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Norwegian Institute of Public Health:

Gro Tunheim

Anne-Marte Bakken Kran

Gunnar Rø

Olav Hungnes

Oslo University Hospital:

Fridtjof Lund-Johansen

Eline Benno Vaage

Trung Tran

Jan Terje Andersen

John Torgils Vaage

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Authors:
Norwegian Institute of Public Health
Gro Tunheim
Anne-Marte Bakken Kran
Gunnar Rø
Olav Hungnes

Oslo University Hospital:
Fridtjof Lund-Johansen
Eline Benno Vaage
Trung Tran
Jan Terje Andersen
John Torgils Vaage

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Content

Summary

COVID-19 is an infectious disease caused by the novel coronavirus SARS-CoV-2. Infection with SARS-CoV-2 induces antibodies to the virus, therefore, in the absence of vaccination, the presence of SARS-CoV-2 specific antibodies in a person's blood indicates that the person has been infected with SARS-CoV-2. This is the third study measuring antibodies against SARS-CoV-2 in residual serum samples collected systematically from various geographical regions in Norway and covering all age groups. The first study with residual sera collected in April/May 2020 and August 2019, was published as a report in June 2020 (1). The second study, with residual sera collected in the late summer of 2020, was published as a report in December 2020 (2). In the present study, data on the seroprevalence in Norway in January 2021, at the end of the second wave of the pandemic, is presented. A total of 1912 residual sera were sampled from 17 microbiology laboratories in January 2020 (week number 53 in 2020/2021 to week number 6, 2021). Most of the samples (85.7%) were collected between week numbers 1-3, 2021. The sera were tested for antibodies against SARS-CoV-2 using an in-house assay established at the Department of Immunology, Oslo University Hospital. Based on these measurements, the estimated seroprevalence in the Norwegian population in January 2021 was 3.2% (95% credible interval (CrI) 2.3 - 4.1). This is an increase from the seroprevalence estimate in the late summer of 2020 (0.6% (95% CrI 0.2- 1.2))(2). Antibodies against SARS-CoV-2 were found in a total of 61 of the 1912 samples and were detected in samples from 10 of the 11 Norwegian counties. There were no significant differences between the seroprevalence estimates for each county. However, the number of samples from each county varied considerably. There were no significant differences between the seroprevalence estimates for the various age groups or between males and females.

Norsk sammendrag

Covid-19 er en infeksjonssykdom som skyldes det nye koronaviruset SARS-CoV-2. Infeksjon med SARS-CoV-2 induserer antistoffer mot viruset, og funn av virusspesifikke antistoffer i blodprøver fra uvaksinerte indikerer gjennomgått infeksjon. Dette er den tredje studien som måler antistoffer mot SARS-CoV-2 i serumprøver som er systematisk samlet inn fra ulike geografiske områder i Norge, og som representerer alle aldersgrupper. Den første studien, basert på restsera samlet inn i april/mai 2020 og august 2019, ble publisert som en rapport i juni 2020 (1). Den andre studien, basert på restsera samlet inn på sensommeren 2020, ble publisert som en rapport i desember 2020 (2). I denne studien, ble til sammen 1912 restsera samlet inn i løpet av januar 2021 (uke 53-6) fra 17 laboratorier. De fleste prøvene (85,7 %) ble samlet inn mellom uke 1-3. Serumprøvene ble testet for antistoffer mot SARS-CoV-2 med en metode som er utviklet og etablert ved Avdeling for immunologi og transfusjonsmedisin ved Oslo universitetssykehus. Ut ifra disse målingene lå den estimerte andelen av den norske befolkningen som har antistoffer mot SARS-CoV-2 (seroprevalensen) på 3,2 % (95 % kredibilitetsintervall 2,3 – 4,1) i denne perioden. Dette er høyere enn den estimerte seroprevalensen sensommeren 2020 (0,6 % (95 % kredibilitetsintervall 0,2 – 1,2)) (2). Antistoffer mot SARS-CoV-2 ble funnet i totalt 61 prøver. De positive prøvene var fra personer bosatt i 10 av de 11 norske fylkene, men det var ingen signifikante forskjeller i estimert seroprevalens mellom de ulike fylkene. Imidlertid var det stor variasjon i antall prøver fra hvert fylke. Det ble ikke funnet noen signifikante forskjeller i estimert seroprevalens mellom ulike aldersgrupper eller mellom ulike kjønn.

