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Seroprevalence of COVID-19 infection in a rural district of Tamil Nadu: A population-based seroepidemiological study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) was a recent global pandemic of the era which posed a great challenge for the health care in terms of preventive, diagnostic and treatment dimensions. The seroprevalence rate of COVID IgG antibodies is very crucial in estimating the susceptibility of a particular area to the viral disease. In our study, we estimated the seroprevalence of COVID-19 in a rural area. **Aims and Objectives:** We aimed to estimate the seroprevalence of COVID-19 in a rural district of Tamil Nadu, 6 months after the index case. **Materials and Methods:** We conducted a cross-sectional study of 509 adults aged more than 18 years. From all the seven Taluks, two gram panchayats (administrative cluster of 8–10 villages) were randomly selected followed by one village through convenience. The participants were invited for the study to the community-based study kiosk set up in all the eight villages through village health committees. We collected sociodemographic characteristics and symptoms using a mobile application-based questionnaire, and we tested samples for the presence of IgG antibodies for severe acute respiratory syndrome coronavirus 2 using an electro chemiluminescent immunoassay. We calculated age-gender adjusted and test performance adjusted seroprevalence. **Results:** The age-and gender-adjusted seroprevalence was 8.5% (95% confidence interval [CI] 6.9–10.8%). The unadjusted seroprevalence among participants with hypertension and diabetes was 16.3% (95% CI: 9.2–25.8) and 10.7% (95% CI: 5.5–18.3), respectively. When we adjusted for the test performance, the seroprevalence was 6.1% (95% CI 4.02–8.17). The study estimated 7 (95% CI 1:4.5–1:9) undetected infected individuals for every reverse transcription polymerase chain reaction confirmed case. Infection fatality rate (IFR) was calculated as 12.38/10,000 infections as on October 22, 2020. History of self-reported symptoms and education were significantly associated with positive status ($P<0.05$). **Conclusion:** A significant proportion of the rural population in a district of Tamil Nadu remains susceptible to COVID-19. A higher proportion of susceptible, relatively higher IFR, and a poor tertiary health-care network stress the importance of sustaining the public health measures and promoting early access to the vaccine are crucial to preserving the health of this population. Low population density, good housing, adequate ventilation, limited urbanization combined with public, private, and local health leadership are critical components of curbing future respiratory pandemics.

Key words: Seroprevalance; IgG antibodies; Anti SARS-CoV2 assay; Reverse transcription polymerase chain reaction; Chemiluminescent immunoassay; Infection fatality rate

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared as a global pandemic by the World Health Organization on March 11, 2020.[1] Globally, more than 60 million confirmed cases of COVID-19, including 1,416,292 deaths, have been reported to the WHO as of November 26, 2020.[2] India has reported more than 9.2 million cases with more than

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with 135,223 deaths and Tamil Nadu – had 894,137 cases with 8512 deaths as of November 26, 2020.[3,4]

There has been substantial evidence that a large proportion of the people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are asymptomatic, but they can infect others. It has been reported based on an analysis of 21 published reports that asymptomatic cases could account from 5% to 80%.[5] It is crucial to recognize an infected person early and break the route of transmission to control COVID-19. However, in reality, they do not require or seek medical attention and contribute to the rapid spread of the disease.[6]

Hence, health authorities cannot totally rely on confirmed cases of COVID-19 detected by reverse transcription-polymerase chain reaction (RT-PCR) as it could potentially miss asymptomatic and pre-symptomatic infections for containment measures. To overcome this challenge, the WHO and others have recommended population-based seroepidemiological studies to generate data and to implement containment measures accordingly.[7]

These surveys also can give us an estimation of the proportion of the population still susceptible to the infection as it is assumed that antibodies provide immunity. Indian Council of Medical Research has conducted a nationwide serosurvey among 21 states and reported a population-weighted seroprevalence of 0.73% between May and June 2020,[8] while a hospital-based survey from Srinagar, Northern India has estimated gender-standardized seroprevalence of 3.6% in July 2020 and our study from one of the largest slums in Dharmapuri revealed a seroprevalence of 57% in September 2020.[9,10]

Government Dharmapuri Medical College has been providing curative and preventive health services through Rural Health centers to residents of Dharmapuri and nearby rural districts over a decade. Government Dharmapuri Medical College and Hospital also runs special programs for chronic diseases, disability rehabilitation, and alcohol de-addiction. Our grass root workers continued to do home visits to provide home care, monitor blood pressure and blood sugar, and to educate the community about COVID-19. However, we had stopped our mobile clinics to reduce the urban-rural transmission of infection. As there can be considerable variation in the seroprevalence based on geographical setting and density of the population, knowledge of seroprevalence in this community helps us to conduct a risk-benefit analysis of certain services like mobile clinics, which improves access to medical care at the cost of spreading the virus to the rural community. Hence, we designed a community-based cross-sectional study to estimate a seroprevalence in Dharmapuri district 6 months after the index case. We also hope that the findings of this study will help the health authorities in disease containment and add valuable data to researchers across the globe.

Aims and objectives

We aimed to estimate the seroprevalence of COVID-19 in a rural district of Tamilnadu, six months after the index case.

