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First wave of SARS-CoV-2 in Santiago Chile: Seroprevalence, asymptomatic infection and infection fatality rate

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ABSTRACT

Background: The first wave of SARS-CoV-2 infection in Chile occurred during the cold season reaching a peak by the end of June 2020, with 80 % of the cases concentrated in its capital, Santiago. The main objective of this study was to estimate the attack rate during this first wave of SARS-CoV-2 in a large, densely populated city with more than seven million inhabitants. Since the number of confirmed cases provides biased information due to individuals' potential self-selection, mostly related to asymptomatic patients and testing access, we measured antibodies against SARS-CoV-2 to assess infection prevalence during the first wave in the city, as well as estimate asymptomatic cases, and infection fatality ratio. To our knowledge this is one of the few population-based cross-sectional serosurvey during the first wave in a highly affected emerging country. The challenges of pandemic response in urban settings in a capital city like Santiago, with heterogeneous subpopulations and high mobility through public transportation, highlight the necessity of more accurate information regarding the first waves of new emerging diseases.

Methods: From April 24 to June 21, 2020, 1326 individuals were sampled from a long-standing panel of household representatives of Santiago. Immunochromatographic assays were used to detect IgM and IgG antibody isotypes.

Results: Seroprevalence reached 6.79 % (95 %CI 5.58 %–8.26 %) in the first 107 days of the pandemic, without significant differences among sex and age groups; this figure indicates an attack rate 2.8 times higher than the one calculated with registered cases. It also changes the fatality rate estimates, from a 2.33 % case fatality rate reported by MOH to an estimated crude 1.00 % (CI95 % 0.97–1.03) infection fatality rate (adjusted for test performance 1.66 % [CI95 % 1.61–1.71]). Most seropositive were symptomatic (81,1 %).

Conclusions: Despite the high number of cases registered, mortality rates, and the stress produced over the health system, the vast majority of the people remained susceptible to potential new epidemic waves. We contribute to the understanding of the initial spread of emerging epidemic threats. Consequently, our results provide better information to design early strategies that counterattack new health challenges in urban contexts.

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1. Introduction

COVID-19, a disease caused by the zoonotic virus SARS-CoV-2 was first reported in Chile on March 3 2020. Early cases mainly corresponded to returning travelers from Europe and the United States of America. Twelve days later, the first death related to the disease was confirmed. Soon after, the health authority declared community transmission and implemented public health and social measures. The Chilean policy response included the declaration of the state of emergency, a national curfew, school closure, cancelation of public events, travel bans, testing tracing and isolation, and public health campaigns to contain the spread of the disease. Despite these efforts, four months later, by mid-June - winter season in the Southern Hemisphere-, Chile reached the first peak of cases (352 per million inhabitants), mainly concentrated in the capital Santiago (Ministerio de Salud, 2020; Ministry of Science Government of Chile, 2020).

The study aimed to obtain more precise estimates of the SARS-CoV-2 attack rate during the first pandemic wave in Santiago, Chile. Additionally, to estimate the proportion of asymptomatic infections and determine infection fatality rate instead of case fatality rate. Results might help understanding the early development of an emerging disease in a large, densely populated city. Additionally, the real attack rate could help estimate the resources required for new waves of the disease and future pandemic outbreaks.

2. Methods

2.1. Study design setting and participants

We performed a cross-sectional, population-based study to estimate the seroprevalence of SARS-CoV-2 antibodies in Santiago, a city with seven million inhabitants (National Institute of Statistics Government of Chile, 2018) distributed in 34 urban municipalities, located at −33.437, −70.6501 degrees of latitude and longitude. To this end, we used a random sample of non-institutional dwellings from a long-standing panel survey representative of Santiago, conducted by the Universidad del Desarrollo School of Government since 2017 (more details in Supplement 1).

2.1.1. Study size

For the purpose of this study, the sample size was determined assuming an unknown SARS-CoV-2 seroprevalence (p = 0.5), with a precision of ±3 %, resulting in a minimum sample of 1066 individuals. An overpopulated sample of 1533 was randomly selected from the panel sample, considering refusal. Each selected panel member was contacted and enquired to take part in the study and in those who accepted, all family members seven years and older were invited to engage. Fieldwork was carried out from April 24 to June 21, 2020, amid the first wave of the pandemic in the city (Fig. 1).

