

Seroprevalence of SARS-CoV-2 in Guilan Province, Iran, April 2020

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We determined the seroprevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in an affected area in northern Iran in April 2020. Antibodies to SARS-CoV-2 were detected in 528 persons by using rapid tests. Adjusted prevalence of SARS-CoV-2 seropositivity was 22.2% (95% CI 16.4%–28.5%).

Coronavirus disease (COVID-19) was first reported in China and has now spread throughout the world. Global estimates of disease spread are based on confirmed cases in symptomatic patients (1). However, these estimates do not accurately reflect actual infection rates in the community because they exclude persons with mild or no symptoms or for whom testing is unavailable. Knowledge about actual infection rates is vital for accurately estimating the case-fatality rate, a public health measure of COVID-19 (2), and for projecting the course of the pandemic and determining public policy guidelines (3).

Guilan Province was the second-largest province in Iran to have multiple confirmed cases of COVID-19 soon after the beginning of the pandemic. The epidemic curve has subsided in this province, making it an appropriate location to test for the presence of past infections through a seroprevalence survey. In this study, we provided a population-based seropositivity estimate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection based on World Health Organization protocol.

We conducted a cross-sectional population-based study among persons in Guilan Province during April 11–19, 2020. The study was approved by the Institutional Review Board of Guilan University of Medical Sciences (Rasht, Iran). All persons living

in a household, regardless of age, were invited through multistage cluster random sampling. We selected clusters from the list of Comprehensive Healthcare Centers (CHCs) (the top units of the healthcare network in Iran) and used simple random sampling method to select households from those covered by CHCs. On the day participants arrived at the CHC, we took 10 μ L capillary blood samples from each participant and collected information on demographics, disease history, COVID-19 symptoms in previous 3 months, and history of SARS-CoV-2 exposure. Samples were tested by using VivaDiag Rapid test kit (VivaChek, <https://www.vivachek.com>) for a SARS-CoV-2-specific serologic assay.

The design-adjusted prevalence of seropositivity was estimated by using inverse probability weighting with weights equal to the inverse of probability of selection for each participant (4). The prevalence estimates were then adjusted for test characteristics. We used a Monte Carlo bias analysis with 100,000 samples for sensitivity of 83.3% and specificity of 99% for IgM or IgG (5,6). The number of infections was calculated by multiplying infection prevalence by total population of Guilan Province. All analyses were performed in Stata version 14 (Stata, <https://www.stata.com>). Additional information about methods and results has been provided in the Appendix (<https://wwwnc.cdc.gov/EID/article/27/2/201960-App1.pdf>).

Of 632 households contacted, 196 households, consisting of a total of 551 persons, participated in this study. Eleven of those 551 participants refused blood sampling and could not be tested, and 12 had invalid test results. Of the remaining 528 participants, 117 were positive for either IgM or IgG (22.1% [95% CI 0.19%–0.26%]). Adjusted for design and test performance, prevalence was 22.2% (95% CI 16.4%–28.5%).

Seropositivity prevalence estimates varied most substantially according to age group, occupation, presence of COVID-19 symptoms in the previous 3 months, and county of residence (Table). Office workers had the highest prevalence of SARS-CoV-2 infection, followed by taxi drivers. Among counties, the highest prevalence of seropositivity was in Anzali, followed by Rasht.

In this study, the seroprevalence estimate of SARS-CoV-2 antibodies after adjusting for population and test characteristics was 22.2%. This result is much higher than those for previous seroprevalence estimates using an immunoassay test to detect antibodies in Spain (7); California, USA (8); and Geneva, Switzerland (9). Unlike Guilan Province, those places enacted severe lockdown policies to

Table. Severe acute respiratory syndrome coronavirus 2 seropositivity prevalence estimates according to study variables, Guilan Province, Iran, April 2020*

