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Low prevalence of active COVID-19 in Slovenia: a nationwide population study on a probability-based sample

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Abstract

Objectives: Accurate population-level assessment of the COVID-19 burden is fundamental for navigating the path forward during the ongoing pandemic, but current knowledge is scant. We conducted the first nationwide population study using a probability-based sample to assess active SARS-CoV-2 infection, combined with a longitudinal follow-up of the entire cohort over the next 6 months. Baseline SARS-CoV-2 RNA testing results and the first 3-week follow-up results are presented.

Methods: A probability-based sample of the Slovenian population (N = 2.1 million) was selected from the Central Population Register (n = 3,000). SARS-CoV-2 RNA was detected in nasopharyngeal samples using the cobas 6800 SARS-CoV-2 assay. Each participant filled in a detailed baseline questionnaire with basic sociodemographic data and current and past medical history compatible with COVID-19. After 3 weeks participants were interviewed for the presence of COVID-19–compatible clinical symptoms and signs, including in household members, and offered immediate testing for SARS-CoV-2 RNA if indicated.

Results: 1,368 (46%) individuals consented to participate and completed the questionnaire. Two of 1,366 participants tested positive for SARS-CoV-2 RNA (prevalence 0.15%; posterior mean 0.18%, 95% Bayesian CI 0.03–0.47%; 95% HDR 0.01–0.41%). No newly diagnosed infections occurred in the cohort during the first 3-week follow-up round.

Conclusions: The low prevalence of active COVID-19 infections found in this study accurately predicted the dynamic of the epidemic in Slovenia over the subsequent month. Properly designed and timely executed studies using probability-based samples combined with routine target-testing figures provide reliable data for informed decisions on relaxing or strengthening mitigation strategies.
Introduction

The WHO announced a coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on March 11, 2020, after rapid global spread of the disease. Starting as a local emergence in late 2019 [1-3], almost 12 million cases and 550,000 SARS-CoV-2-related deaths had been confirmed worldwide as of July 07, 2020. Due to the wide spectrum of clinical presentation, ranging from asymptomatic infection to severe respiratory failure requiring intensive care treatment and mechanical ventilation, the burden of disease varies across the world, and the true prevalence of both active and resolved COVID-19 is still largely unknown.

Countries’ success in curbing the first wave of the SARS-CoV-2 epidemic was greatly influenced by the speed and extent of health-care authorities’ containment efforts and mitigation strategies to reduce the spread among the population, keeping the influx of new COVID-19 patients into hospitals manageable and sustainable for the health-care system’s capacities [4-7].

Cultural differences and community discipline were additional important factors influencing the level of compliance with decisions by health-care authorities and politicians. Currently, the main uncertainty is how to determine the point on the epidemic curve when reopening the society and cautiously relaxing measures is safe and sustainable. Accurate assessment of the COVID-19 burden at the community level is fundamental, and a survey using a probability-based sample is an essential component needed for informed decisions on measures to help navigate the path forward during the evolving epidemic [8].

We present the study design, baseline results of SARS-CoV-2 RNA detection in nasopharyngeal samples, and the first 3-week follow-up results of an ongoing nationwide population study on the SARS-CoV-2 burden in Slovenia using a probability-based population sample with a planned 6-month longitudinal follow-up. To the best of our
knowledge, this study is the first to use a probability-based sample representative of the whole country and across all age categories, combined with a longitudinal follow-up of the cohort over the next 6 months. The low prevalence of active COVID-19 infection assessed in this study provided important complementary data to daily epidemiological surveillance and routine target-testing data. Combination of both approaches accurately predicted the epidemic dynamic in Slovenia over the subsequent month and provided a basis for informed decisions on the gradual and controlled relaxation of mitigation strategies, which ultimately led to Slovenia being the first country in Europe to officially declare the end of the first wave of the epidemic, as of May 31, 2020.

