic microarrays, SARS-CoV-2 antibody detection kit, ICG strip assay, ICA rapid test etc. See Appendix 1 and 2 for details.

Three case studies (37-39) 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. The number of analysed samples ranged from 4 to 7 across studies, and three different serological tests were used for the analyses. See Appendix 3.

Studies of relationship between seroconversion, antibody titres, age and severity of disease

Ten of the 29 studies described above (median sample size 88; range 2 to 285; N=1,104 patient in total) evaluated the relationship between seroconversion rate, timing, antibody titres and severity of disease (4, 5, 7, 8, 10-13, 40). Median age of included patients with COVID-19 ranged from 47 to 66 years across these studies. Infection with SARS CoV-2 was in all studies confirmed with RT-PCR. Antibodies (IgM, IgG, and in some cases also IgA) in serum were assessed using a number of different serological tests (See Appendix 2). A majority of patients were hospitalised at the time of sampling, while a couple of studies included convalescents (11), or recovered patients (12). Follow up of antibody kinetics ranged across studies from around 14 days and up to 53 days after disease. See Appendix 2 for details.

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

Three studies, including in total eight neonates, assessed transmission of antibodies from women with confirmed COVID-19 to the foetus during pregnancy (14-16). One short communication of a case study was from Peru (14), and two research letters (describing a case study and retrospective study) were from China (15, 16). Infants were delivered by C-section in all studies. The women with COVID-19 wore protective masks in two studies (15, 16), and in one study also the personnel wore masks (16)). In one study it was unclear if any protective equipment were worn during delivery (14). All eight infants were isolated directly after delivery, without skin-to-skin contact. Antibodies (IgM and IgG) in serum of women and infants were assessed post-partum with a CLIA kit in one study (16), a solid-phase Immunochromatographic assay was used in one study (15), and in one study it was unclear what test had been used for detection of antibodies (14). All infants were tested for SARS-CoV-2 with RT-PCR: In one study the infant was tested twice (16 hours after delivery and again after 48 hours) (14), in one study the test was repeated five times (from 2 hours after birth and up to 16 days after) (15). In one study only one test was performed (16). All tests were based on nasopharyngeal swabs. None of the studies assessed the presence of SARS-CoV-2 specific antibodies (or the virus) in amniotic fluid, cord blood, placental tissue or breast milk. Follow up ranged from 1 to 16 days after delivery. See Appendix 3.

Results

Protection against infection or reinfection with SARS-CoV-2

Bao and colleagues 's study of rhesus macaque monkeys (N=4) suggests a protective effect of primary infection against reinfection with SARS-CoV-2 (17). The study only included four monkeys, and since there was no time gap between the time-point 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.

Guo et al. reported sustained IgG levels in healthcare workers (N=34) one year after SARS-CoV infection, and persisting levels up to 13 years after infection (19). Wu and colleagues reported that IgG levels after SARS-CoV infection may be maintained in people previously infected (N=176) for up to two years after infection, but that during the third year IgG levels are seen to decrease (20).

Cross-protection from SARS CoV-infection from previous infection with seasonal coronaviruses

We found no direct evidence for cross-protection from SARS-CoV-2 infection from previous infection with other coronaviruses.

Long-term coexistence of SARS-CoV-2 virus and SARS-CoV-2 specific antibodies

One retrospective study (18) of (N=26) patients with mild COVID-19 , aged 5 to 72 years, reported co-existence of SARS-CoV-2 virus and IgG antibodies, in four cases for between 26-50 days after disease onset. One patient did not develop any SARS-CoV-2 specific antibodies but cleared the virus within 46 days. The authors did not attempt to cultivate the virus to assess its viability.