Characteristic	Sample size (%), N = 528	No. positive	Design-adjusted prevalence (95% CI)	Design- and test performance- adjusted prevalence (95% CI)†
Sex				
M	257 (48.7)	55	16.8 (13.2–21.2)	19.0 (12.7–25.4)
F	271 (51.3)	62	22.2 (14.7–32.1)	25.6 (15.4–36.8)
Age group, y				
<5	26 (4.9)	4	8.7 (2.1–30.2)	9.8 (0.9–22.6)
5–17	101 (19.1)	20	17.0 (11.6–24.2)	19.1 (11.2–27.5)
18–59	329 (62.3)	74	21.0 (16.9–25.8)	24.1 (17.5–31.6)
≥60	72 (13.6)	19	22.4 (15.7–31.0)	25.7 (16.6–36.1)
Obesity, BMI >30				
No	474 (89.8)	107	19.8 (16.9–22.9)	22.6 (16.8–29.0)
Yes	54 (10.2)	10	15.4 (7.8–28.2)	17.3 (6.2–29.0)
SARS-CoV-2 exposure history				
No	452 (85.6)	95	18.1 (12.7–25.1)	20.4 (12.6–28.8)
Yes	76 (14.4)	22	26.9 (13.5–46.5)	31.2 (13.4–50.8)
COVID-19 symptoms in previous 3 mo				
No	382 (69.3)	65	15.3 (11.03–20.9)	17.2 (10.3–24.1)
Yes	169 (30.7)	52	30.05 (25.3–36.4)	35.5 (27.8–45.8)
Underlying condition				
No	420 (79.5)	89	18.2(13.6–24.03)	20.7 (13.5–28.3)
Yes	108 (20.5)	28	25.3 (18.3–33.9)	29.2 (19.8–40.2)
Place of residence				
Village	162 (30.7)	38	21.0 (16.0–27.1)	24.0 (16.5–32.4)
Town	366 (69.3)	79	19.2 (16.0–23.0)	21.9 (15.8–28.4)
Occupation‡				
Employee	53 (10.04)	19	46.0 (35.9–56.5)	54.3 (41.8–71.1)
Housekeeper	159 (30.1)	39	21.8 (13.4–33.5)	25.0 (13.6–37.5)
Student	114 (21.6)	22	15.6 (12.1–20.0)	17.5 (11.3–23.7)
Unemployed	67 (12.7)	11	11.8 (7.6–18.0)	12.9 (5.9–19.6)
Farmer	16 (3.03)	3	17.4 (9.9–28.8)	19.7 (9.1–31.0)
Salesman	46 (8.7)	5	7.9 (2.0–26.7)	8.7 (0.8–20.0)
Healthcare personnel	43 (8.1)	12	13.2 (6.5–24.9)	14.5 (4.5–25.0)
Taxi driver	13 (2.5)	5	24.0 (7.1–56.7)	28.0 (4.5–56.3)
Worker	17 (3.2)	1	2.5 (0.1–32.1)	28.0 (4.5–56.3)
County				
Rasht	226 (42.8)	56	20.8 (19.7–21.9)	23.7 (18.6–29.6)
Anzali	75 (14.2)	23	30.0 (29.7–30.4)	34.8 (29.7–43.2)
Astara	78 (14.8)	12	15.4 (14.3–16.6)	17.4 (12.0–21.8)
Lahijan	74 (14)	12	15.0 (13.6–16.5)	16.9 (11.5–21.4)
Rudbar	75 (14.2)	14	17.7 (15.5–20.2)	20.1 (14.5–25.7)

*BMI, body mass index; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

†Calculated using Monte Carlo simulation method.

‡Employee was defined as a government employee working in an office. Worker was defined as a person performing manual jobs in nongovernmental locations.

contain the pandemic, which might explain the higher prevalence of infection in our study.

Our study's limitations include possible selection bias if persons with previous COVID-19-like symptoms sought to participate in the study. However, in our study only 11 participants had a history of COVID-19 diagnosis. Otherwise, bias toward persons in good health who could participate in the study might result in an underestimation of actual prevalence. In addition, household sampling might result in an overestimation of prevalence compared with random sampling of persons because of clustering of infection in household contacts. We excluded persons in institutional residences (i.e., nursing homes, boarding schools, and prisons), for whom close contact with others might increase risk

for infection, resulting in an underestimation of actual prevalence. Finally, our study used rapid test kits that have lower sensitivity than the ELISA test method, particularly for patients in the acute phase of infection. However, the study was designed to detect previous infection in healthy persons, in whom the test has better sensitivity.

