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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 the presence of these antibodies in a person's blood indicates that the person has been infected with SARS-CoV-2. This is the first study measuring antibodies against SARS-CoV-2 in serum samples collected systematically from various geographical regions in Norway and covering all age groups. A total of 900 residual sera from nine laboratories were sampled in week numbers 17-20, 2020, and tested for antibodies against SARS-CoV-2 using a novel in-house assay established at the Department of Immunology, Oslo University Hospital. Based on these measurements, the estimated seroprevalence in the Norwegian population is probably close to 1% (1.0% (95% credible interval 0.1% - 2.4%)). We did not find any differences in seroprevalence by gender or age group. However, there seem to be geographical differences in the prevalence of seropositive individuals; there was a non-significant trend indicating that the number of positive samples and the estimated seroprevalence was higher in Oslo than in other regions. However, the sample size was limited as not all counties were included, and only an average number of 100 samples have been collected from each laboratory. Therefore, these results should be interpreted with caution. Follow-up studies of antibodies against SARS-CoV-2 in future collections of residual sera can provide further information about the development of the COVID-19 pandemic in Norway.

Norsk sammendrag

Covid-19 er en infeksjonssykdom som skyldes det nye koronaviruset SARS-CoV-2. Infeksjon med SARS-CoV-2 induserer antistoffer mot viruset. Funn av antistoffer mot SARS-CoV-2 i blod indikerer derfor gjennomgått infeksjon med SARS-CoV-2. Dette er den første 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. Til sammen 900 restsera fra 9 laboratorier ble samlet inn i uke 17-20 2020 og testet for antistoffer mot SARS-CoV-2, ved hjelp av en ny metode som er utviklet og etablert ved Avdeling for immunologi og transfusjonsmedisin ved Oslo universitetssykehus. Den estimerte andelen av den norske befolkningen som har antistoffer mot SARS-CoV-2 (seroprevalensen) ligger antagelig nær 1 % ut fra disse målingene (1.0% (95% kredibilitetsintervall 0.1 %- 2.4%)). Vi fant ingen forskjeller mellom kjønn eller forskjellige aldersgrupper, men dataene indikerer geografiske forskjeller i andelen positive prøver. Seroprevalensen ble estimert til å være høyere i Oslo enn i andre områder av landet, men forskjellen var ikke statistisk signifikant. Ikke alle fylker er inkludert i denne undersøkelsen, og det var relativt få prøver fra hvert laboratorium (gjennomsnittlig 100 prøver). Resultatene må derfor tolkes med forsiktighet. Oppfølgingsstudier av antistoffer mot SARS-CoV-2 i fremtidige innsamlinger av restsera kan gi ytterligere informasjon om utviklingen av covid-19 pandemien i Norge.

Background

A new infectious disease, Coronavirus disease 2019 (COVID-19) was first reported in China in January 2020 and spread rapidly across the world. In Norway, the first COVID-19 case was confirmed on February 26th, 2020. On March 11th, 2020, the World Health Organization (WHO) stated that COVID-19 constitutes a pandemic. COVID-19 is caused by a novel virus belonging to the coronavirus family, SARS-CoV-2, that is closely related to the Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) identified in 2003. By late April/beginning of May 2020, 7847 confirmed cases and 208 deaths had been recorded in Norway, with a peak in the incidence on March 26th 2020 (week number 13) and diminishing numbers since then (1, 2). In the present analysis, we estimate the seroprevalence of SARS-CoV-2 in the Norwegian population from residual sera collected in April/May 2020 as proxy for the percentage of the population that has had SARS-CoV-2 infection.

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 (3). In order to study the exposure to SARS-CoV-2 at a population level, residual serum samples were collected over four weeks in April and May 2020 (i.e. week numbers 17-20). Nine microbiological laboratories across the country each contributed with approximately 100 sera (overall, 900 samples). The ages of the persons the samples were collected from ranged from 0-91 years and were 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 hepatitis or HIV diagnosis, or samples submitted for analysis of antibodies against SARS-CoV-2.

Because other related coronaviruses causing common cold have been circulating in Norway, residual serum samples collected in Norway prior to the COVID-19 pandemic were also analysed. We included a subset of the annual collection, sampled in August 2019 (n=216), selected from two laboratories, and with all age groups represented. The purpose was to reveal the presence of potential cross-reacting antibodies against SARS-CoV-2, providing a baseline status for the Norwegian population prior to the pandemic.

The sera were analysed using an in-house flow cytometer-based method detecting IgG antibodies against SARS-CoV-2 derived antigens (Manuscript in preparation, Lund-Johansen and Andersen groups). The estimated sensitivity of the test is 86% (95% Credible Interval (CrI) 74%-94%), based on the detection of antibodies against SARS-Cov-2 in serum samples collected >21 days from onset of symptoms from individuals with PCR-confirmed COVID-19. The estimated specificity of the test is 100% (95% CrI 99%-100%), based on analysis of 236 pre-pandemic sera sampled in 2019 and 2018. Test sensitivity and specificity have been used to convert proportions of test positives into estimated seroprevalences.