Seroconversion rate after SARS-CoV-2 infection

Seroconversion rate varied across studies, antibodies, and stage of Covid-19 disease. In eight studies (8, 12, 24-26, 28, 40-42) that reported seroconversion rate for IgM and IgG at different stages of the disease the rate ranged between 10.3%-60% and 3.6%-53% at the early stage (d 1- 7 after symptom onset), between 53.8%-86.7% and 57.1%-100 % at intermediate stage (d 8-14), and between 52.2%-96.7% and 91.3-100% at late stage (>14 d) for IgM and IgG respectively. For six studies that reported overall seroconversion rate) it ranged from 50% to 100% for IgM, and from 64.7% to 100% for IgG (9-11, 27, 36, 43). Higher seroconversion rate was reported for IgG in all studies.

One study (12) reported that 30% of 175 recovered patients had very low Neutralising antibody (Nab) titres of which most of them were younger people, and that 10 patients had antibody levels below the detection limit. For details on the seroconversion rate in individual studies see Appendix 1 and Appendix 2.

Seroconversion timing after SARS-CoV-2 infection

Seroconversion timing for IgM and IgG varied across studies and antibody class. Production of virus specific antibodies were detected at an early stage after symptom onset in some cases (around d 5), in other cases at the intermediate (many studies suggest seroconversion around d12-14 for IgG) or late stage (see below) and in some patients not at all. In three studies the seroconversion was reported to be induced earlier for IgM than for IgG (11, 36, 41), while results from three other studies suggest earlier timing for IgG than for IgM (10, 39, 42). One study reported different dynamics between IgM and IgG response for different groups of patients: earlier IgM response in some patients, earlier IgG response in some, and similar IgM and IgG response in some patients (9).

Two studies reported median seroconversion timing ranging from 10-12 days for IgM and from 12 to 14 days for IgG (36, 41). One study reported median seroconversion timing for IgM at day 14, and for IgG at day 21 (13). One study (8) reported 100% seroconversion for IgA and IgM between 11 and 15 days after disease onset, and between 16 and 20 days for IgG. Late peak seroconversion rate for IgM and IgG was reported in three studies: in one study at between 31-35 days after disease onset for IgM, and after>35 days for IgG (40). , and in another study at day 28 after disease onset for IgM and day 49 for IgG (9) . In one study (11) seroconversion of neutralising antibodies was reported within 20 days after disease onset in all patients, and sustained levels until day 41-53. The levels were further highest at 31-43 days after disease onset, and decreased slightly thereafter. In the three case studies seroconversion timing for IgM was 9 days after symptom onset in two studies (37, 39), and between 7 to 9 days for IgG in three studies (37-39). For details on the seroconversion timing see Appendix 1 and Appendix 2.

Seroconversion, antibody titres, age and severity of disease

Three studies (N= 40, 133 and 23 cases respectively) reported no relationships between severity of disease and IgM and IgG antibody titres, or seroconversion rate (4, 10, 40). One of these studies (N=23) however, reported some evidence for a faster peak in antibody response in people with COVID-19 disease who later died, than in patients who recovered (10).

Higher antibody titres in patients with a more severe clinical condition than for patients with milder COVID-19 disease (N=67, 70 and 643 respectively) was reported in three studies (9, 11, 34), but in one of these studies (34), titres were only significantly higher for IgG and only at 2 weeks after disease onset. One study (11) reported that high IgM levels at early stage of disease, and high IgG levels at later stage were more frequent in patients with severe disease. Also Zhang and colleagues (N=222) reported that high IgG levels at late stage (> 14 d) were more frequent in patients with severe disease (44).

Tan et al further reported that IgG titres in addition to being higher in patients with severe disease appeared earlier (high responders), and that weak responders (with lower IgG titres) have significantly higher virus clearance rate, than high responders (9). According to Tan and colleagues 52% of patients were non-responders for IgM and 17% for IgG (i.e. antibody titres were below detectable levels).

One case series study (5), including only two patients, reported a strong IgA response soon after disease onset in a mild COVID-19 case, and a delayed but eventually very strong and broad IgA response in a more severe case. One study (8), including N=87 patients, reported a correlation between serum IgA level and severity of disease.