Background

A new infectious disease, Coronavirus disease 2019 (COVID-19), was first reported in China in December 2019 and spread rapidly across the world. On March 11th, 2020, the World Health Organization (WHO) stated that COVID-19 constitutes a pandemic (3). COVID-19 is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), a novel virus belonging to the coronavirus family.

Infection with SARS-CoV-2 induces antibodies to the virus, therefore, in the absence of vaccination, the presence of SARS-CoV-2 specific antibodies in a person's blood indicates that the person has been infected with the virus. Some studies have shown that, after two weeks of infection, more than 90% of individuals infected with SARS-CoV-2 will have developed antibodies to the virus (4, 5). Seroprevalence is the percentage of a population with antibodies against a certain infectious agent based on analyses in serum or plasma samples. From measurements of antibodies against SARS-CoV-2 in samples from a smaller population, it is possible to estimate the seroprevalence in the Norwegian population.

In Norway, the first COVID-19 case was confirmed on February 26th, 2020. Subsequently, there was a rise in confirmed COVID-19 cases with a peak incidence in March 2020 (week number 13), followed by diminishing numbers towards and during the summer (Figure 1) (2, 6). In the autumn of 2020, the numbers of PCR-confirmed COVID-19 cases again started rising, representing a second wave of the pandemic, a tendency also observed in other European countries (7, 8)(Figure 1). In the first week of January, there was a new peak in the incidence of COVID-19 cases. Various additional non-pharmaceutical measures were taken from November 2020 in an attempt to contain the pandemic. By the end of January 2021, the number of confirmed COVID-19 cases had started decreasing. However, after the introduction of a new SARS-CoV-2 variant with increased transmissibility by January 2021 (9, 10), the case numbers against started rising in February 2021, representing a third wave of the pandemic. On the 27th of December 2021, the first dose of COVID-19 vaccine (Comirnaty from Pfizer-BioNTech) was administered in Norway. The COVID-19 Vaccine from Moderna has been administered since the 15th of January (11). Elderly individuals and health care workers were the first to receive COVID-19 vaccines in Norway, but comparatively few doses had been administered by the end of January 2021 (10) .

Based on antibody measurements in 900 residual sera collected between mid-April to mid-May 2020 (week numbers 17-20), we estimated the seroprevalence of SARS-CoV-2 in the Norwegian population to be close to 1% in the spring of 2020 (1.0% (95% Credible Interval (CrI) 0.1 %-2.4%)) (1). In the late summer of 2020, based on 1812 residual sera, the estimated seroprevalence was 0.6% (95% CrI 0.2 - 1.2) (2). This was not different from the seroprevalence estimate in the spring of 2020. We here present the results of the third study of SARS-CoV-2 seroprevalence in the Norwegian population, based on antibody measurements in residual sera collected in January 2021.