The 95% confidence intervals (CI) for percentage positives were estimated using the exact method. Seroprevalence was estimated for Norway and by laboratory, gender, age group, county of residence 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 taking into account uncertainties in sensitivity and specificity of the test (4). We adjusted the overall seroprevalence by a multilevel regression and poststratification on counties, age groups and gender (4). For seroprevalence results we present a point estimate and a 95% CrI.

Results

Of the 900 samples tested, 10 samples tested positive for antibodies against SARS-CoV-2. This corresponds to 1.1% (95% CI 0.5-2.0) positive samples, giving an estimated seroprevalence of 1.0% (95% CrI 0.1-2.4) in the Norwegian population when corrected for the estimated test sensitivity and specificity (Table 1).

The estimated seroprevalence varied (non-significantly) between the different laboratories in Norway; the highest estimated seroprevalence against SARS-CoV-2 was found in Oslo (4.3% (95% CrI 0.9-10.4%)) (Table 1). Three laboratories did not have any samples that tested positive. We did not find any differences in seroprevalence by gender (Table 2) or age group (Table 3). The youngest person for whom the serum tested positive was 9 years old, while the oldest was 76 years old. The seroprevalence estimated based on county of residence is presented in Table 4. There were no significant differences; however, some counties were represented by few samples making the credible intervals very large.

Most samples were collected in week number 20 (11th – 17th of May) (55.6%) and 11.3% of samples had an unknown sampling week; note that all samples were collected between week numbers 17-20 2020 (20th of April – 17th May). There were no differences in the estimated seroprevalence between the week numbers (Table 5).

All 216 tested samples from August 2019 were negative for antibodies against SARS-CoV-2 (data not shown). This indicates that there were no antibodies cross-reacting with the selected SARS-CoV-2 derived antigens prior to the pandemic in Norway.

Tables

Table 1. Estimated seroprevalence, overall and by laboratory

	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Seroprevalence [%] (95% CrI)
Total	**10**	**900 (100)**	**1.1 (0.5 - 2.0)**	**1.0 (0.1 - 2.4)**
By laboratory				
Oslo (Ullevål)	3	90 (10.0)	3.3 (0.7 - 9.4)	4.3 (0.9 - 10.4)
Bergen	0	119 (13.2)	0 (0 - 3.1)	0.7 (0 - 3.5)
Lillehammer	0	92 (10.2)	0 (0 - 3.9)	0.9 (0 - 4.4)
Molde	3	102 (11.3)	2.9 (0.6 - 8.4)	3.9 (0.8 - 9.6)
Tromsø	1	86 (9.6)	1.2 (0 - 6.3)	2.0 (0.1 - 6.9)
Trondheim	1	105 (11.7)	1.0 (0 - 5.2)	1.6 (0.1 - 5.8)
Kristiansand	1	92 (10.2)	1.1 (0 - 5.9)	1.9 (0.1 - 6.8)
Fredrikstad	1	102 (11.3)	1.0 (0 - 5.3)	1.7 (0.1 - 5.8)
Bodø	0	112 (12.4)	0 (0 - 3.2)	0.7 (0 - 3.8)

Table 2. Estimated seroprevalence by gender

Gender	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Seroprevalence [%] (95% CrI)
Male	6	383 (42.6)	1.6 (0.6 - 3.4)	1.6 (0.3 - 3.6)
Female	4	509 (56.6)	0.8 (0.2 - 2.0)	0.8 (0.1 - 2.1)
Missing	0	8 (0.9)	0 (0 - 36.9)	n.a.*

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

Table 3. Estimated seroprevalence by age groups in years

Age groups	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Seroprevalence [%](95% CrI)
0-4	0	41 (4.6)	0 (0 - 8.6)	1.9 (0.1 - 9.6)
5-14	2	115 (12.8)	1.7 (0.2 - 6.1)	2.33 (0.2 - 6.8)
15-24	2	166 (18.4)	1.2 (0.2 - 4.3)	1.54 (0.2 - 4.7)
25-59	4	372 (41.3)	1.1 (0.3 - 2.7)	1.13 (0.1 - 2.9)
≥60	2	206 (22.9)	1,0 (0.1 - 3.5)	1.16 (0.1 - 3.8)

