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Community seroprevalence and risk factors for SARS-CoV-2 infection in different subpopulations in Vellore, India, and their implications for future prevention

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ABSTRACT

Objectives: The aim of this study was to inform public health policy decisions through the assessment of IgG antibody seroprevalence in the population and the risk factors for SARS-CoV-2 infection.
Methods: The seroprevalence of IgG antibodies among different subpopulations at the end of the first and second waves of the pandemic was estimated. Various risk factors associated with seropositivity, including sociodemography, IgG antibodies against endemic human coronavirus, and vaccination status, were also assessed.
Results: For all 2433 consenting participants, the overall estimated seroprevalences at the end of first and second waves were 28.5% (95% CI 22.3–33.7%) and 71.5% (95% CI 62.8–80.5%), respectively. The accrual of IgG positivity was heterogeneous, with the highest seroprevalences found in urban slum populations (75.1%). Vaccine uptake varied among the subpopulations, with low rates (< 10%) among rural and urban slum residents. The majority of seropositive individuals (75%) were asymptomatic. Residence in urban slums (OR 2.02, 95% CI 1.57–2.6; $p < 0.001$), middle socioeconomic status (OR 1.77, 95% CI 1.17–2.67; $p = 0.007$), presence of diabetes (OR 1.721, 95% CI 1.148–2.581; $p = 0.009$), and hypertension (OR 1.75, 95% CI 1.16–2.64; $p = 0.008$) were associated with seropositivity in multivariable analyses.
Conclusion: Although considerable population immunity has been reached, with more than two-thirds seropositive, improved vaccination strategies among unreached subpopulations and high-risk individuals are suggested for better preparedness in future.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused an unprecedented public health challenge in India, with over 32 million confirmed cases and over 400 000 deaths as of the end of August 2021 (JHU CSSE, 2021). India imposed a universal, strict

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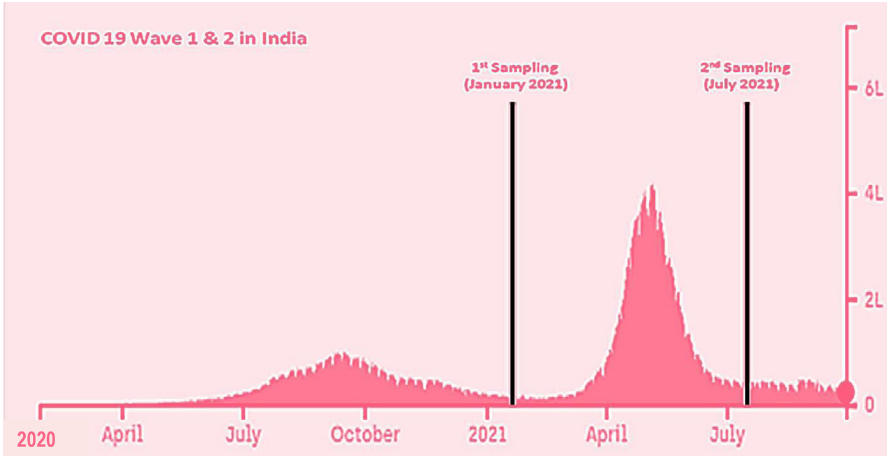

Figure 1. COVID-19 peaks in India during wave 1 and wave 2, with two sampling periods (modified from Covid19India.org, 2021). The *x*-axis represents the timeline in months and the y-axis gives the number of infected cases in lakhs. The study samples at the end of wave 1 were collected in January 2021, and those at the end of wave 2 were collected in July 2021.

lockdown, which began in March 2020 as the pandemic started, and lasted for several months.This provided a window of opportunity to prepare the healthcare system and helped in flattening the epidemic curve and reducing mortality. After the first wave — by the end of January 2021 — a low case fatality rate (CFR) of 1.4% was reported, with 154, 428 deaths among the 10.76 million cases (Purkayastha et al., 2021). However, the second wave, which was largely caused by the delta variant, caught the nation uninformed with its rapidity and magnitude. A much higher number of cases was reported during the second wave when compared with the first. India's most recent serosurvey, which is yet to be published, shows that two-thirds of the Indian population carries antibodies against COVID-19 either because of prior exposure to the virus or vaccination (Anand et al., 2021).

A serosurvey from 70 districts across India conducted between December 2020 and January 2021 reported a population-weighted seroprevalence of 24.1% (Murhekar et al., 2021). However, a cross-sectional study conducted among people living in urban slums around the same time reported a much higher seroprevalence of 57.9% (George et al., 2021). The extent of the spread of infection into the general population has been underestimated, because the majority of the infections are presymptomatic or asymptomatic (Wuet al., 2020). Indeed, there is heterogeneity in the transmission dynamics, with subsequent seroprevalence among the population. A vast majority (90–99%) of transmission in the community is reported to be asymptomatic (George et al., 2021; Kshatriet al.,2021). Such asymptomatic cases complicate and prevent the reliable estimation of transmission and planning of tracking strategies for containing the spread of infection. Nevertheless, asymptomatic infections contribute substantially to community transmission and population immunity (Oran et al., 2020). Based on the seroprevalence and proportion of asymptomatic transmission in the community, the estimated infection fatality rate (IFR) in India is reported to be 0.04%, which is low when compared with the reported IFR of 0.31% from high-income countries like the USA over the same period (Laxminarayan et al., 2021; Pei et al., 2020).This could be due to the much younger median age of the Indian population. Whether factors such as pre-existing seasonal coronavirus antibodies offer any partial cross-protection, leading to milder or asymptomatic disease, is unclear (Anderson et al., 2021; Song et al., 2021). With the number of cases dropping significantly, and the subsequent return to near normalcy occurring in most states, studying the current seroprevalence and vaccination rates in the community could help inform future response and prevention strategies.