Methods

Study design

The Slovenian national study using a probability-based sample was planned in two phases (Fig. 1). The first cross-sectional phase, which took place between April 20 and May 1, 2020, was performed to determine the burden of active SARS-CoV-2 infections in the general population that may have gone undetected within the past and current testing approaches and epidemiological contact tracing. Selected persons were sent an invitation letter and a two-page questionnaire by post about their household structure, their recent contacts and travel history, and their own and household members’ potential COVID-19–compatible symptoms experienced in the past 2 months. According to General Data Protection Regulation (GDPR) rules, we were only allowed to contact these persons using regular post and publicly available landline and mobile telephone numbers. Respondents expressed their willingness via telephone or email; however, in line with the study protocol, refusals were asked no further questions, nor were they re-approached. Non-respondents were sent a reminder by post 1 week after the first invitation. The study design is shown in Fig. 1.
The second phase includes longitudinal tracking of the cohort allowing close and active monitoring of the epidemic dynamics at the population level in the following 6 months. Participants are interviewed by medically qualified personnel every 3 weeks for the presence of COVID-19–compatible clinical symptoms and signs, including in household members. If infection is suspected, they are offered immediate testing. In addition, the participants were provided with a dedicated mobile number and email address to actively report their own and household members’ health status at any time during the study. The first follow-up calls took place between May 18 and 24, 2020. After 6 months of follow-up, exit anti-SARS-CoV-2 serological testing of the entire cohort is planned for October 2020 to determine the cumulative incidence of SARS-CoV-2 infections in the general population.

Participants

The sample was created following a well-established national practice for probability-based official, academic, and public health surveys. The sample was selected on March 31, 2020 from the Central Population Register (CPR), which is maintained by the Ministry of the Interior and includes all permanent and temporary residents of Slovenia (Fig. 1). The chosen gross sample size ($n=3,000$) matched the available resources and time limitations (1-2 weeks of fieldwork) and was also sufficient for the study aims. The sampling design minimized fieldwork costs, which involved ten to twelve trained medical teams with ambulances per day, by selecting 300 census enumeration areas as primary sampling units. The selection of these units followed the implicit stratification according to region and settlement type. Within each unit, ten persons were randomly selected; data from the CPR on age, sex, region, and size and type of settlement were also attached.

All study participants provided written informed consent; for participants under 18, consent was provided by parents/guardians. To ensure confidentiality, all samples and
questionnaires were coded and analysed anonymously. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (consent number 0120-199/2020/19) and registered with ClinicalTrials.gov (NCT04376996).

SARS-CoV-2 RNA testing

Detection of SARS-CoV-2 RNA in nasopharyngeal samples was performed using the clinically validated fully automated sample-to-result two-target PCR-based assay cobas 6800 SARS-CoV-2 (Roche, Branchburg, NJ) according to the manufacturer’s instructions, as previously described in detail [9]. Briefly, the sample was considered positive if either both the ORF1 (target 1) and E (target 2) genes or only the ORF1 gene tested positive. Internal validation showed assay’s 100% sensitivity and 100% specificity [9]. The assay received U.S. FDA Emergency Use Authorization on March 12, 2020.

Statistical analysis

We estimated the prevalence $\theta$ with a binomial-beta conjugate model with non-informative (Jeffrey’s) prior on prevalence: $y \sim \text{Binomial}(n, \theta)$; $\theta \sim \text{Beta} \left(\frac{1}{2}, \frac{1}{2}\right)$, with $n$ being the sample size and $y$ the number of positive cases. The analysis was performed in R [10]. We used 1,000 warmup and 1 million sampling iterations, which is sufficient for the sampling-based approximation error to be lower than the number of decimal places reported. Confidence intervals (CI) are based on the 2.5% and 97.5% percentiles of the posterior distribution.

Results

The response rate, adjusted for non-eligible persons, was 47% (AAPOR RR2) (Fig. 1). The study included 1,368 participants; 663 (48.5%) men and 705 (51.5%) women; the mean age was 46.0 years (range 3 months to 99 years). Of these, 1,366 participants were tested for
SARS-CoV-2 RNA between April 20 and May 1, 2020. The sample matched the population structure well; the differences in sex, region, and settlement type were not statistically significant ($\chi^2, p > 0.01$). The age structure was mismatched only for the age groups 0 to 10 years (7.3% instead of 11.0%) and 51 to 60 years (18.3% instead of 14.0%). However, due to small differences, the weighting procedures have little effect, and – when optimizing the mean squared error – the corresponding reduction in the bias component was smaller than the related increase in the variance component due to weighting. Therefore, the study results, as reported here, are based on the unweighted data.