2.2. Variables and data sources

The outcome variable was the presence of IgM or IgG antibodies, measured with immunochromatographic assays. The crude seroprevalence was adjusted by rapid test performance (based on manufacturers' reports) using Rogan's methodology with 95 % CIs of Lang-Reiczigel as suggested by Flor et al. (2020).

Participants also answered a questionnaire that included basic demographic variables (age, sex), presence of symptoms compatible with COVID-19 (i.e., fever, cough, shortness of breath, headache, and anosmia or ageusia) before the fieldwork (3 months), self-reported PCR status for SARS-CoV-2, and comorbidities.

Additionally, we estimated the infection fatality rate (IFR) for people of seven years and older, using as a numerator the total number of deaths due to COVID-19 (ICD-10 code U07.1 = COVID-19, virus identified) registered by the Chilean Ministry of Health (Ministerio de Salud Gobierno de Chile, 2021); the denominator was our estimates of the total number of infected people based on the crude and adjusted results of seroprevalence.

2.3. Detection of SARS-CoV-2 antibodies

All enrolled subjects underwent venipuncture, and a blood sample was collected to detect SARS-CoV-2 antibodies. Sera were processed in a centralized manner at the Instituto de Ciencias e Innovación en Medicina laboratories. We used four different commercially available immunochromatographic assays for IgM/IgG detection, namely Acro Biotech,

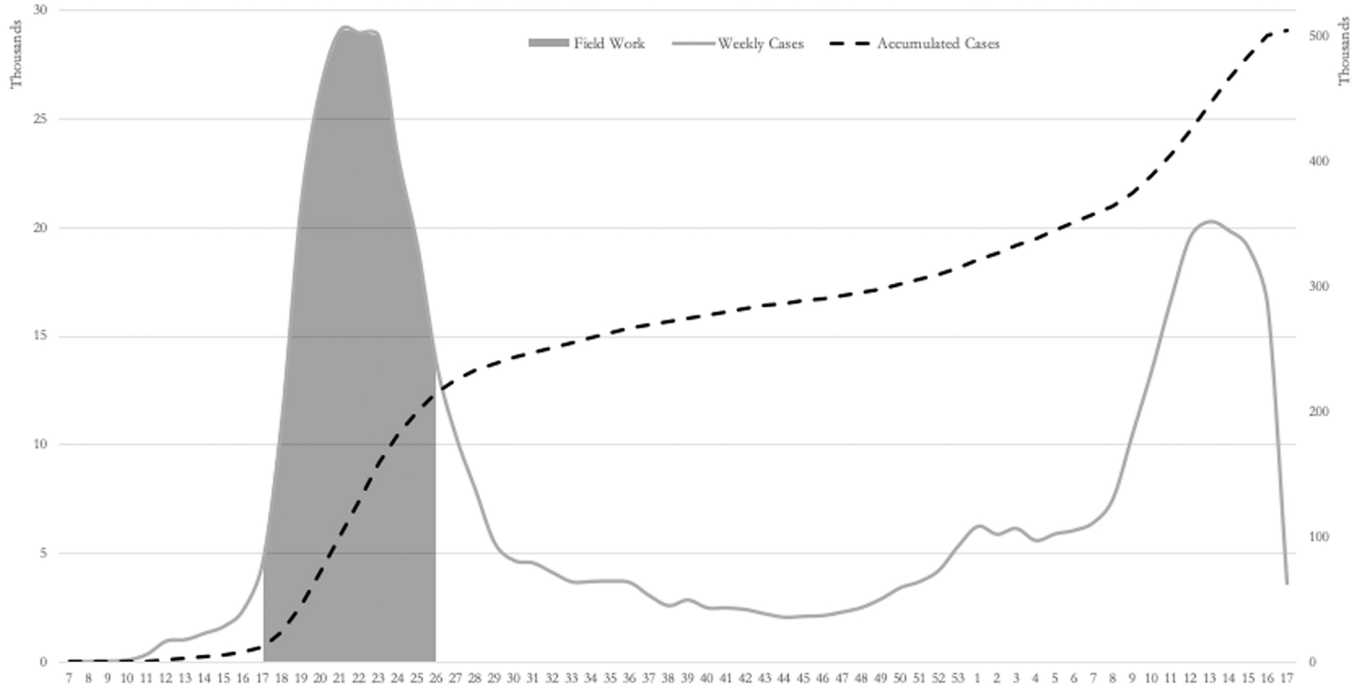

Fig. 1. COVID-19 Reported cases by epidemiological week and fieldwork period. Santiago 2020–21.