This cross-sectional study assessed the seroprevalence of IgG antibodies to SARS-CoV-2 infection in Vellore district of Tamil Nadu, and compared the same among participants across four different subpopulations: urban slum, urban affluent, rural areas, and healthcare workers (HCW). IgG seropositivity was investigated in the four subgroups over two time periods — the end of wave 1 (January 2021) and the end of wave 2 (July 2021). Various risk factors associated with SARS CoV-2 infection were also evaluated — IgG antibodies against two other endemic strains (NL63 and OC43) of human coronavirus (HCoV) to evaluate possible cross-protection against SARS-CoV-2, and vaccination status at the end of wave 2. The seropositivity rates at the end of wave 1 and wave 2, combined with the vaccination status at the end of wave 2 for the four subgroups will provide valuable insight into the level of population immunity developed against SARS-CoV-2 infection. Based on this information, subgroups that warrant attention can be targeted for future prevention strategies.

Methods

Study design and participants

This cross-sectional serosurvey was performed among the permanent residents of Vellore district, Tamil Nadu in south India over two time periods: January 2021, at the end of wave 1; and July 2021, at the end of wave 2 (Figure 1). Vellore district, with six taluks (Vellore, Katpadi, Gudiyattam, Anaicut, Pernambet, and KV Kuppam), had 57% of the population living in rural areas and 43% in urban areas, according to the 2011 census. Villages in each of the taluks were randomly selected for the survey. Additionally, two different subpopulations in the urban area of Vellore — namely urban slums and urban affluent areas — were surveyed separately. The survey team randomly chose willing participants of all age groups from each sampling area. At least 30 individuals were enrolled from each random location, with a total of 250 individuals enrolled from each subpopulation. Healthcare workers who were willing to take part in the study were recruited from among doctors, nurses, paramedical staff, and support staff of Christian Medical College (CMC), Vellore.

Procedure

Individuals who agreed to participate answered an interview-based semi-structured questionnaire after providing written informed consent or assent, as applicable. The questionnaire comprised questions relating to sociodemographic variables, including age, gender, and socioeconomic status, comorbidities, respiratory symptoms or fever in the 6 months prior to enrolment in the study, hospitalization for COVID-19 since March 2020, and mask usage in the workplace and public places. Vaccination status by the second wave was also included in the questionnaire at the end of wave 2. After administration of the questionnaire, 5 ml blood samples were drawn from the participants and transported in a sample carrier box with gel packs to the laboratory, where they were centrifuged. Plasma samples were collected and stored at −70°C until IgG ELISA testing was carried out.

SARS-CoV-2 serological testing was performed using the SCoV-2 Detect™ IgG ELISA kit (InBios International, Seattle, USA), an indirect ELISA that detects the presence of IgG antibodies against SARS-CoV-2 S proteins in human serum. Incurred sample reanalysis values above 1.1 were considered positive. The specificity of the SCoV-2 Detect™ IgG ELISA kit is reported to be 97.6% (Deshpande et al., 2021). Additionally, Recombivirus™ Human Anti-Human Coronavirus NL63/OC43 Spike 1 IgG ELISA Kit (Alpha International Diagnostics, USA) was used on human serum or plasma for quantifying IgG antibody specific for the S1 subunit of the spike protein of two other HCoV viruses (NL63 [alpha coronavirus] and OC43 [beta coronavirus]), which are etiologic agents for human endemic respiratory disease. Incurred sample optical density values above 3.5 were considered positive.

The primary outcome assessed was seropositivity (seroprevalence) to SARS-CoV-2 antibodies overall and in the different subgroups. The secondary outcomes included the various factors associated with seropositivity, symptomatic and asymptomatic infection, seropositivity to HCoV, and vaccination status.

The study was approved by the Institutional Review Board and Ethics Committee of CMC Vellore (number: 13165).

Statistical analysis

A target sample size of 1000 participants was estimated for each time point to detect differences by subpopulation (approximately 2000 participants for both waves), assuming a seroprevalence in the general population of 20% at the end of wave 1, with an α error of 0.05 and power of 80%, to detect at least a 12% difference in seroprevalence; this gave a sample size of 225 per subpopulation. In order to account for a 10% loss to follow-up from different subpopulations, 250 samples were targeted in each sampling period. The eventual sample was 2433 for both waves (1228 for wave 1 and 1205 for wave 2), which was slightly higher than the target sample size and, hence contributed to an increase in power.

The summary measures of participants, seroprevalences, and odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated by subpopulation, time period, and participant characteristics. The seroprevalence estimates were calculated by subpopulation and previously known test performances. The overall seropositivity for each wave was weighted using the Vellore population. Post-stratification weighting was used to align the composition of the respondents' sampling fraction with the known distribution of the whole population's subgroup proportions, thereby reducing sampling error. Weights were computed based on the expected proportion of the population for each location.

