COVID-19 Seropositive Rates between the Waves, Israel

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ABSTRACT

Background: Israel has experienced four waves of coronavirus disease-2019 (COVID-19) infection since late February 2020, with lockdown and other measures employed to contain infection rates. In cooperation with the Israel Ministry of Health, serological testing was conducted by all four health maintenance organizations (HMO) in order to estimate national infection rates and the proportion of previously undetected disease.

Objectives: To estimate the proportion of the population that was seropositive, identify factors associated with seropositive outcome, and approximate the proportion of residents that were asymptomatic.

Methods: Seroconversion rates (IgG) were measured in a representative sample of over 17,000 members of Maccabi Healthcare Services. Direct standardization was used to estimate the seropositive rates for COVID-19 infection for members of the HMO. Rates were adjusted for sensitivity and specificity of the testing products used. In addition to blood sampling, respondents were asked to complete a digital survey regarding potential exposures and symptoms experienced.

Results: It was estimated that 1.9% of the adult HMO population was seropositive 4 months after the first infected person was identified in the country. Seroconversion was associated with travel abroad and exposure to infected individuals. Loss of smell and taste, fever, cough, and fatigue are associated with infection. Of those found to be seropositive for COVID-19, 160 (59%) had a prior negative polymerase chain reaction (PCR) or no PCR test at all.

Conclusions: Adult seropositive rates of infection were low relative to other countries. The findings suggest that early initiatives to limit infection entry and spread were effective.

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One of the many challenges of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) since its discovery has been accurately measuring infection rates. Initial figures were based only on polymerase chain reaction (PCR) results, influenced by numbers tested, and biased toward symptomatic-only patients [1]. SARS-CoV-2 antibody testing has less than optimal sensitivity and specificity rates (between 30% and 91%). Sensitivity depends on how soon after infection the test is performed and whether both IgG and IgM are tested [2]. While it became apparent early on that people infected with coronavirus disease-2019 (COVID-19) could be asymptomatic, particularly among younger age groups, it has been difficult to determine what proportion of the infected population are asymptomatic. Estimates have ranged from 3–67% [3].

In addition to these challenges, most countries have used various levels of lockdown strategies to reduce infection rates, resulting in fluctuating infection rates [4,5]. The source and consequent characteristics of the infected population in each wave can vary. Like in most other countries, the first wave of infection in Israel, which started at the end of February 2020, was brought by citizens returning from travel abroad [6]. At its peak at the end of March 2020, 738 new cases per day were diagnosed (PCR positive) [7]. The number of new cases dropped in response to the first lockdown in mid-March and by the middle of May, there were less than 20 new cases identified per day [7]. However by the end of May, the number of new cases started to rise again, reaching a second peak of just over 9000 new cases per day by the end of September [7].

The current study was conducted in cooperation with the Israel Ministry of Health in July 2020 to estimate the infection rates within Israel. During this period, the daily number of new cases rose from an average of 700 in the first week to almost 1700 by the fourth week of the study period (maximum 2048 on 27 July 2020) with a total of 64,000 new cases in Israel from the start of the pandemic to the end of the study period [7].

Community healthcare services are provided to all citizens in Israel by four HMOs. Maccabi Healthcare Service is the second largest HMO in Israel, responsible for the care of over 2.5

million members (a quarter of Israel's population). The HMO maintains a database of demographic and medical data of all its members, including all laboratory results. PCR testing during the first wave was limited by the Ministry of Health policy to test only symptomatic patients and referral from a physician. Our concern was that infection rates may be higher secondary to under-testing and asymptomatic patients. The study objective was to measure seropositive rates in the HMO to determine whether the infection rate among HMO members and estimate the proportion of otherwise undetected cases.

PATIENTS AND METHODS

As part of an initiative of the Israel Ministry of Health to conduct serology testing on a representative sample of the Israeli population, every municipal area, town, and city, which we refer to as target sites, was assigned to one of 31 homogenous strata based on age, sex, socioeconomic status, and proportion of minority population (Orthodox Jew and Arab) distribution. The nationwide study sample was based on a sample of target sites selected from each stratum. Based on the relative proportion of citizens registered with each HMO for each target site, age and sex quotas were developed by the Ministry of Health for each target site for each HMO. Maccabi Healthcare Services was asked to test 17,800 members in 53 target sites. Members of all HMOs who visited a service branch at one of the target sites between 28 June 2020 and 27 July 2020 for the purposes of getting a blood test for any reason were invited to participate. Blood samples were sent for serology analysis for all members who agreed to participate. Blood samples were evaluated using the CE-labeled SARS-CoV-2 IgG kit with nucleoprotein-based antigen on the Architect i2000SR Analyzer (Abbott, Abbott Park, IL, USA). Positive blood samples (≥ 1.4 S/C) were followed using a chemoluminescence immunoassay (Diasorin©, DiaSorin, Italy) to confirm initial results (≥ 15 AU/ml). Members who agreed to participate were sent a link to a short questionnaire asking about potential exposure, prior PCR testing and outcome, and flu-like symptoms experienced in the last few months. The study was approved by the internal review board of Maccabi Healthcare Services and the Ministry of Health.