Cellex, Dynamiker Biotechnology, Zhuhai Livzon. Manufacturer instructions for each test were followed for antibody measurement. The tests used had a sensitivity ranging between 91 % and 100 % and a specificity of 95–99 %. Test results were sent in a written report to each participant. Given that tests detect IgG and IgM, each time that IgM result was positive one of the investigators called by phone the participant and gave advice regarding further testing, isolation and clinical awareness.

Study data were collected and managed using REDCap® electronic data capture tools hosted at *Universidad del Desarrollo*. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for data integration and interoperability with external sources (Harris et al., 2009, 2019).

2.4. Statistical methods

The seroprevalence was estimated as the proportion of individuals who had a positive result with the immunochromatographic assays (IgG or IgM) using exact binomial estimates to construct the 95 % CIs. We estimated a pooled prevalence by weighting the number of samples tested by each method. Using bivariate logistic regression analysis, seroprevalence confidence intervals were estimated to examine subgroups and explore associations between antibody presence and the variables included in the study. All statistical analyses were done using STATA software v15.

The study protocol and informed consent were approved by the ethics committee of the Faculty of Medicine of Universidad del Desarrollo. All participants were informed about the study's objectives, explaining its voluntary and confidential character, and the signature of the informed consent was obtained.

3. Results

From the 1533 randomly selected households, 672 were enrolled in the study in which a total of 1368 residents (from 7 to 97 years old) accepted the immunochromatographic test and answered a short survey. Our resulting sample had a higher proportion of women and was moderately older than the census population (Table 1). Fig. 2 shows the distribution of the sample in the Greater Santiago territory.

By mid-June 2020, the seroprevalence of SARS-CoV-2 antibodies in Santiago reached 6.79 % (95 %CI 5.58 %−8.26 %) in the first 107 days of the pandemic; this figure indicates an attack rate 2.8 times higher than the one calculated with registered cases in the study area (Ministerio de Salud, 2020). The crude seroprevalence was adjusted by rapid test performance resulting in an adjusted seroprevalence of 4.1 % (CI95 % 3.11–5.28).

There were no significant differences in the seroprevalence by sex, age groups, education level, or type of health insurance coverage.

Table 1
Comparison of the sample's distribution with Santiago population (sex and age).

		Sample		Population 2020*	
		n	%	N	%
Sex	Male	590	43.1	2676,017	48.2
	Female	778	56.9	2879,633	51.8
Age	7–14	67	4.9	600,786	10.8
	15–24	167	12.2	935,904	16.8
	25–39	455	33.3	1478,072	26.6
	40–59	470	34.4	1578,638	28.4
	60 +	209	15.3	962,250	17.3

* 7 + years old, Greater Santiago urban areas. Projection National Census 2017. National Institute of Statistics, Chile. (National Institute of Statistics Government of Chile, 2018).

However, a significantly higher prevalence was observed in people with foreign nationalities than Chileans (OR 2.04; 95 %CI 1.0–4.0) (Table 2).

Regarding clinical characteristics, 21.5 % (20/93) of seropositive individuals self-reported COVID-19 diagnosis (PCR+ for SARS-CoV-2). This group exhibited the highest seroprevalence (76.9 %) and the highest association with the presence of SARS-CoV-2 antibodies (OR 57.3 95 %CI 22.3–147.4), compared to those without the antecedent of COVID-19 diagnosis.

The proportion of individuals with positive tests who experienced COVID-19 compatible symptoms was 81.1 % (73/90). Furthermore, the presence of any COVID-19 symptom was associated with the detection of SARS-CoV-2 antibodies, and higher numbers of symptoms were also associated with more likelihood of having a positive antibody test (Test Mantel-Haenszel: 59.76, p-value: <0.0001).