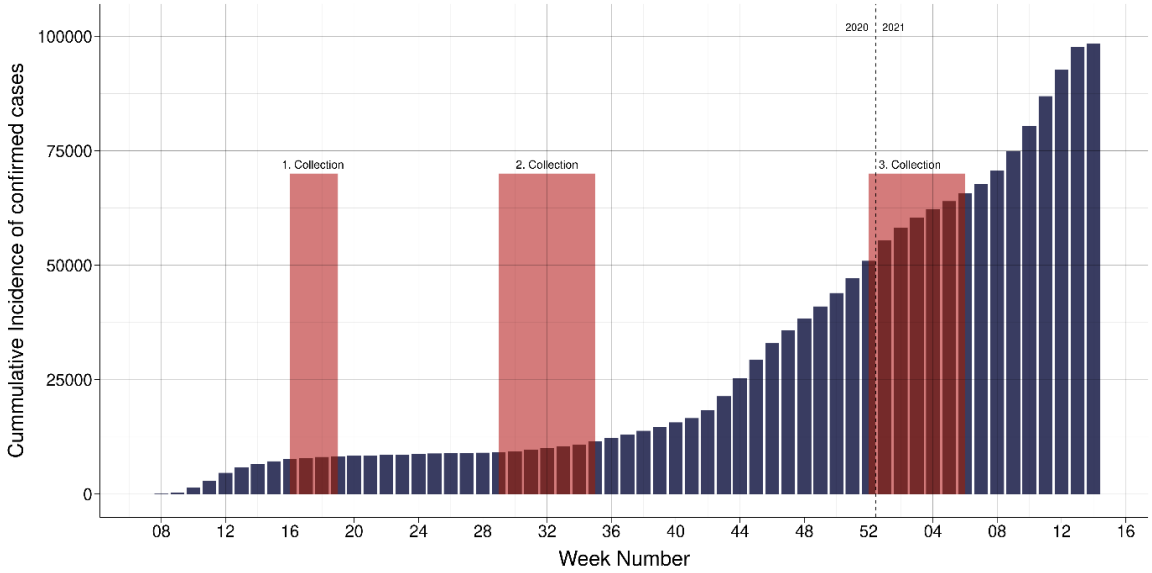

Figure 1. Cumulative incidence of PCR-confirmed COVID-19-cases in Norway by week number as reported to the Norwegian Surveillance System for Communicable Diseases (MSIS). The first collection of residual serum samples occurred between week numbers 17-20 in 2020 (1), the second collection between week numbers 30-37 (2) in 2020 and the third, and present collection between week numbers 53-6 in 2021.

Methods

Panels of anonymised residual serum samples were solicited according to a scheme for annual collection that has been operated since the late 1970s as part of serosurveillance of influenza in Norway (12). In order to study the exposure to SARS-CoV-2 at a population level, 1912 residual serum samples were collected from 17 microbiological laboratories across Norway over 7 weeks, mostly in January 2021 (spanning week numbers 53, 2020/2021 to 6, 2021, i.e. between the 28th of December 2021 and the 14th of February, 2021). The age of participants was grouped as follows: 0-4, 5-14, 15-24, 25-59 and ≥60 years of age. The laboratories were asked to not include sera from individuals with a known HIV, hepatitis B or C diagnosis, or very turbid or haemolysed serum samples.

The sera were analysed using an in-house flow cytometer-based method detecting IgG antibodies against SARS-CoV-2 derived recombinant antigens (13). In the present study, samples were defined to be positive for antibodies against SARS-CoV-2 if they had antibodies against both the receptor binding domain (RBD) of the spike protein and the nucleocapsid protein (method 1) or, as an alternative approach, against both the RBD and the full length spike protein (HexaPro) (14) (method 2).

The estimated sensitivity of the test is 96% (95% CrI 94%-98%), based on the detection of antibodies against SARS-CoV-2 in serum samples collected at least three weeks from onset of symptoms from individuals with PCR-confirmed COVID-19. In a validation panel of 1814 samples, the estimated specificity of the test was 99.8% (95% CrI 99.5%-99.9%) compared to the Roche Elecsys® Anti-SARS-CoV-2, based on reanalysing all test-positive sera with the Roche antibody test. Test sensitivity and specificity have been used to convert proportions of test positives into estimated seroprevalences.

95% confidence interval (CI) for fraction positives were estimated using the exact method. Seroprevalence was estimated for Norway and by laboratory, county of residence, sex, age group and sampling week for subgroups with more than 30 sera. Sera lacking information on county of residence were provisionally attributed to the county corresponding to the laboratory. For the estimation, we used a Bayesian method that incorporates the uncertainties in the sensitivity and the specificity of the test (15). We adjusted the overall seroprevalence by a multilevel regression and poststratification on counties, age groups and sex (15). For seroprevalence results, we present a point estimate and a 95% CrI.

Results

Seventeen microbiological laboratories across the country contributed with on average 112 sera each (range 95-120). Of the overall 1912 samples tested, antibodies against SARS-CoV-2 were detected in 61 samples (3.2% (95% CI 2.4-4.1)). This gives an estimated seroprevalence of 3.2% (95% CrI 2.3-4.3) in the Norwegian population in January 2021 when adjusted for the estimated test sensitivity and specificity, as well as for county, age and sex (Table 1).

The results for samples from the different laboratories in Norway are shown in Table 1. Fourteen of the 17 contributing laboratories had samples positive for antibodies against SARS-CoV-2. The highest positivity rate was found for the laboratory in Fredrikstad (10.3% (95% CI 5.2- 17.7)).