Neutralising antibody (NAbs) titres and spike-binding antibodies, age, and severity of disease

Results from one study (12) which included 175 patients recovered from COVID-19 disease suggest that SARS CoV-2 specific neutralising antibodies (NAbs) and spike-binding antibodies develops day 10-15 after infection. Further, that NAb-titres and spike binding antibodies were significantly higher in middle-aged and elderly people, than in younger people. Thirty percent of the patients who recovered from mild COVID-19 disease had very low NAb titres (mostly younger patients 15-39 years of age), and in 10 of these patients the NAb titres were below detectable level. Results from a second study (11) also showed higher antibody titres in middle-aged and older patients, than in younger patients (16-30yrs), and higher titres in patients with a severe clinical classification.

Antibody transmission during pregnancy

Results of increased postpartum levels of SARS-CoV-2 antibodies in sera in all infants (and their mothers) in two of the included studies (N=6 and 1 infants, respectively) suggest transmission of antibodies from SARS-CoV-2 infected mothers, with mostly mild COVID-19, to the foetus during pregnancy (15, 16). None of the infants in these two studies tested positive for SARS-CoV-2. In the third study both the woman, who had severe COVID-19 disease, and the infant were seronegative post-partum, and the infant tested positive for SARS-CoV-2(14).

Discussion and conclusion

We included 36 original studies in this rapid review update of research related to immunity after SARS-CoV-2 infection. A majority of studies were conducted in China, and two studies were from Germany, two from the UK, and one study from France, Finland, Switzerland, Taiwan, Australia and Peru. Five of the latter were case-studies. A majority of the studies were retrospective, and had small sample sizes (median 37 patients). Half of these studies were published or accepted for publication in international peer

reviewed journals, while the others were unpublished pre-prints that had not been subjected to peer review.

Immunity and protection against reinfection

We did not identify any human studies that could help answering whether people once infected with SARS-CoV-2, will be fully or partially protected from future re-infection by the same virus, and if so for how long. Results from a study on rhesus macaque monkeys provide some evidence for protection against reinfection after primary infection, but the study was small and did not provide any insights into the potential duration of immunity. Results from two studies of antibody levels after infection with SARS-CoV, a similar corona virus, suggest that sustained levels of IgG may last for up to 1-2 years after infection (19, 20). 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 provide full protection against reinfection by the same virus or may result in attenuated infection at future exposure to the virus.

It should be noted that co-existence of SARS-CoV-2 virus and SARS-CoV-2 specific antibodies was reported in one study(18), and that one patient who did not seroconvert, still managed to clear the virus. However, this study must be considered methodologically weak, since the authors did not take into account other factors of importance for the immunological response, and the results were not verified by cultivating the virus to assess its viability.

In another study(12), 30% of patients, mostly younger people, had antibody titres under detection level, and 10 patients did not show seroconversion, but they still recovered. Thus, seroconversion may not be a prerequisite for virus clearance, and recovery from the disease. What implications lack of seroconversion has for possible future protection against re-infection is not known. Also, both cellular and humoral (adaptive) immunity play important roles in the immunological response to viral infections, more research is needed on their respective roles in regard to immunity after COVID-19 disease.

Production of disease specific antibodies- seroconversion rate and timing

After infection IgM antibodies appear first and thereafter IgG (2). 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). In regard to this the results from this rapid review were mixed, with some studies reporting earlier seroconversion for IgM, others for IgG, or similar seroconversion time for both antibodies. This discrepancy, may be due to different sensitivity of the tests to different antibodies, but possibly also to real variation in immune responses between patients. One study reported differences in detection rate of antibodies across three tests (CLIA, GICA and

ELISA), with GICA exhibiting higher positive rate in serum IgM detection, while ELISA had comparatively higher rates in serum IgG detection (24). Difference in the proportion of seropositive patients 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, longer follow up and larger sample sizes being conducted.