Our data are the result of all testing and survey responses by members of Maccabi Healthcare Services, age 20 years and older. The proportion of members under the age of 20 years participating in the study was too low to be included in the analysis. We used direct standardization to estimate the expected number of positive members within each stratum in Maccabi Healthcare Services and estimated the overall number of positive Maccabi members (Mpos) as the sum over the strata. The variance of the estimated value Mpos was calculated as the variance of the weighted sum of the independent components. On the assumption that the tests were independent, estimations were corrected for sensitivity and specificity of the two tests reported by the companies that developed the respective tests and were combined in the following manner: sensitivity=sensitivity of test 1*sensitivity of test 2; specificity=specificity test 1+(1-specificity test 1)*specificity test 2. The estimated number of COVID-19 diseased members in the HMO (True_ill) was calculated from the equaltions: Mpos=True_Ill * sensitivity + (Total_HMO – True_ill)(1-specificity); the estimated number of COVID-19 negative members was the complement of True_ill to Total_HMO. We were unable to provide confidence intervals because the variance and covariance of the sensitivity and specificity of both steps are unknown.

For the survey results, univariate association between potential exposures and flu-like symptoms and seroconversion outcome were analyzed using Pearson's chi-square analysis. Multivariate analyses were conducted using a hierarchical model. Demographic variables (age, gender, population group, and socioeconomic status) were entered in the first block and all flu-like symptoms were added in the second block of a logistic regression model. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

In all, 160 of 15,459 members age 20 years and older who were tested for the presence of SARS-CoV-2 antibodies were found to be seropositive. Demographic characteristics by test status are presented in Table 1. Females, members age 60 years and older, and Orthodox Jews were over-represented in the tested population. After direct standardization, 19,106 ± 1680 Maccabi Healthcare Services members were estimated to be seropositive. The crude rate of seropositive members was 1.05 per 100 members and the adjusted rate was 1.23 per 100 members. The seropositive rate, after adjustment for the sensitivity/specificity of the IgG tests, was 1.91 per 100 members.

Of the study population, 89% of 15,459 completed the survey. No differences were found for age and gender distribution by respondent status. Secular Jews were more likely to complete the survey (90%) compared to minority groups (86%) ($P < 0.001$), as were participants with high socioeconomic status (94%) compared to those of middle (88%) or low socioeconomic status (86%) ($P < 0.001$).

With regard to those who reported having been overseas 2.3% (n=1379) were found to be seropositive, compared to 0.9% of those that had not (n=12,448) ($P < 0.001$). Similarly, those reporting having been exposed at least once to a person with confirmed COVID-19 infection were more likely to be seropositive (9.3% of 782 members, compared to 0.5% of 13,045 members, $P < 0.001$). Members who reported being required to go into isolation were also more likely to be found seropositive (6.5% of 1447 members compared to 0.4% of 12,380 members, $P < 0.001$). Members who had been PCR tested were more likely to be seropositive (4.9% of

Table 1. Demographic characteristics of members of Maccabi Healthcare Services, age > 20 years, by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies (IgG) testing status, July 2020, Israel

Characteristic	Category	Tested for antibodies		Total population*	
		N	%	N	%
Age	20–29	2285	14.8	307,578	19.9
	30–39	2675	17.3	289,469	18.7
	40–49	2801	18.1	314,028	20.3
	50–59	2844	18.4	264,233	17.1
	60–69	2708	17.5	193,192	12.5
	70+	2146	13.9	178,901	11.6
Sex	Male	5895	38.1	736,400	47.6
	Female	9564	61.9	811,001	52.4
Population group	Orthodox Jew	1248	8.1	109,729	7.1
	Secular Jew	13,533	87.5	1,355,122	87.6
	Arab	678	4.4	85,550	5.3
Target site size	Small	855	5.5	91,435	5.9
	Medium	5010	32.4	354,313	22.9
	Large	9594	62.1	1,101,635	71.2
Socioeconomic status	Low	3074	19.9	298,806	19.3
	Middle	7459	48.4	779,507	50.5
	High	4894	31.7	466,232	30.2

*Members of Maccabi Healthcare Services

2229 members compared to 0.4% of 13,230 members, $P < 0.001$). Of those members who had also been PCR tested (1494), 91.6% were negative for both PCR and serology tests, 4.4% were found positive for both tests, 2.3% were found PCR positive only and 1.7% found seropositive only. Another 69 members were found to be seropositive but had never been PCR tested.