In conclusion, our findings imply that ≈518,000 persons in Guilan Province may have been infected with SARS-COV-2 as of April 19, 2020, which is substantially higher than the 1,600 cumulative confirmed cases recorded. As of May 3, if we assume a 3-week lag from time of infection to death (10), 625 persons had died of confirmed COVID-19 in Guilan Province. This number would correspond to an infection-fatality rate of 0.12%.

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Dr. Shakiba is an epidemiologist and faculty member at Guilan University of Medical Sciences. Her research interests include survey design and causal inference methodology.

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Intrauterine Transmission of SARS-CoV-2

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We documented fetal death associated with intrauterine transmission of severe acute respiratory syndrome coronavirus 2. We found chronic histiocytic intervillitis, maternal and fetal vascular malperfusion, microglial hyperplasia, and lymphocytic infiltrate in muscle in the placenta and fetal tissue. Placenta and umbilical cord blood tested positive for the virus by PCR, confirming transplacental transmission.

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Appendix

Sampling

The sampling was conducted in the health service structure of Iran that had been exclusively organized during the COVID-19 pandemic as part of the National Mobilization Plan (NMP) against COVID-19. In Iran, public health services are provided through a nationwide referral network system, which following Health Transformation Plan had acceptable coverage in all urban and rural populations (1). This network started at rural and urban Comprehensive Health Care Centers (CHCs) in the periphery providing primary healthcare to a population residing in a predefined geographic area under the coverage of a CHC (2,3). In the NMP against COVID-19, a prevention strategy launched by the Ministry of Health for screening persons with COVID-19 symptoms (4), all households under coverage of CHCs were registered. Those who were not under coverage of CHCs were informed to register at the website salamat.gov.ir through extensive media advertisements. According to the report by Guilan University of Medical Sciences, this plan resulted in more than 92% coverage of households for screening of persons with COVID-19 symptoms (5). In this population-based cross-sectional study, a stratified multistage cluster random sampling approach was used to select participants. The strata were defined according to World Health Organization (WHO) protocol (6) for high- and low-incidence counties based on the ratio of hospitalized cases to total population in each county. The study was conducted in 3 high-incidence (Rasht, Anzali, Lahijan) and 2 low-incidence counties (Astara, Roudbar) as the primary sampling unit. Counties were randomly selected from 16 counties using simple random sampling method. At the second stage of sampling, clusters were selected from the list of urban and rural CHCs, and at the third stage of sampling, households were selected from the list of households under coverage of CHCs using simple random sampling method through computer generated random numbers. Households were defined as ≥ 2

persons living in the same place. The number of clusters in each county was assigned proportionally to the number of CHCs. Therefore, 15 CHCs were considered for Rasht county (the capital city of the province), and 5 CHCs were considered for each of the remaining 4 counties. Considering the almost equal population under coverage of CHCs, a sample size of 15 individuals/cluster was determined in the third stage of sampling by dividing total sample size by the total number of clusters.

Eligibility Criteria and Sample Size

Persons living in institutional residences, such as nursing homes, prisons, and boarding schools, and persons who refused to participate, were under active treatment for COVID-19, or who had contraindication to venipuncture were not invited to participate. With a prior prevalence of 50% for coronavirus infection based on closed cohort population (7), considering a 5% precision, design effect of 1.24 (8), and nonresponse rate of 10%, a total of 530 participants were considered for sample size. Guilan province is located in northern Iran and has a population of 2,354,848 over 16 counties.