Out of 1,366 nasopharyngeal swabs, two tested positive for SARS-CoV-2 RNA using cobas 6800 SARS-CoV-2 assay, corresponding to a prevalence of 0.15% (posterior mean = 0.18%, 95% Bayesian CI 0.03–0.47%; 95% HDR 0.01–0.41%). Both cobas SARS-CoV-2 RNA positive samples were additionally confirmed to be positive by two-target RT-PCRs (SARS-CoV-2 specific and pan-Sarbecovirus) using commercially available primers and FAM-labeled hydrolysis probes [11]. No correction of the estimate of prevalence for sensitivity or specificity was performed. One participant was newly diagnosed with COVID-19, and one had previous PCR-confirmed SARS-CoV-2 infection; both participants experienced COVID-19–defining symptoms 2 and 5 weeks before study sampling, respectively.

Between May 18 and 24, 2020, all enrolled participants were contacted again. Out of 1,331 (97.3%) participants reached by May 24, 2020, 29 reported acute respiratory symptoms and/or fever during 3 weeks after initial sampling and were offered SARS-CoV-2 RNA testing. During detailed telephone medical consultation, for 22 participants it was jointly agreed not to test for SARS-CoV-2 RNA due to the high probability that the symptoms recalled were linked with other medical conditions. Finally, seven participants were tested for SARS-CoV-2 RNA and all were negative. In addition, five participants informed us that they sought testing for
SARS-CoV-2 RNA during the 3 weeks after the initial sampling at their own discretion and for non-medical reasons; all were SARS-CoV-2 RNA-negative and reported no COVID-19–compatible symptoms.

Discussion

Despite almost 12 million recorded cases, knowledge about the population COVID-19 burden is scant. To address this knowledge gap, the WHO recently recommended nationwide population-based, age-stratified epidemiological surveys and designed an investigation study protocol to facilitate the collection and sharing of COVID-19 epidemiological data in a standardized format [12]. Each country that performs such a survey may tailor different aspects of the study protocol (including the diagnostic approach) according to its public health, laboratory, and clinical capacities, availability of resources, and cultural acceptance [12]. However, as of early June 2020, very few population studies have been performed using a probability-based sample assessing the COVID-19 burden on a national or broader regional level, and even fewer have been published in peer-reviewed literature [13,14].

To the best of our knowledge, so far the only peer-reviewed study surveying the active COVID-19 burden using a national probability-based sample was performed in April 2020 in Iceland [13]. In the probability-based sample arm, 2,283 participants (20–70 years old) were tested and 0.6% (95% CI 1.3–0.9%) were positive for SARS-CoV-2 RNA. A similar prevalence (0.8%; 95% CI 0.6–1.0%) was recorded in an open-invitation arm (10,797 participants) but it was significantly higher in the targeted-testing arm (13.3%). Although not directly comparable due to different testing approaches, different age populations tested (0–99 years vs 20–70 years), and the different epidemic dynamic of both countries, the diagnostic yield of targeted testing in Slovenia was also expectedly higher (2.6%; 4.1% in the 4 diagnostically most intensive weeks) than that assessed in our study’s probability-based
sample (0.15%) (Fig. 2). In addition to the Icelandic and Slovenian studies, our intensive language-non-restricted literature search identified a non-peer-reviewed notice of two rounds of an Austrian cross-sectional study on a probability-based sample that estimated active COVID-19 prevalence at 0.33% (95% CI 0.12–0.76%) in the first-round survey, which further decreased in the second-round survey [15-17] and a non-peer-reviewed CON-VINCE Luxembourgian study recently deposited in medRxiv, with an estimated active COVID-19 prevalence of 0.3% (95% CI 0.03–0.56%) in people 18 to 79 years old [18]. Although these studies surveyed different age populations using different diagnostic approaches and are highly sensitive to differences in timing within the epidemic curve, all yielded results comparable with our study. Due to the non-peer-reviewed nature of the identified reports, direct comparison of results using a critical scientific approach is impossible [19,20]; however, this is temporary because many studies are currently underway or have reporting backlogs.