Severity of disease, age and seroconversion

Ten studies assessed whether seroconversion, antibody titres, or age were associated with severity of disease in patients with COVID-19 disease (See Appendix 2). Results were mixed with results from three studies (N= 40, 133 and 23 cases respectively) suggesting no relationship between seroconversion and severity of disease (4, 10, 40), while results from five other studies (N=63, 87, 67, 70, and 222 patients respectively) suggest a relationship between higher antibody titres and/or a more rapid antibody response, and/or high levels of antibodies in serum at late stage of disease, and severity of COVID-19 (8-11, 34, 44). One study (N=175 patients) included, reported that 30 percent of recovered patients with mild COVID-19 disease had very low neutralising antibody titres, and 10 of these, mostly younger patients, had titres that were below detection level i.e. did not show seroconversion (12).There are also indications that higher antibody titres, in so called high-responders, are associated with poorer virus clearance and more severe disease. Not all of the included studies however provided a definition of how patients were classified in terms of severity of disease in their study sample.

Transmission of SARS-CoV-2 specific antibodies during pregnancy

Only two very small studies (including 7 cases in total) supports transmission of protective antibodies from women with mostly mild SARS-CoV-2 infection to the foetus during pregnancy. All infants, and their mothers, had increased levels of antibodies post-partum. None of the new-borns tested positive for SARS-CoV-2 (15, 16). A third study, which included only one woman with severe COVID-19 disease and her offspring, reported that both mother and infant were seronegative post-partum, which, since the infant tested positive for SARS CoV-2 provides some support for a vertical transmission of the infection (14). Limitations of these studies were in addition to the small sample sizes, that the SARS-CoV-2 infection was not confirmed in amniotic fluid, cord blood, or in placental tissue, the serological test for detection of antibodies was not known in one study, and the infants were not followed up later than 5 days after birth in two of the studies, why we do not know whether they, after an incubation period, eventually became infected.

Two related, but not included studies are of interest regarding the possibility of protection against SARSCoV-2 infection during pregnancy. One retrospective study including women with non-severe COVID-19 disease (N=9) reported that all new-borns who were tested (6 of 9) tested negative for SARS-CoV-2 in all analyses (i.e. of throat swabs, amniotic fluid, cord blood, and breast milk) (45). Another retrospective study of (N=28)

women with mild to severe COVID-19 disease, reported that 3.6% (1/28) of the infants tested positive for SARS-CoV-2 after birth (46). In this study cord and placental samples were negative for SARS-CoV-2, which may indicate that this was not a vertically transmitted infection, and possibly a false positive. The infant's symptoms (ARDs) were resolved in 2 days' time. Neither of these studies however assessed the antibody levels of the infants, and we cannot therefore say whether the infants (or their mothers) had seroconverted, nor do we know if this potentially was what protected the infants from infection. In addition, due to lack of follow up, we cannot tell whether the infants developed symptoms at a later time.

In conclusion, we included 36 relatively small studies in this update (median 37 patients). A majority of the studies were from China, and had a retrospective study design. Approximately half of the studies were pre-prints, and thus had not been subjected to peer-review. It is still early days of this new disease, and answering the question regarding immunity after primary SARS-CoV-2 infection must await well-conducted studies with larger sample sizes, using validated methods, and longer follow up. 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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appendices

Appendix 1

Search strategies
MEDLINE and Embase

2020-04-23 COVID-19 immunitet

Databases: Embase 1974 to 2020 April 22; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to April 22, 2020 **Seach interface:** Advanced search		
1	(((corona virus* or coronavir* or coronovirus* or betacoronavirus*) adj3 (new or novel or "2019" or Wuhan or Huanan or Hubei)) or "COVID-19" or COVID19 or "SARS coronavirus 2" or "severe acute respiratory syndrome coronavirus 2" or nCoV or 2019nCoV or nCoV2019 or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or SARSCoV19 or SARS-CoV19 or SARS-CoV-19 or HCoV-19 or WN-CoV).mp.	12898
2	exp *Immunity/ use ppezv	141597
3	exp *Immunity/ use oemezd	494695
4	(immunity or (immune adj (respons* or process*)) or (antibod* adj2 (for-mation or production or response*)) or IgG or IgM or "immunoglobulin G" or "immunoglobulin M" or seroconver* or sero-conver* or seropositiv* or sero-positiv* or crossprotect* or cross-protect* or reinfect* or re-infect*).mp.	1845886
5	1 and (2 or 3 or 4)	624
6	("201948" or "201949" or 20195* or 2020*).em. use oemezd [Embase]	1261102
7	(201912* or 2020*).dt. use ppezv [MEDLINE]	527681
8	5 and 6	205
9	5 and 7	176
10	8 or 9	381