Data Collection

Upon phone call to heads of the household (identified in households' electronic health records), a brief explanation of the research objectives was given and household members were asked to come to the CHC. For acknowledgment and to increase rates of participation, a package of incentives including ethanol alcohol, face masks, and kids' stickers were provided to household members. Appointments were scheduled at intervals to allow social distancing among households. After providing information about the risk and benefits of participation in the study, informed consent was acquired from head of household. An interviewer completed an electronic questionnaire collecting participants' demographic and exposure-history information. Sample collectors in personal protective equipment drew 10 μ L of capillary blood into an EDTA-coated microtainer, and tubes were labeled with participant IDs. VivaDiag COVID-19 IgM/IgG from VivaChek (VivaChek, <https://www.vivachek.com>) was used for COVID-19 –specific serologic assay. According to manufacturer's instruction, 10 μ L of serum or whole blood sample was added into the sample port followed by adding 2 to 3 drops (70–100 μ L) of dilution buffer. Test

kits were read after ≈ 15 minutes. The sensitivity was 80% for IgG and both IgM and IgG, and 83% for IgM and either IgM or IgG (9) and the specificity was 100% (95% CI 95.7–100) For “IgM” and “IgM and IgG” and 99% (95% CI 94.2–100) for “IgM or IgG” and “IgG” (10).

Statistical Analysis

Demographic characteristics were described as frequency and percentage. The design-adjusted prevalence of COVID-19 positive test was estimated with consideration for clustering and unequal probability of sampling (11). Since the probability of selection varied over the participants, inverse probability weighting is required to adjust for selection bias. The weight formula was $\frac{1}{P_1 \times P_2 \times P_3}$, where $P_1 \times P_2 \times P_3$ are probability of selection for each participant, which is equal to the multiplication of the probabilities of selection at each of the 3 stages of sampling (i.e., county, CHC, and household). The highest level of clustering or primary sampling unit (county) was considered in the calculation of CI using Taylor-linearized standard error. The prevalence estimates were further adjusted for Rapid test sensitivity (Se) and specificity (Sp) using the following formula (12,13):

$$TP = (AP + Sp - 1) / (Se + Sp - 1)$$

where TP denotes true prevalence and AP denotes apparent prevalence. For test performance adjustment, we used the results of previously published papers (9,10). We used a Monte Carlo bias analysis with 100,000 samples for sensitivity (14,15): β distribution with parameters $a = 25$, $b = 5$ for seropositivity for “IgM or IgG” and “IgM” (Se = 83.3%), and another β distribution with parameters $a = 24$, $b = 6$ for “IgM and IgG” and “IgG” (Se = 80%). We performed a similar bias analysis for specificity of 100% (95% CI 95.7–100) for “IgM” and “IgM and IgG” and 99% (95% CI 94.2–100) for “IgM or IgG” and “IgG” using β distribution with parameters $a = 47.84$, $b = 0.36$ and $a = 47.84$, $b = 0.64$, respectively. For sensitivity, we set α = the number of true positives and β = the number of false negatives in the reference (9) in the Appendix so that the mean and variance of β distribution approximately equal the mean and variance of sensitivity estimates in reference (9). For specificity, we chose α and β values so that the percentiles 2.5 and 97.5 of β distribution exactly match the 95% confidence limits of specificity in reference (10) using a grid search. The apparent prevalence was drawn from a Normal distribution with mean and standard deviation equal to design-adjusted prevalence

estimate and its standard error, respectively. We derived the point estimates and 95% simulation intervals (for simplicity, called confidence intervals in this paper) using the median and 2.5th and 97.5th percentiles of Monte Carlo distribution. All analyses were performed in Stata version 14 (Stata, <https://www.stata.com/>).

Supplementary Results

In this study, the major reasons for nonparticipation were concerns about acquiring infection in the CHC (17%), busy schedule (20%), lack of assurance to system (2%), no response (31%), and other nonspecified reasons (28%). The distribution of nonparticipation was not substantially different among the counties and ranged between 30% to 33%. The variable distribution in the sample was not substantially different from that of the province except for place of residence (32% in village, 43% in province) (Appendix Table 1).