The risk factors for seropositivity were assessed by univariate mixed-effects logistic regression analysis clustered by time period. A p-value less than 0.05 was considered statistically significant. Multivariate mixed-effects logistic regression analysis was performed to adjust for potential confounding factors and clustering effects. Statistically significant risk factors identified in univariate analyses were selected as variables for the multivariate analyses. Statistical analyses were performed using SPSS version 21 and Stata 16 (College Station, Texas, USA).

Results

In total, 2433 willing participants from four subpopulations — rural, urban slums, urban affluent, and healthcare workers — were included in the study. Samples were collected from these four subpopulations at the end of wave 1 in January 2021 and wave 2 in July 2021, to give a total of 756 samples from the rural subpopulation, 645 from the urban slum group, 534 from urban affluent residents, and 498 from healthcare workers. The sample population comprised 56.6% females with a mean age of 37 years (SD ± 17.5). Of the participants, 18.7% were less than 20 years old, 41.8% were aged 21–40 years, 28.7% 41–60 years, and 10.9% over 60 years. The most commonly reported comorbidities were diabetes (11.1%), hypertension (10.7%), chronic obstructive pulmonary disease (COPD)/asthma (2.1%), and heart diseases (1.4%). The subpopulation-specific baseline demographic characteristics, including education, occupation, and socioeconomic class, are summarised in Table 1.

In total, 588 participants (24.2%) reported symptoms suggestive of acute respiratory infection or fever during the 6 months preceding sample collection. Symptoms were reported by 46.2% of healthcare workers, 28.3% of the urban affluent group, 16.1% of the urban slum residents, and 13.4% of the rural group. Overall reported symptom prevalences among participants were similar during wave 1 (27.6%) and wave 2 (20.7%). Among the SARS-CoV-2-positive participants, 30.7% and 22.5% were symptomatic during wave 1 and wave 2, respectively. Notably, only 4.1% of the study population had symptomatic infection requiring hospitalisation, most of which were for infection control purposes. In public places, cloth masks remained the most common type of mask used (58.1%), followed by surgical masks (35.1%), and N95 (6.8%), respectively. Other human coronavirus antibodies (NL63, OC43) were detected in almost all the participants: 99.6% of participants who were seronegative for SARS-CoV-2 and 100% of the participants who were seropositive for SARS-CoV-2 antibodies.

The overall weighted prevalence of SARS-CoV-2 antibodies adjusted for the population of Vellore was 28.5% (95% CI 22.3–33.7%) at the end of wave 1 and 71.6% (95% CI 62.8–80.5%) at the end of wave 2. At the end of wave 1, seroprevalence was found to be highest among individuals from urban slums (43.7%; 95% CI 38.1–49.4%), followed by healthcare workers (31.6%; 95% CI 26.5–37.0%), rural (26.8%; 95% CI 22.9–32.2%), and urban affluent (24.7%; 95% CI 20.0–30.0%). At the end of wave 2, seropositivity was highest among healthcare workers (95.5%; 95% CI 91.3–98.0%), with a high vaccination rate of 91.6% (95% CI 86.5–95.2%). The urban affluent had similarly high seropositivity of 85.4% (95% CI 80.2–89.6%), with 65.7% (95% CI 59.3–71.7%) of the participants being vaccinated. The urban slums and rural areas also had high seroprevalences of 75.1% (95% CI 70.2–79.7%) and 67.8% (95% CI 63.1–71.9%), respectively, with vaccination rates of only 6.6% (95% CI 4.2–9.8%) and 10.4% (95% CI 7.7–13.5%), respecitvely. The community seropositivities for IgG at the end of waves 1 and 2 for the four different subpopulations are shown in Table 2 and Figure 2. The seroprevalences and vaccination rates for the different subpopulations at the end of wave 2 are shown in Figure 3. Seropositivities according to different characteristics and time periods are shown in Table 3. There was a slight shift in seropositivity noted among older age groups (over 60 and 40–60) in wave 1 to younger age groups (20–40 years and 1–20 years) in wave 2. This may be because of the larger proportion of the population who became infected during the second wave, thus reflecting the country's younger population.

Mixed-effects logistic regression analysis of factors associated with seropositivity was adjusted for the clustering of time peri-