Although baseline blood samples were already collected, due to the current uncertainty regarding the accuracy of anti-SARS-CoV-2 assays (especially specificity and consequently low positive predictive value when testing low-prevalent and random populations) [21–24], we have decided to publish seroepidemiological part of our study after collecting both baseline and exit blood samples for each study participant. We hope that in the meantime some form of consensus regarding gold standard serological assay(s) will have been reached or some form of confirmatory algorithm for screen-positives developed. A similar approach was also recently taken by the US CDC [25].

As summarized in Fig. 2, as of June 10, 2020, a total of 86,994 SARS-CoV-2 tests (41,426 tests/million inhabitants) have been performed in Slovenia, 1,488 laboratory-confirmed COVID-19 cases detected, and 109 deaths reported (https://covid-19.sledilnik.org/en/stats).

This study further confirmed the effectiveness of draconian containment measures in Slovenia.
during the first wave of the epidemic, which were introduced simultaneously with the official 
declaration of the epidemic on March 12, 2020. On March 16, public transport was shut down 
and all educational institutions (preschools, schools, and universities) and public institutions 
such as museums, libraries, theatres, and sport facilities were closed. Non-essential medical 
procedures were cancelled, all non-essential shops and services were closed, and public 
gatherings were prohibited. In addition, international travel was restricted and national 
borders were completely closed. On March 29, 2020 the population mobility was further 
restricted to their home municipalities with strict police control. Containment and mitigation 
efforts, the early availability of reliable and clinically validated PCR tests, and prompt and 
central reporting of the results and immediate epidemiological contact tracing were 
fundamental in limiting the epidemic’s spread in Slovenia in its early phases. However, the 
national testing recommendations changed several times during the course of the epidemic, 
starting with a very conservative approach and initially testing only those with severe clinical 
presentation from March 14 to April 7, 2020 (mainly due to limited supply of reagents and 
consumables) and later expanding recommendations to include patients with milder disease if 
they were over 60 or had any risk factors for a more severe disease course. In addition, the 
contact tracing recommendations also changed several times; unfortunately, due to limited 
personnel capacity, no direct epidemiological contact tracing was in place and no quarantine 
officially introduced from March 30 to April 20, 2020.

There are some important limitations of our study that must be considered. Although 
SARS-CoV-2 RNA testing is indispensable for estimating the burden of active COVID-19 
infections in epidemiological surveys using probability-based sample, the prevalence of 
disease assessed at a single time point can be predictive only for a limited time frame. 
Furthermore, such approach has limited potential to detect smaller focal outbreaks, and is 
probably most appropriate in environment with low viral circulation. Additional limitation is
that negative SARS-CoV-2 RNA testing result does not necessarily rule out COVID-19 if sample is taken during diagnostic window or in case of suboptimal quality of sampling. Lastly, non-respondents could present potential limitation of our study. However, the study sample matched the population structure well and weighting did not change the prevalence estimates. Additionally, for non-response bias there must exist a content-specific missing data mechanism linking participation with prevalence, and there is little evidence to support the assumption that persons who are more likely to be infected might also be more willing to participate. Thus we believe that non-response bias in the present study is relatively small and the study reliably estimated the true prevalence of active COVID-19 infection in Slovenia.

Properly designed and executed studies using probability-based samples combined with target-testing figures are extremely important for accurate and timely disease burden estimates and close monitoring of epidemic dynamics. They cannot be replaced by modelling studies and extensive testing campaigns using an open-invitation (non-probability) sample. We believe that our study provided fast insight into the COVID-19 burden in the general population and proved a suitable alternative to more expensive large-scale testing campaigns using an open-invitation sample. The study results also confirmed the overall effectiveness of the timely, strict implementation of rigorous lockdown measures in Slovenia. The study contributed to the accurate prediction of the disease dynamics and subsequent near disappearance of active cases in the following weeks. Only 37 new cases were identified in the entire country in the month following the study despite extensive testing (25,093 tests; average 810 tests/day; average 385 tests/day/million inhabitants) (Fig. 2).