Table 4. Estimated seroprevalence by county of residence

County	Positive samples	Number of samples tested (% of all)	Percent positive samples (95% CI)	Seroprevalence [%] (95% CrI)
Oslo*	3	71 (7.9)	4.2 (0.9 - 11.9)	5.5 (1.2 - 13.4)
Rogaland	0	24 (2.7)	0 (0 - 14.3)	n.a.**
Vestland	0	92 (10.2)	0 (0 - 3.9)	0.9 (0 - 4.3)
Innlandet	0	89 (9.9)	0 (0 - 4.1)	0.9 (0- 4.8)
Møre og Romsdal*	3	108 (12.0)	2.8 (0.6 - 7.9)	3.6 (0.7 – 9.0)
Vestfold og Telemark	0	3 (0.3)	0 (0 - 70.8)	n.a.**
Viken	1	121 (13.4)	0.8 (0 - 4.5)	1.4 (0.1 - 4.9)
Agder*	1	94 (10.4)	1.1 (0 - 5.6)	1.9 (0.2 - 6.3)
Trøndelag*	1	99 (11)	1.0 (0 - 5.5)	1.7 (0.1 – 6.0)
Troms og Finnmark	1	83 (9.2)	1.2 (0 - 6.5)	2.0 (0.2 - 7.3)
Nordland	0	116 (12.9)	0 (0 - 3.1)	0.7 (0.03 - 3.6)

* Sera from the laboratory in Molde and a few sera from Oslo/Ullevål, Trondheim and Kristiansand were attributed to the corresponding counties (Møre og Romsdal, Oslo, Trøndelag and Agder, respectively), as these sera did not include information on county of residence. **N.a.: not applicable. The seroprevalence was not estimated for subgroups with less than 30 samples tested.

Table 5. Estimated seroprevalence by sampling week

Sampling week	Positive samples	Number of samples tested (%)	Percent positive samples (95% CI)	Seroprevalence [%] (95% CrI)
17	0	11 (1.2)	0 (0 - 28.5)	n.a.*
18	2	188 (20.9)	0 (0 - 3.7)	0.8 (0 - 4.1)
19	5	500 (55.6)	1 (0.3 - 2.3)	1.0 (0.1 - 2.5)
20	0	99 (11.0)	0 (0 - 3.7)	0.8 (0 - 4.1)
Unknown (within 17-20)	3	102 (11.3)	2.9 (0.6 - 8.4)	3.7 (0.8 - 9.3)

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

Discussion

This is the first study measuring antibodies against SARS-CoV-2 in sera sampled from various geographical regions and covering all age groups in Norway. The number of residual serum samples that tested positive for antibodies against SARS-CoV-2 was low, indicating an estimated seroprevalence of 1.0% (95% CrI 0.1% - 2.4%) in the Norwegian population. This matches the relatively low number of PCR-confirmed cases in Norway (7,847 cases notified to the Norwegian Surveillance System for Communicable Diseases (MSIS) by week 18, corresponding to 0.15% of the population (1, 2, 5). The seroprevalence matches well with the estimated cumulative incidence from mathematical modelling based on hospitalisations, estimating that 0.58-0.75% of the population had been infected by week number 18 (2). Our data also corresponds with the proportion of seropositives among a random sample of participants from The Norwegian Mother, Father and Child Cohort Study (MoBa) living in Oslo (1.2% positive samples of 3339 tested)(6). In our study, there was a trend that (the number of positive samples and) the estimated seroprevalence was higher in Oslo than in the rest of Norway, probably reflecting that Oslo had the highest cumulative incidence of PCR-confirmed cases at the time of sampling (1, 2, 5). However, not all counties were included, and only a limited number of samples have been tested from each laboratory. Therefore, these results should be interpreted with caution. We did not find any differences in seroprevalence by gender or age group.

The samples were collected in April/May 2020. Studies have found that, after an infection with SARS-CoV-2, IgG antibodies 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 (7) In our study, estimation of the sensitivity of the test was based on samples from individuals with PCR-confirmed cases, and with more than 3 weeks since symptom onset. We cannot rule out that some residual sera included in the study were collected from individuals recently infected with SARS-CoV-2. These individuals may not have developed antibodies at the time of sample collection but could seroconvert at a later time point. This will affect the interpretation of the results, and the estimated seroprevalence presented therefore represents the situation in mid-April 2020 (i.e. approximately 3 weeks prior to sampling). Furthermore, as the laboratories were asked to not include samples submitted for analysis of antibodies against SARS-CoV-2, some positive samples may have been excluded. This could lead to a potential underestimation of the seroprevalence; however, at the time of sample collection there was not extensive testing for antibodies against SARS-CoV-2.

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. Conversely, testing of sera from invited persons may lead to healthy-person biases or non-participation of certain groups (8). The consistent procedure of sampling of residual sera in 2019 and 2020, makes the findings comparable over time.

Conclusion

The estimated seroprevalence in the Norwegian population is low (1.0% (95% CrI 0.1% - 2.4%)), indicating that the proportion of the population that has been infected with SARS-CoV-2 is probably close to 1%. There seem to be geographical differences; however, the number of samples in some of the sub-analyses were too small to reach statistical significance. 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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