Headache, odynophagia, and myalgia were the most frequent symptoms in the overall sample, while headache, myalgia, and fatigue showed the highest seropositivity (61.1 %, 52.2 %, and 35.6 %, respectively). However, the highest association with seropositivity was observed in those reporting dysgeusia or anosmia (OR 15.8 and 10.2 respectively) (Table 3).

Regarding comorbidities, 17.8 % of participants self-reported having a chronic disease, reaching a seroprevalence of 4.5 %. The highest seroprevalence was observed among those who reported cancer, obesity, and endocrine diseases; however, none of them were significantly associated with the presence of SARS-CoV-2 antibodies.

3.1. Infection fatality rate estimates

Using our seroprevalence results, we estimated the number of infected cases within the range of 434.000 and 262.000 persons (for crude and adjusted test performance results, respectively). The number of registered deaths due to COVID-19 (ICD-10 code U07.1) at the end of the study period in Santiago was available from the Ministry of Health (Ministerio de Salud Gobierno de Chile, 2021). With this, the risk of death for SARS-CoV-2 infected people during the first wave in Greater Santiago reached 1.0 % using crude seroprevalence and 1.66 % using the adjusted seroprevalence for test performance (Table 4).

4. Discussion

We report the first population-based seroprevalence study in the capital city of Chile, reaching a crude seroprevalence of 6.8 % (4.1 % adjusted) during the first pandemic wave. At the end of the fieldwork, 107 days after detecting the first case, Santiago was one of the world's pandemic hotspots, with 203,580 reported cases for the whole Metropolitan Region of Santiago (cumulative incidence: 2414/100,000 inhabitants) (Ministerio de Salud, 2020). According to our estimates, the seroprevalence of infection was 2.8 times higher than the officially reported cases. This figure is lower than previous estimates for the city, ranging from 4 to 8 times for Mena, and 10 times for Gozzi, both based on modelling (Mena et al., 2021; Gozzi et al., 2021). The prevalence found in our study is within the range of those reported by other studies, varying between 2.8 % in Santa Clara 67 days after the first case started (Bendavid et al., 2021), 11.5 % in Madrid at 85 days (Pollán et al., 2020), and 20.8 % in Lima 115 days after the start of the pandemic (Reyes-Vega et al., 2021). In addition, a systematic review and meta-analysis of 47 SARS-Cov-2 seroprevalence studies in 23 countries estimated a global pooled seroprevalence of 3.38 % in August 2020, varying from 0.36 % in Greece, to 22.1 % in Iran (Rostami et al., 2021).

The small number of seropositive cases detected in our study did not allow us to find significant differences for many variables. We found no significant differences in seroprevalence according to sex, age, education, comorbidities, or health insurance coverage. However, a significant association was found with foreign nationality which could indicate higher exposure risk (i.e. contact with travelers, face-to-face working environments) or social vulnerability (migrants). But also, the foreign