The estimated seroprevalence based on county of residence is presented in Table 2. Positive samples were found in sera from individuals living in 10 of the 11 counties. Most positive samples (n=23) were found among individuals living in Viken, but Viken was also the county of residence with the largest number of samples tested (20.6% of all samples). There were no significant differences in the estimated seroprevalence between the various counties; however, the number of samples tested from each county varied considerably (range 107-393).

We did not find any differences in seroprevalence by sex (Table 3) or age group (Table 4). The residual sera were from 43.3% males and 56.3% females and came from individuals aged 0 to 100 years. The youngest person with a positive sample was 1 year old, while the oldest was 83 years old. Positive samples were found for all age groups. The highest seroprevalence estimates were found in the youngest and the oldest age groups.

The residual sera were collected between week number 53, 2020 and week number 6, 2021, i.e., between the 28th of December 2020 to the 14th of February 2021 (range 2-1063 samples collected per week) (Table 5). Most samples were collected in week number 1 (4th of January – 10th of January) (55.6%), and 85.7% of the samples were collected between week numbers 1-3. For the 120 (6.3%) samples from the laboratory in Hammerfest, information about the specific sampling week was missing. There were no differences between the seroprevalence estimates for the different weeks, but most of the credible intervals were wide.

As an alternative approach, the number of serum samples positive for antibodies against both the spike protein and the RBD were also calculated. By this approach, a total of 65 samples were found among the 1912 tested samples (3.4% (95% CI 2.6–4.3)). This was an increase of 4 positive samples. When estimating the overall seroprevalence based on these 65 samples, the seroprevalence was 3.3% (95% CrI 2.4-4.3). This was not different from the seroprevalence estimate based on sera positive for antibodies against the nucleocapsid protein and the RBD.

However, this alternative approach cannot be used to distinguish between vaccinated and infected individuals.

Tables

Table 1. Estimated seroprevalence, overall, and seropositivity rates by submitting laboratory

	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Estimated seroprevalence, % (95% credible interval)
Total				
	61	**1912 (100%)**	**3.2 (2.4 - 4.1)**	**3.2 (2.3 – 4.2)***
By submitting laboratory				
Ullevål	2	107 (5.6%)	1.9 (0.2 - 6.6)	2.4 (0.4 - 6.6)
Tønsberg	0	104 (5.4%)	0.0 (0.0 - 3.5)	0.7 (0.0 - 3.7)
Lillehammer	3	111 (5.8%)	2.7 (0.6 - 7.7)	3.3 (0.9 - 7.5)
Stavanger	8	118 (6.2%)	6.8 (3.0 - 12.9)	7.3 (3.5 - 13.0)
Bergen	1	120 (6.3%)	0.8 (0.0 - 4.6)	1.3 (0.1 - 4.5)
Trondheim	0	108 (5.6%)	0.0 (0.0 - 3.4)	0.6 (0.0 - 3.7)
Kristiansand	2	107 (5.6%)	1.9 (0.2 - 6.6)	2.3 (0.4 - 6.7)
Bodø	4	119 (6.2%)	3.4 (0.9 - 8.4)	3.8 (1.2 - 8.3)
AHUS	3	119 (6.2%)	2.5 (0.5 - 7.2)	3.0 (0.7 - 7.2)
Drammen	9	112 (5.9%)	8.0 (3.7 - 14.7)	8.6 (4.3 - 15.4)
Skien	2	120 (6.3%)	1.7 (0.2 - 5.9)	2.0 (0.3 - 5.8)
Molde	2	95 (5.0%)	2.1 (0.3 - 7.4)	2.7 (0.5 - 7.6)
Tromsø	9	105 (5.5%)	8.6 (4.0 - 15.6)	9.3 (4.6 - 16.1)
Førde	1	120 (6.3%)	0.8 (0.0 - 4.6)	1.3 (0.1 - 4.6)
Levanger	4	120 (6.3%)	3.3 (0.9 - 8.3)	3.8 (1.3 - 8.3)
Hammerfest	0	120 (6.3%)	0.0 (0.0 - 3.0)	0.6 (0.0 - 3.2)
Fredrikstad	11	107 (5.6%)	10.3 (5.2 - 17.7)	11.0 (5.8 - 18.3)