Table 1
Demographic characteristics

Demographics	Categories	Total $N = 2433$; n (%) or n/N (%)	Rural $N = 756$; n (%) or n/N (%)	Urban slum $N = 645$; n (%) or n/N (%)	Urban affluent $N = 534$, n (%) or n/N (%)	Healthcare workers $N = 498$, n (%) or n/N (%)
Age	< 20 years	454 (18.7)	159 (21)	198 (30.7)	92 (17.2)	5 (1)
	21–40 years	1017 (41.8)	220 (29.1)	198 (30.7)	181 (33.9)	418 (83.9)
	41–60 years	698 (28.7)	253 (33.5)	185 (28.7)	188 (35.2)	72 (14.5)
	> 60 years	264 (10.9)	124 (16.4)	64 (9.9)	73 (13.7)	3 (0.6)
Gender	Male	1,055(43.4)	273 (36.1)	255 (39.5)	298 (55.8)	229 (46)
	Female	1,378 (56.6)	483 (63.9)	390 (60.5)	236 (44.2)	269 (54)
Education	Illiterate	194 (8)	107 (14.2)	87 (13.5)	0 (0)	0 (0)
	Primary to high school*	1361 (55.9)	573 (75.8)	517 (80.2)	213 (39.9)	58 (11.6)
	Graduate	878 (36.1)	76 (10.1)	41 (6.4)	321 (60.1)	440 (88.4)
Occupation	Professional	514 (21.1)	8 (1.1)	2 (0.3)	126 (23.6)	378 (75.9)
	Semi-professional	231 (9.5)	28 (3.7)	14 (2.2)	107 (20)	82 (16.5)
	Skilled worker	528 (21.7)	272 (36)	116 (18)	102 (19.1)	38 (7.6)
	Unskilled/daily wage laborer	174 (7.2)	89 (11.8)	85 (13.2)	0 (0)	0 (0)
	Housewife/unemployed/students	986 (40.5)	359 (47.5)	428 (66.4)	199 (37.3)	0 (0)
Socioeconomic class	Upper	313 (12.9)	0 (0)	0 (0)	116 (21.7)	197 (39.6)
	Middle	923 (37.9)	144 (19)	75 (11.6)	418 (78.3)	286 (57.4)
	Lower	1197 (49.2)	612 (81)	570 (88.4)	0 (0)	15 (3.0)
Comorbidities	Diabetes	271 (11.1)	93 (12.3)	82 (12.7)	83 (15.5)	13 (2.6)
	Hypertension	261 (10.7)	99 (13.1)	66 (10.2)	73 (13.7)	23 (4.6)
	COPD***/asthma	51 (2.1)	11 (1.5)	5 (0.8)	10 (1.9)	25 (5)
	CAD/heart disease	34 (1.4)	13 (1.7)	2 (0.3)	16 (3)	3 (0.6)
Presence of symptoms**		588 (24.2)	103 (13.4)	104 (16.1)	151 (28.3)	230 (46.2)
Symptomatic infection requiring hospitalization		99 (4.1)	0 (0)	6 (0.9)	18 (3.4)	75 (15.1)
Mask usage in public places	Cloth	1,414 (58.1)	606 (80.2)	584 (90.5)	164 (30.7)	60 (12)
	Surgical	855 (35.1)	150 (19.8)	57 (8.8)	300 (56.2)	348 (69.9)
	N95	164 (6.8)	0(0)	4 (0.6)	70 (13.1)	90 (18.1)
HCoV antibody positivity among SARS-CoV-2 +ve		391/391 (100)	81/81 (100)	136/136 (100)	73/73 (100)	101/101 (100)
HCoV antibody positivity among SARS-CoV-2 –ve		834/837 (99.6)	221/221 (100)	172/175 (98.2)	222/222 (100)	219/219 (100)

*< 12 years of formal education
**Suggestive of recent respiratory infection in the last 6 months
***COPD — chronic obstructive pulmonary disease

Table 2
Community seroprevalence and vaccination status in different subpopulations

Subpopulation	End of wave 1 (January 2021) ($N = 1228$)		End of wave 2 (July 2021) ($N = 1205$)			
	Serology IgG, n/N (%) or %	95% CI	Serology IgG, n/N (%) or %	95% CI	Vaccination status[#], n/N (%)	95% CI
Rural	81/302 (26.8)	22.9–32.2	307/454 (67.6)	63.1–71.9	47/454 (10.4)	7.7–13.5
Urban slum	136/311 (43.7)	38.1–49.4	251/334 (75.1)	70.2–79.7	22/334 (6.6)	4.2–9.8
Urban affluent	73/295 (24.7)	20.0–30.0	204/239 (85.4)	80.2–89.6	157/239 (65.7)	59.3–71.7
Healthcare workers	101/320 (31.6)	26.5–37.0	170/178 (95.5)	91.3–98.0	163/178 (91.6)	86.5–95.2
Overall weighted prevalence adjusted for Vellore population	**28.5**	**22.3–33.7**	**71.6**	**62.8–80.5**	20.3	0–46.7

n — seropositives, N — total number of participants sampled, CI — confidence interval
Received at least one dose of vaccine

ods (Table 4). Healthcare workers and individuals among the urban affluent showed 2.1 and 1.5 times higher odds for seropositivity, respectively, when compared with the rural population in the univariate analysis. However, these were not found to be significant in the multivariate analysis. People living in urban slums showed about two times higher odds for seropositivity compared with those living in rural areas in both univariate and multivariate analysis, with an OR of 2.02 (95% CI 1.57–2.60; $p < 0.001$). Middle socioeconomic class based on the modified Kuppuswamy scale (Kattula et al., 2016) showed higher odds for seropositivity when compared with upper class both in univariate analysis, with an OR of 1.40 (95% CI 1.05–1.86; $p = 0.024$), and in multivariate analysis, with an OR of 1.77 (95% CI 1.17–2.67; $p = 0.007$). Although skilled workers showed a 30% lower risk of seropositivity in univariate analysis when compared with professional workers, the difference was not found to be significant on multivariate analysis. Among the comorbidities, diabetes and hypertension showed 1.5 and 1.3times higher odds for seropositivity in univariate analysis, respectively, as well as in multivariate analysis, with ORs of 1.70 (95% CI 1.15–2.58; $p = 0.009$) and 1.75 (95% CI 1.16–2.64; $p = 0.008$), respectively. There was no significant difference in protection noted between the use of N95 masks and the use of cloth masks in public places. However, use of surgical masks showed slightly higher odds for seropositivity of 1.38 (95% CI 1.13–1.28; $p = 0.001$) compared with cloth masks in univariate analysis. This difference was not found to be significant on multivariate analysis. Smoking habits and alcohol consumption were not found to be potential risk factors for seropositivity. The presence of symptoms suggestive of recent respiratory infection in the past 6 months and close contact with confirmed cases were not found to be independent risk factors for COVID-19 infection. Close contact with confirmed SARS-CoV-2-positive cases was also insignificant.