In total, 31% of respondents reported experiencing at least one symptom in the last few months: 12% sore throat, 11% cough, 5% fever, 5% shortness of breath, and 3% loss of smell/taste. Of those with no reported symptoms, 0.4% were seropositive compared to 2.3% among those with at least one symptom ($P < 0.001$). Symptoms associated with a seropositive result were as follows: loss of taste/smell, fever, cough, shortness of breath, and sore throat [Table 2]. When each of the symptoms was entered into a hierarchical model, including demographic variables, shortness of breath was no longer found to be associated with having a seropositive result [Table 2]. Members who reported having had a sore throat were less likely to be seropositive after controlling for demographic variables [Table 3].

Table 2. Reported flu-like symptoms by seropositive status, respondents from Maccabi Healthcare Services, age > 20 years, July 2020, Israel

Symptom	Symptom present		Symptom absent		Chi-square	*P* value
	N	%	N	%		
Loss of sense of taste/smell	378	16.9	13,328	0.6	965	< 0.001
Fever	718	7.0	13,053	0.7	261	< 0.001
Cough	1494	3.8	12,257	0.7	126	< 0.001
Shortness of breath	683	3.1	12,999	0.9	29	< 0.001
Sore throat	1616	2.0	12,087	0.9	16	< 0.001

Table 3. Flu-like symptoms associated with seropositive result; logistic regression model, respondents from Maccabi Healthcare services, age > 20 years, July 2020, Israel

Characteristic	Category	N	Odds ratio	95% confidence interval
Age	20–29	1980	2.21	1.04–4.70
	30–39	2360	1.06	0.46–2.41
	40–49	2435	1.63	0.75–3.56
	50–59	2418	2.19	1.02–4.68
	60–69	2339	1.64	0.73–3.56
	70+	1809	1	
Sex	Male	5075	2.17	1.54–3.07
	Female	8266	1	
Population group	Orthodox Jew	1024	9.62	3.46–26.74
	Secular Jew	11,766	1.62	0.56–4.67
	Arab	551	1	
Socioeconomic status	Low	2541	2.51	1.38–4.57
	Middle	6356	1.30	0.76–2.21
	High	4444	1	
Loss of taste/smell	No	12,979	1	
	Yes	362	21.60	13.20–33.60
Fever	No	12,651	1	
	Yes	690	3.65	2.23–5.89
Cough	No	11,917	1	
	Yes	1,424	1.79	1.08–2.98
Shortness of breath	No	12,693	1	
	yes	648	0.94	0.51–1.73
Sore throat	No	11,801	1	
	Yes	1540	0.52	0.30–0.89

DISCUSSION

We estimated that 1.9% of the adult HMO population was seropositive after the first wave of infection in July 2020. Similar adjusted prevalence rates were found in May 2020 in Denmark [8]. Other countries reported higher seropositive rates. In May 2020 a national sample in Spain reported a 5% prevalence of seroconversion [9] and 23% in a study of residents living in north eastern Italy in May [10]. Variance between the countries may be attributed to when the first cases were identified. In Spain and Italy the first cases were identified in December. Differences in population age distribution and differing speed of response and scope of strategies were implemented to curb the spread of the virus. Israel was quick to close its borders (within a fortnight of the first case reported) and implement a national lockdown (within one month) [6]. As found in other studies [9], seropositive rates were higher among those with known exposure risks (travel overseas and exposure to people with confirmed infection).

We found that of the 160 members who tested seropositive, 94 (59%) had a PCR negative result or had not been tested at all. These findings suggest that a significant proportion of the population that is infected with SARS-CoV-2 virus in Israel may be going undetected. However, PCR testing was not widely conducted in the first wave, secondary to testing kit availability and access to testing sites. While the estimates of undetected disease vary widely, a meta-analysis of 79 studies suggested that 20% of all infected, are asymptomatic [3].

Although the least prevalent in presentation, the symptom most strongly associated with being sero-positive was the loss of smell or taste. Agyeman and colleagues [11], in a meta-analysis measuring olfactory and gustatory dysfunction among COVID-19 patients, found a pooled proportion of 41% and 38%, respectively. As in other studies, cough, fever, and fatigue have been associated with SARS-CoV-2 infection [12,13]. While patients reporting a sore throat have also been implicated in some studies [14,15], we found that, after controlling for covariates, members with a sore throat were less likely to be seropositive than those who did not report the symptom.

A major limitation of this study is the potential for bias inherent in inviting only those who presented to an HMO clinic for a blood test to participate. This population is characteristically older and more likely to present with other illnesses. Furthermore, our study was based on IgG testing only.

CONCLUSIONS

After the first wave of infection, 1.9% of our members were seropositive for SARS-CoV-2 infection. Risk factors for infection, such as travel abroad and exposure to the infected, were associated with increased infection rates. Loss of smell/taste, fever, cough, and fatigue were the symptoms associated with infection. As of the summer 2021, Israel was in its third and largest wave of infection. The rapidly changing make-up of the virus and populations at risk require ongoing evaluation.

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Flattery won't hurt you if you don't swallow it.
Kin Hubbard (1868–1930), American cartoonist, humorist, and journalist