***The overall seroprevalence for Norway was adjusted for age, sex and county.

Table 2. Estimated seroprevalence by county of residence

County of residence	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Estimated seroprevalence, % (95% credible interval)
Oslo*	4	123 (6.4%)	3.3 (0.9 - 8.1)	3.7 (1.2 - 8.3)
Rogaland	8	130 (6.8%)	6.2 (2.7 - 11.8)	6.6 (3.1 - 11.9)
Møre og Romsdal	2	108 (5.6%)	1.9 (0.2 - 6.5)	2.3 (0.4 - 6.5)
Nordland	4	122 (6.4%)	3.3 (0.9 - 8.2)	3.7 (1.2 - 8.0)
Viken*	23	393 (20.6%)	5.9 (3.7 - 8.7)	6.0 (4.0 - 8.8)
Innlandet	3	125 (6.5%)	2.4 (0.5 - 6.9)	2.8 (0.6 - 6.8)
Vestfold og Telemark	0	113 (5.9%)	0.0 (0.0 - 3.2)	0.7 (0.0 - 3.6)
Agder*	2	107 (5.6%)	1.9 (0.2 - 6.6)	2.4 (0.4 - 6.6)
Vestland*	2	250 (13.1%)	0.8 (0.1 - 2.9)	0.9 (0.1 - 2.7)
Trøndelag	4	216 (11.3%)	1.9 (0.5 - 4.7)	2.0 (0.6 - 4.6)
Troms og Finnmark*	9	225 (11.8%)	4.0 (1.8 - 7.5)	4.2 (2.0 - 7.6)

*2 sera from the laboratory in Bergen and 1 serum from each of the following laboratories: Hammerfest, Kristiansand, Drammen, AHUS and Ullevål, were attributed to their corresponding counties (Vestland, Troms og Finnmark, Agder, Viken (Drammen and AHUS), and Oslo, respectively), as these sera did not have information on county of residence.

Table 3. Estimated seroprevalence by sex

Sex	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Estimated seroprevalence [%] (95% credible interval)
Male	36	827 (43.3%)	4.4 (3.1 - 6.0)	4.4 (3.0 - 6.1)
Female	25	1077 (56.3%)	2.3 (1.5 - 3.4)	2.3 (1.4 - 3.4)
Missing	0	8 (0.4%)	0.0 (0.0 - 36.9)	n.a.*

*n.a.: not applicable. The seroprevalence was not estimated for subgroups with less than 30 samples tested.

Table 4. Estimated seroprevalence by age

Age groups (years)	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Estimated seroprevalence [%] (95% credible interval)
0-4	9	158 (8.3%)	5.7 (2.6 - 10.5)	6.3 (2.8 - 10.7)
5-14	14	335 (17.5%)	4.2 (2.3 - 6.9)	4.4 (2.3 - 6.9)
15-24	8	320 (16.7%)	2.5 (1.1 - 4.9)	2.7 (1.1 - 4.9)
25-59	15	708 (37.0%)	2.1 (1.2 - 3.5)	2.1 (1.1 - 3.4)
≥60	15	391 (20.4%)	3.8 (2.2 - 6.2)	4.0 (2.2 - 6.2)

Table 5. Estimated seroprevalence by sampling week

Sampling week number	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Estimated seroprevalence, % (95% credible interval)
53	3	88 (4.6%)	3.4 (0.7 - 9.6)	4.1 (1.1 - 9.8)
1	30	1063 (55.6%)	2.8 (1.9 - 4.0)	2.8 (1.8 - 4.0)
2	19	365 (19.1%)	5.2 (3.2 - 8.0)	5.4 (3.3 - 8.1)
3	6	211 (11.0%)	2.8 (1.1 - 6.1)	3.1 (1.2 - 6.1)
4	2	58 (3.0%)	3.4 (0.4 - 11.9)	4.4 (0.9 - 12.1)
5	0	5 (0.3%)	0.0 (0.0 - 52.2)	n.a.*
6	1	2 (0.1%)	50.0 (1.3 - 98.7)	n.a.*
Unknown (within 53-6)**	0	120 (6.3%)	0.0 (0.0 - 3.0)	0.6 (0.0 - 3.0)

*n.a.: not applicable. The seroprevalence was not estimated for subgroups with less than 30 samples tested.
**All samples with missing week numbers were from the laboratory in Hammerfest.