Appendix 2

Table 1 Seroconversion rate and timing (N=17)

Author Year	No of patients with confirmed COVID 19: age; gender	Severity of disease (asymptomatic -mild –moderate-severe-critical)	Test for detection of SARS-CoV 2 specific antibodies	No of serum samples and time-points of sampling	IgM	IgG	IgA	Publication type/ Journal/Impact factor (IF)
Baettig 2020 Retrospective case series Switzerland	2 members of Swiss Armed Forces; 54 close contacts	2 mild cases	Immunochromatographpy rapid test	One test each 14 days after the first person was diagnosed	The two confirmed cases were seropositive after 14 days, but none of the other 54 cases (even though 7 of 9 persons who were put in quarantine together showed symptoms)		-	BMJ Health
Gao 2020 Retrospective China	N=22 Median age: 40 years (4-73) F:8; M:14	Not reported (most patients received oxygen therapy and antiviral medication)	CLIA, ELISA, GICA	N=37* d 1-7: n=10 d 8-14:n=13 d14 -24: n=14	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)		Chinese Medical Journal/ IF: 1.053 in 2014
Grzelak 2020 Retrospective France	N=51 hospitalised patients	Severe to critical cases	ELISA-N; ELISA tri_S; S-flow assay; LIPS assay	N=161 (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.			medRxiv
Jiang 2020 Cohort study China	N=29 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

Liu 2020 Retrospective China	N=214 (100 controls) No other patient characteristics.	No information	Rn-based and rs-based ELISA kits (only results for rs-based kit is reported due to the higher sensitivity of the test)	N=214	Seroconversion rate and timing 0-5d: 36.4% 6-10d: 50% 11-15d:83.3% 16-20d: 96.4% 21-30d: 87.5% 31-35d:100% >35d:86.7%	Seroconversion rate and timing: 0-5d: 40.9% 6-10d:50% 11-15d:75.9% 16-20d: 92.7% 21-30d:84.4% 31-35d:83.3% >35d:100%	-	Accepted manuscript J Clin Microbiol
Lou 2020 Cohort study China	N=80 cases and N=300 controls Median age: 55 (45-64) F:37%	65 non-critical cases and 15 critical cases	ELISA, LFIA, and CMIA assays	N=304 Mean: 4 samples per/patient	Seroconversion rate and timing: 0-7d::33.3% 8-14d::86.7% 15-24d:96.7% Median seroconversion time: 10 d	Seroconversion rate and timing: 0-7d: 33.3% 8-14d: 76.0% 15-24d: 93.3% Median seroconversion time:12 d		medRxiv
Padoan 2020 Retrospective Italy	N=37 No patient characteristics reported.	No information	Chemiluminescence analysis system (MAGLUMI 2000)	N=87 residual serum samples	Seroconversion rate and timing after fever onset: <5d: 0% 6-7 d: 3/6 (50%) 8-9 d: 7/12 (58.3%) 10-11 d: 5/4 (35.7%) 12-13d: 7/9 (77.8%) >13 d:22/25 (85.0%)	Seroconversion rate and timing after fever onset: <5d:0% 6-7 d: 4/6 (66.7%) 8-9 d: 9/12 (75%) 10-11 d: 10/14 (71.4%) 12-13d: 9/9 (100%) >13 d: 25/25 (100%)	-	Cllin Chem Lab Med