Based on the favourable epidemiological situation in the country, supported by the study results, mobility restrictions within the country were lifted on May 1, 2020, followed by gradual reopening of health-care and dental services (May 9), reopening of public transport (May 11), and partial opening of preschools and schools (May 16). All of this ultimately led
to Slovenia being the first country in Europe to officially declare the end of the first wave of
the epidemic as of May 31, 2020. With the close follow-up of our cohort coupled with
ongoing, extensive routine and commercial testing in the following weeks (500 to 900
tests/day/million inhabitants), we hope to be able to closely monitor the epidemic dynamics in
the coming months and to predict possible COVID-19 recurrence in Slovenia, allowing us to
remain alert and prepared to take the necessary preventive measures in a timely manner.
Transparency declaration

Conflict of interest: The authors have no conflict of interest to disclose.

Author contributions: PMV and AOV contributed equally to this work.

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Contribution: AOV, PMV, MPO, and TAZ were responsible for study concept and design. AOV, PMV, TAZ, MPE, MPO, NK, MK, BZ, JD, ES, SK, and VV were responsible for the acquisition, analysis, or interpretation of data. AOV, PMV, and MPO drafted the manuscript and NK, MK, BZ, JD, ES, SK, and VV provided essential parts. BZ, JD, ES, SK, and VV were responsible for statistical analysis. All authors approved the final version of the manuscript submitted to CMI. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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**Fig. 1: Study design.**

**Fig. 2: Total number of molecular tests performed, individuals tested, and newly diagnosed individuals with SARS-CoV-2 infection in a given week in the COVID-19 epidemic in Slovenia.** On March 4, 2020 the first case of COVID-19 infection was confirmed in Slovenia. *As of March 13, 2020 strict quarantine measures were introduced: closing the borders with neighbouring countries (Italy, Croatia, Austria, and Hungary), closing preschools, primary schools, high schools, and universities, shutdown of public transport, closure of all non-essential shops and services, including cancellation of non-essential medical procedures, and, later, restriction on movement outside one’s municipality of residence. **The gradual lifting of quarantine measures started on May 1, 2020, with removal of restrictions on travel outside the municipality of residence, reopening all health and dental services, restarting public transport, and reopening preschools and schools for selected age groups.*
2,076,901 residents of Slovenia (as of March 31, 2020)

3,000 randomly selected participants

38 invalid postal addresses
5 deceased

2,957 eligible participants

517 refused to participate
1,064 non-respondents

1,376 confirmed participation in the study

2 withdrawn consent
6 not available for sample collection

1,368 participants with samples collected

50 participants with nasopharyngeal swab alone
1,316 participants with nasopharyngeal swab and blood sample
2 participants with blood sample alone

1,366 nasopharyngeal swabs tested
2 positive for SARS-CoV-2 RNA

1,331 participants reached during first follow-up round

Follow-up rounds every 3 weeks

Exit serology round

March 31, 2020
April 15, 2020
April 18, 2020
April 20, 2020
May 1, 2020
May 3, 2020
May 18–24, 2020
June-October 2020
October 2020
2,078,961 residents of Slovenia (as of March 31, 2020)

- 3,000 randomly selected participants
  - 38 invalid postal addresses
  - 5 deceased

2,857 eligible participants

- 517 refused to participate
- 1,064 non-respondents

1,378 confirmed participation in the study

- 2 withdrawn consent
- 6 not available for sample collection

1,368 participants with samples collected

- 50 participants with nasopharyngeal swab alone
- 1,316 participants with nasopharyngeal swab and blood sample
- 2 participants with blood sample alone

1,366 nasopharyngeal swabs tested
- 2 positive for SARS-CoV-2 RNA

1,331 participants reached during first follow-up round

Follow-up rounds every 3 weeks

Exit serology round

March 31, 2020

April 15, 2020

April 18, 2020

April 20, 2020

May 1, 2020

May 3, 2020

May 18–24, 2020

June–October 2020

October 2020