Discussion

Our results revealed a high community seroprevalence of SARS-CoV-2 in Vellore, India and demonstrated variability in transmission dynamics and vaccine utilization across different subpopulations. The overall weighted seroprevalence for Vellore district increased almost three-fold from 28.5% at the end of wave 1 in Jan-

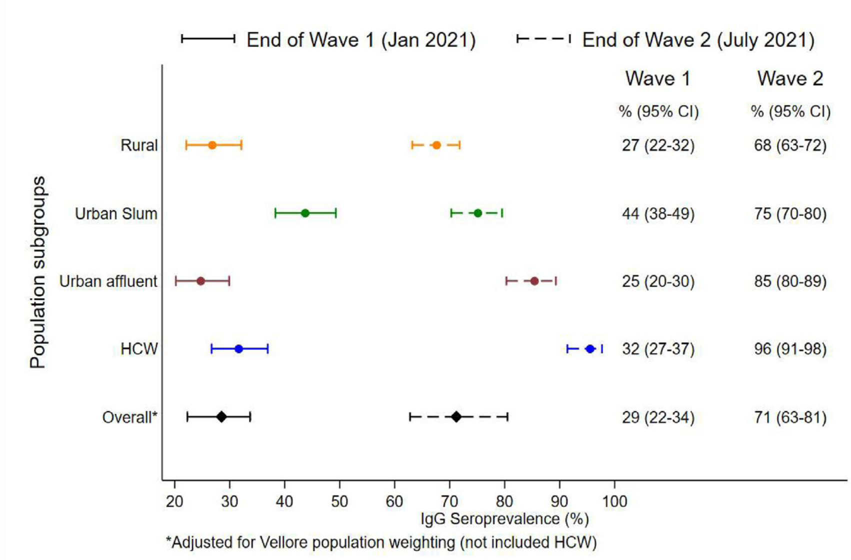

Figure 2. Visual representation of community seroprevalence, with 95% confidence intervals, in various subpopulations at the end of wave 1 and wave 2. The *x*-axis represents IgG seropositivity as a percentage, and the *y*-axis shows the various subpopulations.

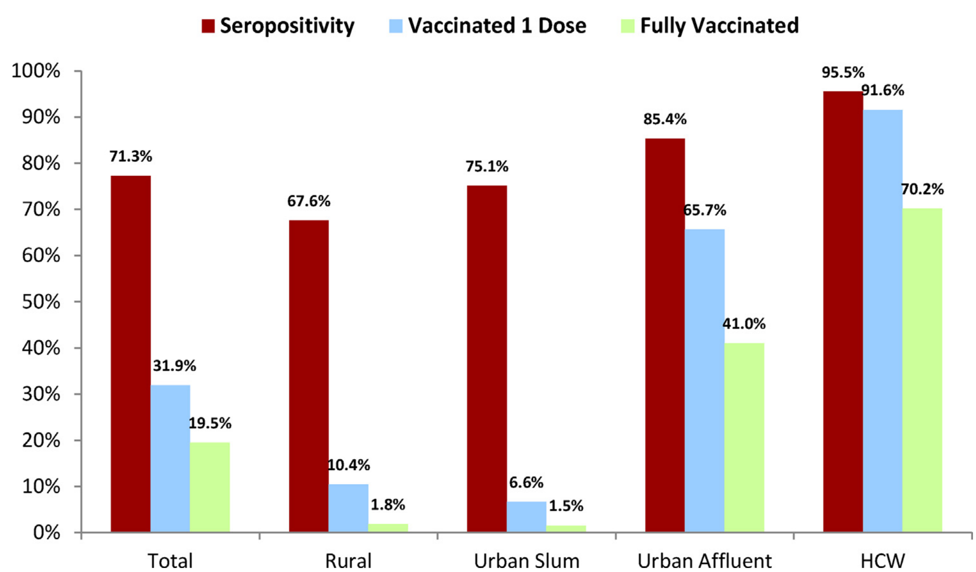

Figure 3. Seropositivity and vaccination status (participants who received one dose and those fully vaccinated) in the total study population and the various subpopulations. The rural areas and urban slums had the lowest vaccination levels – of 10.4% and 6.6%, respectively. Healthcare workers had the highest vaccination rate of 91.6%, followed by the urban affluent subpopulation, with a rate of 65.7%.

uary 2021 to 71.6% at the end of wave 2 in July 2021, suggesting that population immunity had been achieved. Transmission dynamics varied across different subpopulations. Seroprevalence was highest among the urban slum population, both at the end of wave 1 (43.7%) and wave 2 (75.1%). As transmission progressed, the lower seroprevalences at the end of wave 1 among the rural and urban affluent subpopulations increased rapidly at the end of wave 2 to 67.6% and 85.4%, respectively, and probably reached considerable population immunity. The high seroprevalences achieved among the healthcare workers and the urban affluent was perhaps largely due to the high vaccination rates of 91.6% and 65.7%, respectively. In contrast, it is likely that natural infections had caused the high seroprevalences among the rural and urban slum populations, since vaccination rates in these populations were low (10.4% and 6.6%, respectively). The majority of individuals (75%) positive for SARS-CoV-2 antibodies did not report any symptoms in the 6 months prior to sample collection, suggesting significant asymptomatic transmission in the community.