Pan 2020 Retrospective China	N=67	No information	ICG strip assay	N=86 1 (78 pat.) 2 (25 pat.) 3 (2 pat.)	Seroconversion rate and timing: 1-7 d: 11.1% 8-14 d:: 78.6% >15 d::74.2%	Seroconversion rate and timing: 1-7 d: 3.6% 8-14 d: 57.1% >15 d: 96.8%	-	medRxiv
Wølfel 2020 Retrospective Germany	N=9 young to middle-aged cases, with no co-morbidities	Mild cases	IFA	N=not reported	Seroconversion rate at d 7 was 50%,,and 100% at d 14 after symptom onset. -			Accepted for publication in Nature
Xiang 2020 Retrospective China	N= 85 Median age: 51.0 (32 to 65 years) M: 36.5 %; F:63.5% Comorbidities:38.8%	78.8% 'normal' cases, 21.2% severe cases	ELISA	N=216 Collected at 14 different time-points	Seroconversion rate and timing: ranged from 44.4% to 85.7% across time-points (60% at <5 d after onset, but very few samples)	Seroconversion rate and timing: ranged from 39.1% to 100% across time points (40% at <5 d after onset, but very few samples at each time-point)	-	OxfordUniversity Press for the American Infectious Disease Society.
Xiao 2020 Cohort study China	N=34 Mean age: 55 (26-87) years F:12; M:22	Not reported (but 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 and 4 (but declining), week 5 and 7: declining and 2 patients negative	Seroconversion timing: (-) week 1[2] (+) week 3, 4 (and increasing), and week 5 and 7 all patients still positive		Pre-proof /Journal of Infection/ IF: 4.603 (2017)
Yong 2020 Retrospective China	N=38	3 severe cases, and 35 mild cases	GICA	N=76 0-7 d: N=13	Seroconversion rate and timing: 0-7 d: 23%	Seroconversion rate and timing: 0-7 d: 53.0%	-	Accepted for publication.

	Median age: 40.4 (IQR:31 to 49.5 years) M:55.3%; F:44.7%			8-14d:N=8 >15d: N=23	8-14d:50.0% >15d:52.2%	8-14d:87.5% >15d:91.3%		
Yongchen 2020 Retrospective China	N=21 Age:37 (10 to 73 yrs) M:61.9%; F:38.1%	5 asymptomatic cases; 11 non-severe cases; 5 severe cases	GICA	N=no information Timing of sampling: w 1, w2, w3, and w 6	All non-severe and severe cases were seroconversed during hospitalisation, but only 1 of 5 asymptomatic carriers. All severe cases were sero-conversed within 2 weeks after symptom onset.		-	Accepted for publication in Emerging Microbes and Infections. IF: 6.2
Zhao 2020 Cohort study China	N=173 Median age: 48 years (IQR:35-61) F:51.4%; M:48.6%	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: 12 d	Seroconversion rate:64.7% (112/173) Median seroconversion time: 14 d	-	Published by Oxford university press for the Infectious Disease Society of America.
Case-studies								
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

Appendix 3

Table 2 Seroconversion rate and timing, age, and severity of disease (N=10)

Author Year	**No of patients with confirmed COVID 19: age; gender**	**Severity of disease** (asymptomatic -mild –moderate-severe-critical)	**Test for detection of SARS-CoV 2 specific antibodies**	**No of serum samples and time-points of sampling**	**IgM**	**IgG**	**IgA**	**Publication type**
Adams 2020 Retrospective study UK	N=40 confirmed cases; and 50 negative controls Age: > 18 yrs Gender: - Co-morbidities: -	22 acute cases (≤28 days after symptom onset): 9 mild ;4 severe, 9 critical cases 18 convalescent samples (≥ 28 d after symptom onset):1 mild, 17 asymptomatic cases	ELISA, and nine commercially available LFIA* devices was compared *Due to poor sensitivity of all LFIA devices only results for ELISA are reported here.	N=90 samples Median sampling time (after symptom onset): Acute cases: 10 d (range 4 to 19) Convalescent samples:48 d (range 31 to 62)	IgM or IgG were positive in 34/40 samples (across all time points). The six negative samples were all taken earlier than 9 d after symptom onset.	100% (31/31 seropositive) ≥ 10 days after symptom onset IgG titres rose during 3 weeks post symptom onset, and begun to fall by 8 weeks (but were still detectable) **No relationships between severity of disease and antibody titres were found.**	-	medRxiv
Dahlke 2020 Case series Germany	N=2 confirmed cases; a 64-year old man, and a 62-year old woman	1 mild case, and one more severe case that needed hospitalisation	Proteome Peptide Microarrays	4-5 tests each	Mild case: a strong IgA response soon after disease onset. **More severe case: a delayed but eventually very strong and broad IgA response**			medRxiv