Discussion

This is the third study measuring antibodies against SARS-CoV-2 in residual sera sampled from various geographical regions and covering all age groups in Norway. The estimated seroprevalence of 3.2% (95% CrI 2.3 – 4.1) was higher than the previous estimate of 0.6% from the late summer of 2020 (95% CrI 0.2 - 1.2) (2). This increase corresponds well with the considerable number of reported infections in the autumn of 2020.

Our two previous seroprevalence studies indicated that the seroprevalence in the spring and in the late summer of 2020 was approximately 1% (1, 2), compared to the 0.15%-0.17% of the population having laboratory-confirmed infection reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) (16, 17). By week 1, 2021, when 58.8% of the samples from the present study had been collected, 56,032 cases of COVID-19 (1.0% of the population) had been notified to MSIS (Figure 1) (6). However, there is a delay of at least two weeks from the time of infection to the time when antibodies can be detected. Consequently, the number of positive samples in the present study mainly represents infections from the start of the pandemic until December 2020. By week number 52 in December, 47,462 cases of COVID-19

(0.9% of the population) had been reported to MSIS (18). Therefore, according to the estimated seroprevalence in the present study, the number of cases of COVID-19 in the Norwegian population was more than three times higher than the confirmed number of cases. The estimated seroprevalences indicate that there has been a significant number of undetected infections and that this pattern also holds for the second wave of the pandemic in the autumn of 2020.

According to mathematical modelling, a total 102,000 (95% CI 88,000- 116,000) persons in Norway had been infected by the end of 2020 (19). This corresponds to 1.9% of the population, which is lower than the estimated seroprevalence of 3.2% reported here. The Norwegian Mother, Father and Child Cohort Study (MoBa) and The Norwegian Influenza Study (NorFlu) measure antibodies against SARS-CoV-2 among a random sample of participants living in Oslo. In week number 50 (i.e. in mid-December), the proportion of positive samples were 3.1% in the MoBa/NorFlu study (20). This is similar to the estimated seroprevalence presented here, and comparable to the percent positive samples among individuals with Oslo as their county of residence.

A large seroprevalence study from Norway with 27,700 tested samples has recently been conducted (21). The participants, aged 16 years or older, volunteered to take part in the study. Most of the samples were collected mid–to-late December 2020. The study reported a seroprevalence of 0.9% (95% CI 0.7-1.0). The highest seroprevalence was found among teenagers aged 16-19 years. Although the samples of the study by Anda *et al*. and our study were collected in overlapping weeks, there was a 3-fold difference in the proportion of positive samples reported. A part of this difference may be explained by when the bulk of the samples were collected for the study by Anda *et al*. and our study (mid-to-late December versus beginning of January), as this was at a time when the number of COVID-19 cases were steadily increasing. Moreover, differences may also be explained by a healthy volunteer bias and not including children in study by Anda *et al*., and by an opposite bias toward residual sera being sampled from individuals with more morbid conditions in our study (see also below) (22, 23).

The residual sera were collected between the end of December 2020 to mid-February 2021 (week numbers 53-6) with most of the samples from the week numbers 1-3. After an infection with SARS-CoV-2, studies have found that IgG antibodies against SARS-CoV-2 are generally detected 6-14 days following symptom onset, with antibodies being detected in 90% of individuals after 2 weeks, and 100% after 4 weeks (4). We cannot rule out that some residual sera included in the study were collected from individuals recently infected with SARS-CoV-2, especially as the incidence was relatively high during the sampling period. These individuals may not have developed antibodies at the time of sample collection but could seroconvert later. This will affect the interpretation of the results, as most of the samples were from week numbers 1-3, and the estimated seroprevalence therefore represents infections that occurred up until approximately 3 weeks prior to sampling (i.e. until week numbers 51-53).

By the end of January 2020, 11 months has ensued since the first cases of COVID-19 were reported in Norway. Some of the samples in the present study may have been from individuals infected early in the pandemic. The duration of antibodies against SARS-CoV-2 after infection is not known. Antibodies against SARS-CoV, a related coronavirus, have been found to be detectable for up to one year (5, 24). Some studies suggest that the antibodies to SARS-CoV-2 last long, while other indicate that antibodies wane quickly after infection (24-27). More specifically, antibody levels against the nucleocapsid protein seems to wane more rapidly than antibodies against other viral antigens of SARS-CoV-2 (28). As antibodies to the nucleocapsid

protein is used to define positive samples in the present study, the seroprevalence estimate may therefore be somewhat underestimated. However, this did not seem to be the case in our study. Our data showed that the estimated seroprevalence was not different if antibody responses against either the nucleocapsid protein and the RBD (method 1) or the spike protein and the RBD (method 2) were used to define positive samples.