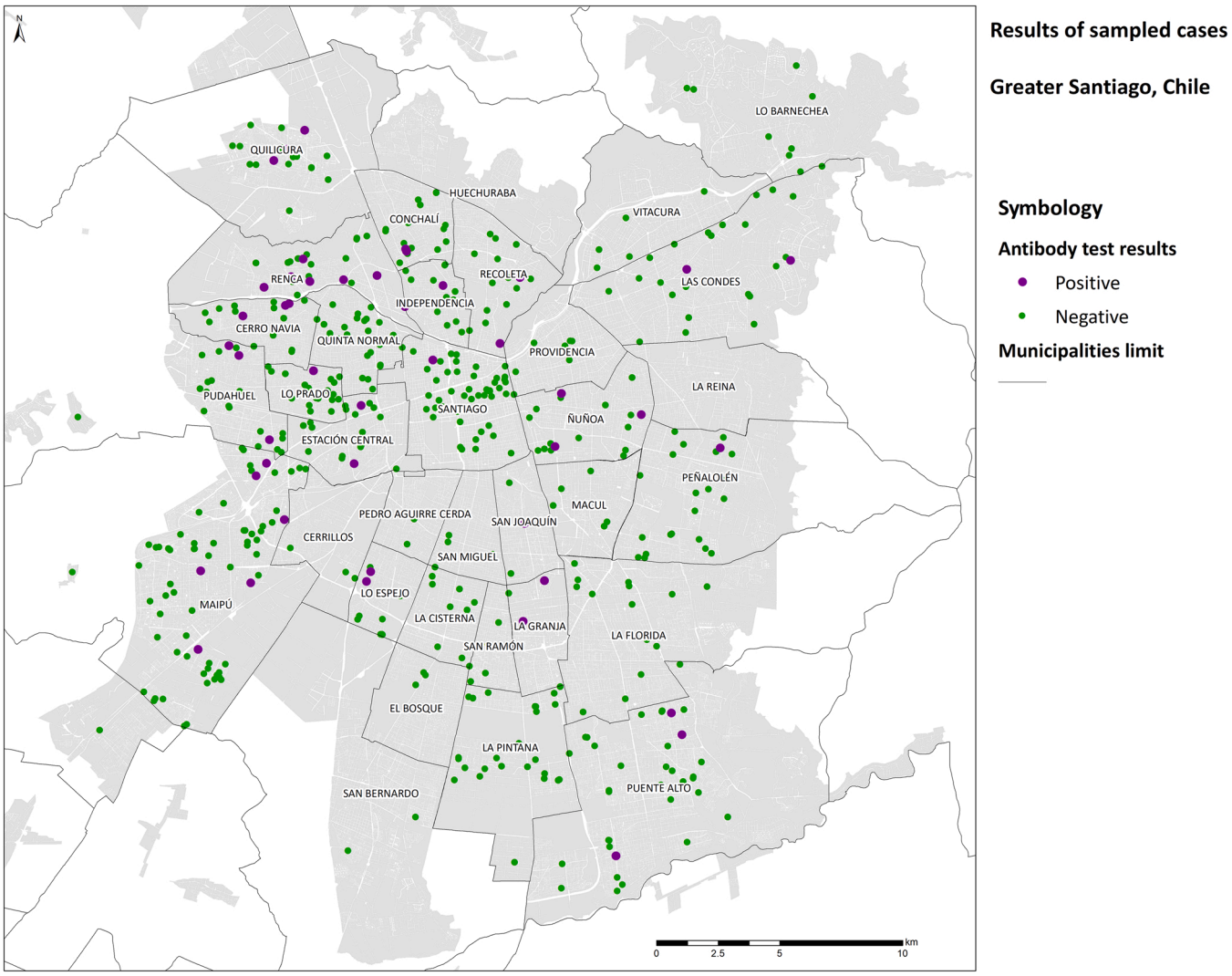

Fig. 2. Geographical distribution of sample and results for SARS-CoV-2 Seroprevalence in Santiago, June 2020.

citizens resulted underrepresented in the sample: 6.5 % vs. 10 % estimated for the city (https://www.extranjeria.gob.cl/noticias/la-region-metropolitana-lidera-la-mayor-concentracion-de-extranjeros-residentes-en-chile/), so it is challenging to give conclusions.

Future seroprevalence studies can provide more evidence about the association between seroprevalence and socioeconomic status. In fact, ecological studies performed in Santiago have highlighted the consequences of socioeconomic and health care disparities in COVID-19 incidence and mortality in Greater Santiago (Mena et al., 2021; Gozzi et al., 2021; Bilal et al., 2021).

The ratio of undocumented cases over reported confirmed cases is a critical epidemiological variable to estimate the cumulative burden of COVID-19. We expected a higher attack rate determined by seroprevalence considering the extended notion that the surveillance system can capture only a fraction of the real burden of cases, reinforced by the results of previous seroprevalence studies: seven-fold greater than the official statistics in Orange County, 11-fold in Switzerland, and to 50–85-fold in Santa Clara (Bendavid et al., 2021; Stringhini et al., 2020). However, our result of an attack rate 2.8 times higher than the one calculated with registered cases in the study area is consistent with the Center for Diseases Control and Prevention estimates of COVID-19 burden in the United States (Estimated COVID-19 Burden, 2021). Our fieldwork took ten weeks and coincided with a dynamic epidemiological situation with an incidence uprise so prevalence was higher every week. On the other hand seroconversion takes several days after infection; both factors could have contributed to obtaining lower seroprevalence results (Pinotti et al., 2021). Seroconversion for IgG antibodies occurs in almost 100 % of patients approximately 17–19 days after symptom onset with titers plateauing within six days after seroconversion (Long et al., 2020). Although immunochromatographic rapid assays have been used in large seroepidemiological studies and shown to perform as well as ELISA tests (Pollán et al., 2020), at the time this study was done, supplies in Chile were very irregular thus it became quite difficult to use a single test, and four tests with some degree of variation in their sensitivity and specificity had to be used.