Achieving population immunity, either by natural infection or vaccination, is a major goal for future management of the pandemic (Papachristodoulou et al., 2020). Emerging data from different parts of India suggest that this goal has been reached or is not far off (George et al., 2021; Laxminarayan et al., 2021, Dyer et al., 2021). The heterogeneous nature of transmission dynamics in the community was evident by the end of wave 1. High seroprevalence was reported among the urban slum population, characterized by overcrowding, where social distancing and diligent personal hygiene, such as frequent hand washing, were virtually impossible (George et al., 2021; Malaniet al., 2021). The subsequent spread of infection among other subpopulations followed, resulting in a large second wave in India between April and June 2021 (Gupta et al., 2021). The majority of transmissions in India were due to the

Table 3
Seropositivity by characteristics and time period

Demographics	Categories	Seropositivity, n/N (%) End of wave 1	End of wave 2	Overall
Subpopulation	Rural	81/302 (26.8)	307/454 (67.6)	388/756 (51.3)
	Urban slum	136/311 (43.7)	251/334 (75.1)	387/645 (60.0)
	Urban affluent	73/295 (24.7)	204/239 (85.4)	277/534 (51.9)
	Healthcare workers	101/320 (31.6)	170/178 (95.5)	271/498 (54.4)
Age	< 20 years	75/237 (31.6)	162/217 (74.7)	237/454 (52.2)
	21–40 years	166/540 (30.7)	385/477 (80.7)	551/1017 (54.2)
	41–60 years	105/317 (33.1)	294/381 (77.2)	399/698 (57.2)
	> 60 years	45/134 (33.6)	91/130 (70.0)	136/264 (51.5)
Gender	Male	168/558 (30.1)	379/497 (76.3)	547/1,055 (51.8)
	Female	223/670 (33.3)	553/708 (78.1)	776/1378 (56.3)
Education	Graduate	161/534 (30.1)	307/344 (89.2)	468/878 (53.3)
	Primary to high school*	199/616 (32.3)	552/745 (74.1)	751/1361 (55.2)
	Illiterate	31/78 (39.7)	73/116 (62.9)	104/194 (53.6)
Occupation	Professional	94/332 (28.3)	170/182 (93.4)	264/514 (51.4)
	Semi-professional	31/109 (28.4)	111/122 (91.0)	142/231 (61.5)
	Skilled worker	71/214 (33.2)	222/314 (70.7)	293/528 (55.5)
	Unskilled/daily wage laborers	29/63 (46.0)	71/111 (64.0)	100/174 (57.5)
	Housewife/unemployed/student	166/510 (32.5)	358/476 (75.2)	524/985 (53.1)
Socioeconomic class	Upper	41/197 (20.8)	106/116 (91.4)	147/313 (47.0)
	Middle	188/554 (33.9)	319/369 (86.4)	507/923 (54.9)
	Lower	162/477 (34.0)	507/720 (70.4)	669/1197 (55.9)
Smoking habit	Smoker	14/38 (36.8)	0/0 (NA)	14/38 (36.8)
	Non-smoker	377/1190 (31.7)	932/1205 (77.3)	1309/2395 (54.7)
Alcohol Consumption	Alcohol consumer	14/41 (34.1)	2/2 (100.0)	16/43 (37.2)
	Non-consumer	377/1187 (31.8)	930/1203 (77.3)	1307/2390 (54.7)
Comorbidities	No comorbidities	301/989 (30.4)	749/976 (76.7)	1050/1965 (53.4)
	Diabetes	33/70 (47.1)	56/72 (77.8)	89/142 (62.7)
	Hypertension	28/70 (40.0)	54/65 (83.1)	82/135 (60.7)
	Asthma/chronic obstructive pulmonary disease	3/30 (10.0)	12/14 (85.7)	15/44 (34.1)
	CAD/heart disease	3/4 (75.0)	6/8 (75.0)	9/12 (75)
	Any two or more comorbidities	23/65 (35.4)	55/70 (78.6)	78/135 (57.8)
Presence of symptoms**	Yes	120/339 (35.4)	210/249 (84.3)	330/588 (56.1)
	No	271/889 (30.5)	722/956 (75.5)	993/1845 (53.8)
Close contact with confirmed cases	Yes	102/320 (31.9)	171/182 (94.0)	273/502 (54.4)
	No	289/908 (31.8)	761/1023 (74.4)	1050/1931 (54.4)
Mask usage in public places	Cloth	218/645 (33.8)	552/769 (71.8)	770/1414 (54.5)
	Surgical	148/473 (31.3)	333/382 (87.2)	481/855 (56.3)
	N95	25/110 (22.7)	47/54 (87.0)	72/164 (43.9)

*< 12 years of formal education
**Suggestive of recent respiratory infection in the last 6 months

prevalent delta variant (Sarkar et al., 2021; Adamoskiet al., 2021). However, a similar large second wave in Brazil was predominantly due to the gamma variant, with the delta variant only contributing a small proportion (De Souza et al., 2021; Singh et al., 2021). This evidence suggests that, although SARS-CoV-2 variants play a role in the transmission dynamics in the community, other factors such as overcrowding and personal hygiene play bigger roles.