Even though COVID-19 vaccination status is not available for the anonymised residual sera, vaccination is not expected to influence the seroprevalence in the present study. By the end of week 3 2021, when most of the sera had been collected, only 1.4% of the population had received their 1st dose of COVID-19 vaccine (11). For all the approved COVID-19 vaccines used in Norway, the antigen is based on the spike protein of SARS-CoV-2. Infected individuals have been shown to develop antibodies recognizing the spike protein, but antibodies are also induced against the other SARS-CoV-2 antigens, such as the nucleocapsid protein. The main method used to define positive samples in the present study, measures antibodies against both the receptor binding domain (RBD) of the spike protein and the nucleocapsid protein (method 1). Vaccinated, non-infected individuals will not have antibodies against the nucleocapsid protein, and it is therefore possible to distinguish between serum samples from vaccinated and infected individuals. This will become increasingly useful in future seroprevalence studies using residual sera since a larger proportion of the population will become vaccinated.

Seroprevalence studies may help to determine the number of cases of COVID-19 in a population, as not all cases are tested and confirmed at the time of infection. However, there are several limitations to these studies (29). The level of antibodies against SARS-CoV-2 has been reported to be linked with severity, where individuals who are asymptomatic or have mild COVID-19 may have lower levels of antibodies than individuals with severe disease (5, 26). If these less severe cases are not detected in antibody assays due to low levels of antibodies, this can lead to underestimation of the seroprevalence. Furthermore, it is possible that not all individuals infected with COVID-19 will mount an antibody response. In the present study, only IgG antibodies were measured and used to estimate the seroprevalence of SARS-CoV-2 in the Norwegian population (29). The inclusion of analyses of IgA and as well as IgM antibodies against SARS-CoV-2 may increase the sensitivity of serological testing (29). Using residual sera to estimate population prevalence could lead to selection bias, as the samples came from medical laboratories, potentially including persons with more morbidity, comorbidities or different risk and health-seeking behaviours. It should be noted that many of the participating laboratories receive patient samples for routine analysis of SARS-CoV-2 antibodies, that may have been included in the sample selection. This could introduce a bias resulting in an increased positivity rate if samples received for this purpose are included. Conversely, testing of sera from invited persons may lead to healthy-person biases or non-participation of certain groups (22, 23). Thus, results from studies based on residual sera are not directly comparable with studies with different study designs. However, the consistent procedure of sampling of residual sera for our three seroprevalence studies, makes the findings comparable over time.

Conclusion

In January 2021, the estimated seroprevalence in the overall Norwegian population was 3.2% (95% CrI 2.3-4.1). This was higher that the estimated seroprevalence in the late summer of 2020, shortly before the second wave of the pandemic begun in Norway. The finding fits well with the high number of PCR-confirmed cases of COVID-19 reported between October 2020 and January 2021. However, the estimated seroprevalence suggests that the cumulative number of

COVID-19 infections in Norway may have been three times higher than the recorded number of confirmed cases by January 2021. Measurements of antibodies against SARS-CoV-2 in future collections of residual sera may provide further information about development of the COVID-19 pandemic in Norway.