Liu 2020 Retrospective study 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% (IgM); 93.18% (IGG) Severe: 82.69% (IgM); 100% (IgG) Critical:72.97% (IgM); 97.30%(IgG) **No significant differences due to severity of disease**.			medRxiv
Long 2020 Cohort study China	N=285; N=63 in follow up cohort Median age:47 (IQE:34 to 56) M:55.4%; F:44.6%	39 severe cases, 246 mild cases	MCLIA	N=364 , and N=281 in follow-up	Median day of seroconversion: d13; reached 100% at d20 for IgG **Higher titres in severe patients, but only significantly higher for IgG at 2 weeks**. Two patients remained seronegative during hospitalisation (but were lost to follow up)			medRxiv
Ma 2020 Retrospective study China	N=87 Median age: 48 (21-94 years) Gender: - Co-morbidities: 42.5%	No information	Chemiluminiscence-immuno-analysis	N=216 (and 483 sera from COVID-19 negative controls)	Seroconversion rate and timing: 4-10d: 88.2 (15/17) 11-15d: 100% 16-20d 100% 21-25d:98.2%(55/58) 26-30d:100% 31-41d:100%	Seroconversion rate and timing: 4-10d: 76.5% (13/17) 11-15d: 100% 16-20d 100% 21-25d: 100% 26-30d: 100% 31-41d: 87% (20/23)	Seroconversion rate and timing: 4-10d: 64.7% (11/17) 11-15d:97% (29/30) 16-20d 100% 21-25d: 100% 26-30d: 100% 31-41d: 100% Serum IgA level correlated with severity of disease.	medRxiv
Tan 2020	N=67 Age:49 (range 10 to 77 years)	22 non-severe cases; 29 severe and 9 critical cases	ELISA	N=342	Seroconversion at d 7 (10.3%), and peaked	Seroconversion at d 10 (3.4%), and peaked at d	-	medRxiv

Prospective cohort study China	M:52.2%: F:47.8%; Co-morbidities: 37,3%				at 28 days (57.1%) after disease onset. **IgM titres appear earlier and are higher in patients with severe disease** Non-responders (titre below detection): 30(51.7%)	49 (86.7%) after disease onset. **IgG titres appear earlier and are higher in patients with severe disease.** Weak responders of IgG had significantly higher virus clearance rate, than high responders. Non-responders; 9 (16.7%)		
To 2020 Cohort study China	N=23 patients Median age:62 (37-75) M:10; F:13 46% had chronical illnesses	13 mild cases and 10 severe cases	EIA	N=108 Mean no of tests per patient: 4.7 Note: Only 16 of included patients had samples 14 days or later 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