For those living in the urban slum population, overcrowding was strongly associated with SARS-CoV-2 infection, with twice the risk for seropositivity on multivariate analysis when compared with the other subpopulations. Our study findings were similar to those of a multi-state serosurvey conducted by the Indian Council of Medical Research reporting the highest seroprevalence in urban slum areas, followed by urban non-slum and rural areas (Murhekar et al., 2021). Our observations that low and middle socioeconomic status and comorbidities such as diabetes mellitus and hypertension showed a higher risk for seropositivity in both univariate and multivariate analysis have been noted in other studies (Roy and Soumya, 2020; Royo et al., 2021). Since diabetes is an important risk factor for viral, bacterial, and fungal infections, presumably these emerging data suggest that there is an increased risk for SARS CoV-2 infection (Feehan et al., 2021; Mora et al., 2021).

The disease transmission among different age groups varied based on their exposure to infection at different time points during the pandemic. Our study found a shift in seroprevalence among the age groups between wave 1 and wave 2, which was similar to other observations (Laxminarayan et al., 2021; Miragliaet al., 2021). Among urban slum, rural, and urban affluent subpopulations, maximum seropositivity was seen in the 40–60 years and over 60 years age groups after wave 1, but at the end of wave 2 slightly higher seropositivity rates were seen in the 1–20 years and 20–40 years age groups. An age-stratified regional modelling study from France predicted that wave 2 would affect the middle-age and younger population more, which is in agreement with our observations (Roederer et al., 2021).

The vast majority of infections were asymptomatic. Among the individuals with SARS-CoV-2 antibodies, only 24.9% reported any symptoms during the recall period of 6 months. Several other studies from India and other parts of the world have reported similar high proportions of asymptomatic infection (Purkayastha et al., 2021; George et al., 2021; Feaster and Goh, 2020; Varghese and John, 2020). Although there is a possibility of recall bias, the high proportion of asymptomatic seroprevalence reported worldwide underscores the limitations of widely used syndromic surveillance for COVID-19. Asymptomatic transmission in the community coupled with the high exposure ratio undermines the utility of contact tracing and surveillance measures. Therefore, mitigation strategies targeting individuals with risk factors for severe disease, such as those with medical comorbidities and the elderly, might be more pragmatic and effective (Khan et al., 2021).

Table 4
Univariate and multivariate analysis of factors associated with seropositivity, adjusted for clustering effects of time periods

Demographics	Categories	Univariate odds ratio (OR) (95 % confidence interval)	p-value	Multivariate (adjusted) OR (95% confidence interval)	p-value
Subpopulation	Rural	(ref)		(ref)	
	Urban slum	1.95 (1.52–2.49)	< 0.001	2.01 (1.57–2.59)	< 0.001
	Urban affluent	1.51 (1.17–1.95)	0.002	0.95 (0.65–1.39)	0.786
	Healthcare workers	2.13 (1.64–2.78)	< 0.001	1.472 (0.93–2.33)	0.099
Age [a]	< 20 years	(ref)			
	21–40 years	1.13 (0.88–1.45)	0.342		
	41–60 years	1.10 (0.84–1.44)	0.482		
	> 60 years	0.93 (0.66–1.31)	0.695		
Gender [a]	Male	(ref)			
	Female	1.14 (0.95–1.36)	0.163		
Education	Graduate	(ref)			
	Primary to high school*	0.76 (0.63–0.93)	0.006	0.92 (0.66–1.29)	0.641
	Illiterate	0.62 (0.44–0.89)	0.009	0.77 (0.48–1.25)	0.295
Occupation	Professional	(ref)		(ref)	
	Semi-professional	1.13 (0.79–1.60)	0.516	0.85 (0.53–1.36)	0.496
	Skilled worker	0.70 (0.53–0.93)	0.012	0.72 (0.42–1.23)	0.223
	Unskilled/daily wage laborer	0.69 (0.47–1.04)	0.074	0.81 (0.43–1.53)	0.510
	Housewife/unemployed/student	1.81 (0.64–1.03)	0.089	0.86 (0.51–1.47)	0.584
Socioeconomic class	Upper	(ref)		(ref)	
	Middle	1.39 (1.05–1.86)	0.024	1.77 (1.17–2.67)	0.007
	Lower	0.90 (0.68–1.19)	0.471	1.04 (0.59–1.83)	0.900
Smoking habit[a]	Smoker	1.25 (0.64–2.45)	0.509		
	Non-smoker	(ref)			
Alcohol consumption[a]	Alcohol consumer	1.16 (0.61–2.21)	0.65		
	Non-consumer	(ref)			
Comorbidities	No comorbidities	(ref)		(ref)	
	Diabetes	1.46 (1.03–2.08)	0.034	1.72 (1.15–2.58)	0.009
	Hypertension	1.35 (0.94–1.93)	0.101	1.75 (1.16–2.64)	0.008
	Asthma/chronic obstructive pulmonary disease	0.56 (0.28–1.13)	0.104	0.49 (0.24–1.02)	0.056
	CAD/heart disease	2.21 (0.52–9.33)	0.281	2.46 (0.59–10.23)	0.216
	Any two or more comorbidities	1.19 (0.79–1.76)	0.395	1.46 (0.97–2.21)	0.073
Presence of symptoms**,[a]	Yes	1.09 (0.91–1.32)	0.329		
	No	(ref)			
Close contact with confirmed cases[a]	Yes	1.00 (0.82–1.22)	0.998		
	No	(ref)			
Mask usage (public places)	Cloth	(ref)		(ref)	
	Surgical	1.38 (1.13–1.28)	0.001	1.15 (0.89–1.47)	0.271
	N95	0.97 (0.67–1.39)	0.868	0.80 (0.52–1.23)	0.316