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References

1. Folkehelseinstituttet. Seroprevalence of SARS-CoV-2 in the Norwegian population measured in residual sera collected in April/May 2020 and August 2019. www.fhi.no, Division of Infection Control and Environmental Health; 2020 26.06.20.
2. Folkehelseinstituttet. Seroprevalence of SARS-CoV-2 in the Norwegian population measured in residual sera collected in late summer 2020. www.fhi.no, Health DoICaE; 2020 15.12.21.
3. The World Health Organization (WHO). Timeline of WHO's response to COVID-19 www.who.int2020 [Available from: https://www.who.int/news/item/29-06-2020-covidtimeline.
4. Health Information and Quality Authority (HIQA). Evidence summary of the immune response following infection with SARS-CoV-2 or other human coronaviruses www.hiqa.ie; 2020 01.12.20.
5. E OM, Byrne P, Walsh KA, Carty PG, Connolly M, De Gascun C, et al. Immune response following infection with SARS-CoV-2 and other coronaviruses: A rapid review. Rev Med Virol. 2020:e2162.
6. Folkehelseinstituttet. Ukerapport – uke 37. www.fhi.no: Folkehelseinstituttet; 2020.
7. Folkehelseinstituttet. Ukerapport - uke 47. www.fhi.no: Folkehelseinstituttet; 2020.
8. Nørgaard SK, Vestergaard LS, Nielsen J, Richter L, Schmid D, Bustos N, et al. Real-time monitoring shows substantial excess all-cause mortality during second wave of COVID-19 in Europe, October to December 2020. Euro Surveill. 2021;26(2).
9. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021:eabg3055.
10. Folkehelseinstituttet. Ukerapport - uke 6. www.fhi.no: Folkehelseinstituttet; 2021.
11. Folkehelseinstituttet. Ukerapport - uke 3. www.fhi.no: Folkehelseinstituttet; 2021.
12. Waalen K, Kilander A, Dudman SG, Krogh GH, Aune T, Hungnes O. High prevalence of antibodies to the 2009 pandemic influenza A(H1N1) virus in the Norwegian population following a major epidemic and a large vaccination campaign in autumn 2009. Euro Surveill. 2010;15(31).
13. Holter JC, Pischke SE, de Boer E, Lind A, Jenum S, Holten AR, et al. Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. Proc Natl Acad Sci U S A. 2020;117(40):25018-25.
14. Hsieh C-L, Goldsmith JA, Schaub JM, DiVenere AM, Kuo H-C, Javanmardi K, et al. Structure-based design of prefusion-stabilized SARS-CoV-2 spikes. Science. 2020;369(6510):1501-5.
15. Gelman A, Carpenter B. Bayesian analysis of tests with unknown specificity and sensitivity. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2020;69(5):1269-83.
16. Folkehelseinstituttet. Ukerapport – uke 20. www.fhi.no: Folkehelseinstituttet, Område for smittevern moh; 2020 tirsdag 19. mai 2020.
17. Folkehelseinstituttet. Ukerapport - uke 31. www.fhi.no: Folkehelseinstituttet; 2020.
18. Folkehelseinstituttet. Ukerapport – uke 52. www.fhi.no: Folkehelseinstituttet; 2020.
19. FHI COVID-19 modelling team. Situational awareness and forecasting for Norway: Week 53, 30 December 2020. www.fhi.no: Folkehelseinstituttet.
20. Folkehelseinstituttet. Resultater fra MoBa og Norflu - Hvor mange har vært smittet med koronavirus i Oslo og omegn? : Folkehelsesinstituttet; 2020 [Available from: https://www.fhi.no/studier/prevalensundersokelser-korona/resultat---moba/.
21. Anda EE, Braaten T, Borch KB, Nøst TH, Chen SLF, Lukic M, et al. Seroprevalence of antibodies against SARS-CoV-2 virus in the adult Norwegian population, winter 2020/2021: pre-vaccination period. medRxiv. 2021:2021.03.23.21253730.

22. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. Nephron Clin Pract. 2010;115(2):c94-9.
23. Wilson SE, Deeks SL, Hatchette TF, Crowcroft NS. The role of seroepidemiology in the comprehensive surveillance of vaccine-preventable diseases. CMAJ. 2012;184(1):E70-E6.
24. Huang AT, Garcia-Carreras B, Hitchings MDT, Yang B, Katzelnick LC, Rattigan SM, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun. 2020;11(1):4704.
25. Gudbjartsson DF, Norddahl GL, Melsted P, Gunnarsdottir K, Holm H, Eythorsson E, et al. Humoral Immune Response to SARS-CoV-2 in Iceland. N Engl J Med. 2020;383(18):1724-34.
26. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020;26(8):1200-4.
27. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371(6529).
28. Lumley SF, Wei J, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, et al. The duration, dynamics and determinants of SARS-CoV-2 antibody responses in individual healthcare workers. Clin Infect Dis. 2021.
29. Burgess S, Ponsford MJ, Gill D. Are we underestimating seroprevalence of SARS-CoV-2? Bmj. 2020;370:m3364.

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NO-0403 Oslo
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