Supplementary Discussion

The current result is much higher than previous seroprevalence estimates in California (16), Spain (17), and Geneva (18), which were lower than 10%. Our estimate is closer to findings from France (A. Fontanet, unpub. data, <https://doi.org/10.1101/2020.04.18.20071134>) and Germany (H. Streeck, unpub. data, <https://doi.org/10.1101/2020.05.04.20090076>), which were $\approx 20\%$. Prevalence of infection across space and time varies greatly. Geneva repeated cross-sectional seroprevalence studies showing an increase from 4.8% in the first week to 10.8% in the fifth week (18). For one-time cross-sectional investigation, WHO recommended the survey be conducted after the peak of transmission of the epidemic wave (6). This study was conducted during April 11–19 after the peak of the epidemic wave in Guilan province, which had occurred in early April. Study design based on individual or household sample might also influence the results. In the household sampling that formed the basis of our study, we expect an overestimation of seroprevalence, assuming that 1 infection in a household would increase the likelihood of other infections more than 1 infection in random persons. Another factor that might explain the heterogeneity of the reported prevalence of infection among communities is the severity of lockdown policies enacted by different societies to contain the pandemic. In Guilan province, except for school and university closures, the restriction policy was not stringent and

could have resulted in higher rates of infection. The high seroprevalence of COVID-19 in Guilan province might also be related to an economic relationship with China in a free trade zone in northern Guilan province. The zone is in the county of Anzali, which had the highest seroprevalence in Guilan province.

In this study, prevalence of infection in children <5 years of age was 9.8%. For half of seropositive children, no previous COVID-19-associated symptoms were reported. This finding might support the hypothesis that more children might be infected than previously thought. In the current study, the overall prevalence in children and adolescents (0–19 years of age) was 14%. In 2 previous studies, a rate of 3.4% in Spain and 9.6% in Switzerland were reported for similar age groups (17,18). In contrast to a previous study in Geneva with a low seroprevalence among children 5–9 years of age and persons >65 years of age (18), we found that persons ≥ 60 years of age had the highest rate of infection. During the pandemic, schools and universities were closed and the elderly were asked to shelter in place. As to infection rates among children, more studies are needed to clarify the immunologic responses of children to COVID-19.

Employees and taxi drivers were the two occupations that had the highest prevalence of infection compared to other job categories. These jobs require many encounters with other persons. Employees work in governmental offices and interact with many clients during their jobs. Bank employees, also included in this group, are exposed to paper money (a source of infection during the pandemic) in addition to having contact with many clients. In Iran, taxi drivers drive up to 4 persons/trip, making them a high-risk group for COVID-19.

This study found an infection fatality rate of 0.12%, similar to previous seroprevalence studies that estimated rates of between 0.03%–0.5% (J. Ioannidis, unpub. data, <https://doi.org/10.1101/2020.05.13.20101253>). However, the estimated infection fatality rate is much lower than currently reported estimates of case fatality rate for COVID-19 of between 3%–4% (19). Previous estimate of case fatality rate using lag time for fatality in China was between 0.25%–3.0% (20).

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Appendix Table 1. Demographic characteristics of sample relative to Guilan Province population

Characteristics	Sample no. (%)	Guilan Province (%)
Sex		
M	27(49)	50
F	281(51)	50
Age group		
<5	27(5)	6
5–17	107(19)	17
18–59	343(62)	63
≥60	74(13)	14
Living place		
Village	175(32)	43
City	376(68)	56

Appendix Table 2. Severe acute respiratory syndrome coronavirus 2 seropositivity prevalence estimates in Guilan province, April 2020

Antibody seropositivity	No. (%)	Design-adjusted prevalence (95% CI)	Design- and test performance-adjusted prevalence (95% CI*)
IgM	102 (19.3)	17.6% (13.4–22.7)	20.4% (14.3–27.4)
IgG	113 (21.4)	18.9% (15.8–22.4)	22.3% (16.1–29.5)
IgM and IgG	98 (18.6)	16.7% (12.2–22.3)	20.1% (13.3–28.0)
IgM or IgG	117 (22.1)	19.4% (16.5–22.7)	22.2% (16.4–28.5)

*CI calculated using Monte Carlo simulation method.