*< 12 years of formal education
**Suggestive of recent respiratory infection in the last 6 months
[a] This factor was not included in the multivariate analysis because it was not significant in the univariate analysis

The reported infection fatality rate for COVID-19 in India of 0.04% is lower than that reported from several other countries, which could be attributed to the young median age of the population (Laxminarayan et al., 2021; Pei et al., 2020; Wagner et al., 2021; Yang et al., 2021). Cross-protective immunity due to other human coronaviruses (HCoV) are postulated to be contributing to this lower-than-expected IFR (Huang et al., 2020). To answer this question, our study evaluated IgG antibodies against two endemic strains of HCoV (NL63 and OC43) to analyze possible cross-protection against the current SARS-CoV-2 infection. Almost 100% of participants were found to be positive for HCoV antibodies. Similar estimates of high antibody titres due to the acquisition of infection in early childhood are common (Hovi et al., 1979; Ukkonenet al., 1984). However, infection by endemic HCoV strains provides little cross-protection against SARS-CoV. After an acute infection with endemic HCoV, no neutralizing antibodies against SARS-CoV are produced (Che et al., 2005; Liang et al., 2013). Whether endemic HCoV infections will impact COVID-19 severity, and if there is variation in antibody responses between HCoV strains, remains to be studied.

The healthcare worker group had seropositivity of 31.6% at the end of wave 1, which was comparable to the community seroprevalence in Vellore, indicating that the nosocomial acquisition of infection was the same as acquisition of infection in the community if appropriate personal protective measures were taken. The seropositivity in this group rose to 95.5% at the end of wave 2, which can be attributed to the mandatory vaccination drive among healthcare workers. In our study, 91.6% of health workers were vaccinated. Good vaccination take-up was also found among the urban affluent, with a vaccination rate of 65.7% by the second sampling in July 2021.

Many factors have played a role in driving the massive second wave of COVID-19 in a diverse country like India. Firstly, a large proportion of asymptomatic transmission occurred in a huge, susceptible population of the country. This corresponded with the period after travel restrictions were relaxed following the first wave. It was further fuelled by mass gatherings for various religious festivals and election campaigns (Patel et al., 2021). Secondly, the highly prevalent delta variant may have contributed to the larger second wave. India failed to vaccinate the majority and thus take advantage of the flattened epidemiological curve achieved during the initial period through enforced social distancing and strict lockdown. There have been issues with vaccine supply and acceptance (Wouters et al., 2021). As of October 13, 2021, only 19.9% of India's 1.4 billion population were fully vaccinated (Hannah et al., 2020).

The major limitation of our study was that these data may not be representative of the rest of the country. However, observations from the nationwide serosurvey showed a similar seroprevalence, and hence this study adds value and provides deeper insight. The simple random sampling used in our study for convenience may have caused minimal estimation errors. This method was chosen as practical and feasible while apprehension among the general public relating to the COVID-19 pandemic posed a major hindrance to the willingness of individuals to participate in the study.

Our results have important implications for the planning of future health policies. The considerable population immunity achieved predominantly by natural infection and vaccination in certain subpopulations makes future large-scale epidemics less likely. Patients who have had natural infections have been reported to possess comparable immune protection to those who have been vaccinated (Lumley et al., 2021; Khoury et al., 2021). While extensive vaccine drives have their place, focused vaccination of susceptible populations among vulnerable groups in order to decrease morbidity and mortality should be a priority.

High seroprevalences also encourage most activities, including businesses, tourism, and education, to remain open. However, the benefits of a high seroprevalence can be thwarted by the emergence of SARS-CoV-2 variants. The virus has unusually long genomic RNA, with error-prone proofreading mechanisms, and continues to mutate during infections. Therefore, well-coordinated genomic surveillance for emerging SARS-CoV-2 variants remains important.

Conclusion

Our results confirm the high seroprevalence of SARS-CoV-2 in Vellore, and provide insights into the heterogeneity and various factors associated with transmission of infection. Our study also found that urban slum and rural subpopulations need to be targeted for preventive strategies because they have the lowest vaccination rates. Going forward, improved vaccination strategies among less accessible subpopulations, focusing particularly on high-risk individuals, are suggested for better preparedness. Additionally, a rational approach involving a single dose of vaccine for the majority who are already positive for antibodies and thus have natural immunity could be considered. The meaningful inferences drawn from our results can be utilized to target high-risk groups that warrant attention, and to be better prepared to address future challenges.

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Ethical approval

The study was approved by the Institutional Review Board of Christian Medical College, Vellore (IRB minute 13165, dated July 22, 2020).

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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