Wang 2020 Retrospective China	N=70; 12 inpatients and 58 convalescents (including young patients)	No information	Modified cytopathogenic assay based on live SARS-CoV-2	N=117	Seroconversion reached 100% within 20 d after disease onset, and remained 100% until da 41-53. Antibody levels were highest at d31-43, and decreased slightly thereafter. Antibody titres were higher in middle-aged and older patients, than in **younger patients (16-30yrs).** **Patients with a worse clinical condition had higher antibody titres.** Individual variations in changes in antibody levels were observed.		medRxiv
Wu 2020 Retrospective China	N= 175 recovered patients (including young patients)	Recovered from mild disease	ELISA and Pseudotyped-lactiviiral-vector-based neutralisation assay	N=not reported	SARS CoV-2 specific neutralising antibodies (NAbs) and spike-binding antibodies formed d10-15 after infection, and were significantly higher in middle-aged and elderly people, than in younger people- 30% of patients had very low NAb titres (mostly **younger patients 15-39 yrs**), and Nab titres in 10 of them were below detectable level. Plasma from COVID 19 patients showed cross-binding to SARS CoV, but did not neutralise SARS CoV.		medRxiv
Zhang 2020 Retrospective China	N=222 Median age: 62 (IQR:52-69) M:48.2%; F:51.8%	39.2% were severe cases	CLIA	N=unclear Sampled within 35 d from symptom onset.	Seroconversion: could be detected from d 3 after symptom onset, and peaked at 2 weeks Seroconversion rate: 82%	Seroconversion could be detected from d 4 after symptom onset, and peaked at 4 weeks. Seroconversion rate: 98.8% **High IgG levels at late stage (> 14 d) were more frequent in patients with severe disease.**	medRxiv

Appendix 4

Table 3 **Transmission of SARS-CoV-2 antibodies during pregnancy (N=3)**

Author Year	No of patients with RT-PCR confirmed COVID 19: age; co-morbidities	Severity of disease	Delivery	No of test for diagnosis of SARS CoV-2 infection	Test for detection of SARS-CoV 2 specific antibodies[1]	IgM/IgG	Follow up of neonate	Publication type/ Journal/Impact factor (IF)
Alzamore 2020 Case study. Peru	A 41-year old woman, with BMI 35 km/m2, and diabetes mellitus	Severe case with respiratory failure requiring mechanical ventilation	C-section, without delayed cord clamping and skin-to-skin contact. It was unclear whether protective masks or other protective equipment were worn during delivery.	Nasopharyngeal swab taken 16 hours after delivery, and analysed by RT-PCR. Test was positive for SARS-CoV-2 infection in the infant. Repeated test 48 h later was also positive.	Solid-phase immunochromatographic assay.	Mother seronegative at admission (4 days after symptom onset), and offspring negative post-partum Mother seropositive at 9 d after symptom onset, and offspring still seronegative 5 d after birth.	The neonate was isolated directly after delivery, received mechanical ventilation for 12 h, and was there after put on continuous positive airway pressure. No follow up data provided after 5 d post-partum.	Short communication. Theme Medical.
Dong 2020 Case study China	A 29-year old woman with confirmed COVID-19 diagnosis	Not classified, but the woman received antiviral, antibiotic, corticosteroid and oxygen therapy at admission.	C-section in room with negative pressure. The mother wore a protective mask during delivery. No. skin-to-skin contact.	Five PCR tests performed on nasopharyngeal swabs taken 2 hours after birth and up to 16 days after delivery,	Not reported.	Elevated antibody levels in serum post-partum were found in both mother and infant.	The neonate, who had no symptoms, was isolated directlyafter delivery.	Research letter. JAMA.

				were all negative for SARS-CoV-2.			Follow up for 16 d after delivery.	
Zheng 2020 Retrospective study China	Six women with confirmed COVID-19 diagnosis	All women had mild symptoms.	C-section. Mothers and personnel were all wearing protective masks during delivery.	One test (on throat swabs and neonatal blood) was performed. None of the infants tested positive for SARS CoV-2.	CLIA kit	Antibodies in serum assessed post-partum in the women and all infants had increased levels of antibodies.	All infants were isolated directly after delivery, and none presented any symptoms. No follow-up data provided.	Research letter. JAMA.

Published by the Norwegian Institute of Public Health
Mai 2020
P. O. Box 222 Skøyen
NO-0213 Oslo
Tel: +47 21 07 70 00
www.fhi.no