With our seroprevalence results, we estimated an IFR between 1.00 %−1.66 % for Greater Santiago by mid-June, which is almost half of the case fatality rate (CFR) reported by the Chilean Ministry of Health at that time (2.33 %, for deaths with COVID-19 virus identified ICD-10 U07.1 for the Metropolitan Region of Santiago) (Ministerio de Salud Gobierno de Chile, 2021). The Chilean death registries are considered in the best performance category globally (Mikkelsen et al., 2015) and current estimates of excess deaths during the pandemic greatly coincides with COVID-19 attributed deaths in the country (Mena et al., 2021; Tracking covid-19 excess deaths across countries, 2021). Our IFR estimates are similar to what was obtained in previous studies: 0.8–1.1 in Spain (Pastor-Barriuso et al., 2020), and the estimates of Ioannidis, using 61 studies (0.0–1.54 %) (Ioannidis, 2021).

Table 2
Seroprevalence of SARS-CoV-2 antibodies by general characteristics, Santiago 2020.

Characteristics	Number of participants	Number of seropositives	Seroprevalence (%)	95 % CI	OR*	95 % CI	P
Overall	1368	93	6.8	5.5–8.3			
Sex							
Male	590	43	7.3	5.4–9.7	Ref.		
Female	778	50	6.4	4.9–8.4	0.87	0.6–1.3	0.53
Age range							
7–14 years	67	7	10.4	5.1–20.3	Ref.		
15–24 years	167	8	4.8	2.4–9.3	0.43	0.1–1.2	0.12
25–39 years	455	26	5.7	3.9–8.3	0.52	0.2–1.2	0.14
40–59 years	470	35	7.4	5.4–10.2	0.69	0.3–1.6	0.39
60 and more	209	17	8.1	5.1–12.7	0.76	0.3–1.9	0.56
Nationality							
Chilean	1178	76	6.5	5.2–8.0	Ref.		
Foreign	89	11	12.4	6.9–20.9	2.04	1.0–4.0	0.04
Not Answered	101	6	5.9	2.7–12.6			
Education (age >=18)							
Technical education grade	190	10	5.3	2.9–9.5	Ref.		
College graduates	310	18	5.8	3.7–9.0	1.10	0.5–2.5	0.80
Up to Preparatory School (8 years)	144	15	10.4	6.4–16.6	2.09	0.9–4.8	0.08
Up to High School (−12 years)	536	36	6.7	4.9–9.2	1.30	0.6–2.7	0.48
Not known/not answered	96	5	5.2	0.0–11.9			
Health insurance							
Private (ISAPRES)	377	20	5.3	3.4–8.0	Ref.		
Public (Fonasa)	799	66	8.3	6.5–10.4	1.61	1.0−2.7	0.07
Other (Armed forces + none)	80	2	2.5	0.1–1.0	0.46	0.1–2.0	0.30
Not known/not answered	112	5	4.5	1.9–10.3			
COVID-19 compatible symptoms							
No	540	17	3.1	2.0–5.0	Ref.		
Yes	790	73	9.2	7.4–11.5	3.13	1.8–5.4	0.00
Not answered	38	3	7.9	2.6–21.8			
Number of symptoms							
Asymptomatic	540	17	3.1	2.0–5.0	Ref.		
1	241	8	3.3	1.7–6.5	59.76*		<0.0001
2	183	11	6.0	3.4–10.5			
3	137	13	9.5	5.6–15.7			
4	82	9	11.0	5.8–19.8			
5	147	32	21.8	15.8–29.1			
Self-reported PCR status							
Never done	1237	68	5.5	4.4–6.9	Ref.		
Positive	26	20	76.9	57.2−89.3	57.30	22.3–147.4	0.00
Not known/not answered	105	5	4.8	2.0–11.0			

* Mantel Haenszel.

Table 3
COVID-19 related symptoms, SARS-CoV-2 seroprevalence and odds ratios, Santiago 2020.

Symptoms	Total (n = 1.330)		Seropositive (n = 93)		Seronegative (n = 1240)				
	N	%	N	%	n	%	OR*	95% CI	P-value
Dysgeusia	42	3.2	20	22.2	22	1.8	15.8	8.2–30.4	P < 0.01
Anosmia	84	6.3	29	32.2	55	4.4	10.2	6.1 – 17.2	P < 0.01
Myalgia	260	19.5	47	52.2	213	17.2	5.2	3.4–8.2	P < 0.01
Fever	87	6.5	21	23.3	66	5.3	5.4	3.1–9.4	P < 0.01
Dyspnoea	102	7.7	21	23.3	81	6.5	4.4	2.5–7–5	P < 0.01
Cough	166	12.5	29	32.2	137	11.1	3.8	2.4–6.2	P < 0.01
Fatigue	231	17.4	32	35.6	199	16.1	2.9	1.8–4.6	P < 0.01
Chest pain	203	15.3	27	30.0	176	14.2	2.6	1.6–4.2	P < 0.01
Diarrhea/abdominal pain	248	18.6	30	33.3	218	17.6	2.3	1.5–3.7	P < 0.01
Headache	580	43.6	55	61.1	525	42.3	2.1	1.4–3.3	P < 0.01
Odynophagia	296	22.3	30	33.3	266	21.5	1.8	1.2–2.9	P < 0.01

* OR (Odds ratio), Reference category: absence of the specific symptom.

We found a low proportion (18.9 %) of asymptomatic cases. However, a recent systematic review and meta-analysis showed that the proportion of asymptomatic patients could vary from 1.4 % to 78.3 %, with a weighted pooled average of 25 % (95 %CI: 16–38) (Alene et al., 2021). The low proportion of asymptomatic cases could also be explained by a selection bias, in the sense that people who have had symptoms could have been more inclined to accept the study to themselves or their children.

We had a significant proportion of rejection to the study invitation (56 %); our fieldwork was during the city lockdown period, which could have discouraged many people from receiving visits. However, this figure is not significantly different from other seroprevalence studies (Bendavid et al., 2021; Pollán et al., 2020).

We found a significantly lower prevalence of comorbidities (self-reported) than the last National Health Survey, which used biometric tests (Departamento de Epidemiología, 2017). This misclassification bias could explain the lack of association between comorbidities and seroconversion. But also, the presence of chronic conditions may be more related to adverse outcomes than the risk of infection.

Table 4
Estimation of Infection Fatality Ratio COVID-19, Santiago June 2020.

Population*	6382,709	
Registered deaths**	4351	
Case Fatality Rate**	2.33	
Seroprevalence (%)	Crude	Adjusted***
	6.79 %	4.10 %
	(CI 95 % 5.5–8.3)	(CI 95 % 3.11–5.28).
Estimate number of infected cases	433,386	261,691
Infection fatality Ratio %	1.00 %	1.66 %
	(CI 95 % 0.97–1.03)	(CI 95 % 1.61–1.71)

* (National Institute of Statistics Government of Chile, census 2018, projected population for June 2020).
** (Ministerio de Salud Gobierno de Chile, reported deaths by June 2020).
*** Wilson Score.

5. Conclusion

Detection of antibodies to SARS-CoV-2 in a random sample provides a more precise estimation of the infection's attack rate since the start of the pandemic. Therefore, information on this study complements officially reported cases that tend to be biased mainly due to the exclusion of asymptomatic and mild cases. Moreover, the exploration of the first stages of the disease could provide more insights for future pandemic outbreaks (Cereda et al., 2021).

The result also allowed us to explore the risk factors of SARS-CoV-2 infection, estimate the infection fatality rate, and better understand how the virus is spreading over time in a large city. Additionally, it provides insights from the pandemic's accelerated progression during the first wave in a country like Chile, where the virus was introduced at the beginning of the respiratory viruses' peak season. Our results demonstrated a high proportion of susceptible individuals in the city after the SARS-CoV-2 first wave, allowing the succession of future epidemic waves, until natural herd immunity or high effective coverage vaccination is obtained.

Disclaimer

The views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2022.100606.

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