MATERIALS AND METHODS

According to 2011 census, Dharmapuri had a population of 113,218 with a sex-ratio of 1013 females for every 1000 males, much above the national average of 929.11 A total of 6759 were under the age of six, constituting 3470 males and 3289 females. Scheduled Castes and Scheduled Tribes accounted for 6.92% and 0.14% of the population, respectively.[11] The average literacy of the town was 77.08%, compared to the national average of 72.99%.12 The town had a total of 17136 households. There were a total of 26,943 workers, comprising 606 cultivators, 427 main agricultural laborers, 1052 in household industries, 22,566 other workers, 2292 marginal workers, 54 marginal cultivators, 77 marginal agricultural laborers, 213 marginal workers in household industries, and 1948 other marginal workers.[6,12]

Study design and sample size

We conducted a cross-sectional study of 509 adults aged more than 18 years. From all the seven Taluks, two gram panchayats (administrative cluster of 8–10 villages) were randomly selected followed by one village through convenience. The participants were invited for the study to the community-based study kiosk set up in all the eight villages through village health committees. We collected sociodemographic characteristics and symptoms using a mobile application-based questionnaire, and we tested samples for the presence of IgG antibodies for severe acute respiratory syndrome coronavirus 2 using an electro chemiluminescent immunoassay. We calculated age-gender adjusted and test performance adjusted seroprevalence.

We designed a cross-sectional seroepidemiological survey in Dharmapuri district based on the recommendation of the WHO as the most appropriate study design.[13] A serosurvey from a densely populated slum in Mumbai, India reported a seroprevalence 57%, and we assumed a seroprevalence of 30% (lower risk of transmission in rural areas compared to slums) in the rural district. We calculated a minimum sample size of 504 with 5% absolute and a design effect of 1.5.[14]

Ethical Committee Clearance was obtained from the Institutional Ethical Committee (Government Dharmapuri Medical College), wide reference no. 341/21-22/GDMCH-IEC dated August 20, 2020.

Data collection

Dharmapuri district consists of seven sub-districts which are further divided into gram panchayats which are village administrative units. From the seven sub-districts, we randomly chose two gram panchayats. In each gram panchayat, a village which is centrally located was chosen as a sampling unit based on convenience, and a kiosk was set up in one of the trusted community spaces in each village. Our community health workers invited people (adults ≥18 years) from houses to give blood samples. If a household refused to participate, then the next house was approached. In each cluster, mobilization continued until the desired sample size was achieved in each village. We aimed to include 63 adults from each of these villages, adding up to 126 in each sub-district.

We met with the village health committees and discussed the purpose of the study and enlisted their cooperation. Together with the community, we decided that kiosk-based recruitment of the participants was more practical due to strict restriction on the movement of the people by the state government. People were also apprehensive about the health team from cities visiting their homes and increasing the risk of transmission of the disease.

We recruited people after explaining the purpose of the study, took written consent, and then interviewed people with a questionnaire by a trained research coordinator who had previous training in data collection. An Epi-info 7.0™ mobile application-based tool was used to capture responses offline by the interviewer, and it was later downloaded for analysis.

The questionnaire contained questions about demographic information (age, gender, education, and comorbidities such as diabetes, hypertension, lung disease, and cancer), history of exposure to COVID-19 infection (history of being diagnosed as COVID-19 case, interaction and household contacts with persons with confirmed COVID-19), and any history of COVID-19 related symptoms a month before the survey. After the completion of the interview, our phlebotomists collected 5 ml of blood from each participant through venepuncture in a plain vacutainer. They transported it to BBH laboratory within 5 h, maintaining the cold chain.

Sample processing and analysis

The serum was separated and used to test for antibodies using the Elecsys anti-SARS-CoV2 assay, an electrochemiluminescent immunoassay using a recombinant protein representing the nucleocapsid (N) antigen for the determination of high-affinity antibodies (including IgG) against SARS-CoV-2.[15] This assay employs a cutoff index (COI) that is automatically calculated from two calibration standards – a COI of 1.0 or more is considered reactive/positive, and a COI ≤1.0 is reported as nonreactive/negative. The assay sensitivity and specificity were reported to be 97.2% (95.4–98.4) and 99.8% (99.3–100), respectively, in samples taken 30 days or more post symptom onset.[16] A unique identification number was used to link the interview information and laboratory results.

Statistical analysis

We used Statistical Package for the Social Sciences version 20.0 and STATA version 15.0 for statistical analysis. The frequency of characteristics of the survey participants was described. Unadjusted seroprevalence of COVID-19 IgG antibody was reported in per cent with 95% confidence interval (CI). We used rural area figures of Tamil Nadu from the sample registration system statistical report 2018 to calculate weights for reporting age-and-gender standardized seroprevalence.[17]

Case-to-undetected-infections ratio (CIR) was calculated as a ratio of the number of reported RT-qPCR-confirmed COVID-19 cases 2 weeks before the imitation of serosurvey to the number of people who have antibodies in our study. This was based on an earlier study reported median seroconversion times for total antibodies, IgM and then IgG at day-11, day-12, and day-14, respectively, based on hospitalized patients and seroconversion for IgG and IgM is reported to occur simultaneously or sequentially.[18,19] Assuming a 3-week lag time from infection to death, we considered the reported number of fatalities after 3 weeks of the survey to estimate the plausible range of the infection fatality ratio (IFR).[16] It was calculated as the number of deaths reported on the total number of people with high-affinity antibodies per 10,000 infections. We used a projected population of 2020 Dharmapuri district using 2011 census data prepared by Directorate of Economics and statistics, Dharmapuri 2013 to calculate all these parameters.[20] The association of seroprevalence with comorbid conditions and sociodemographic characteristics was tested using Chi-square tests.

RESULTS

Our 509 participants were almost equally distributed in seven taluks of Dharmapuri district. The mean age was 47.0±16.4 years, and the majority were men (52.3%). Hypertension (20.2%) and diabetes (16.9%) were reported as the most common comorbidities (Table 1). Among 509 individuals, 7/509 (1.37%) had at least one symptom suggestive of COVID-19 in the last 3 months before the interview, 5/509 (0.98%) reported a history of an infected family member, and none of them gave a history exposure to an infected person in the past or tested positive for COVID-19.

The overall seroprevalence of COVID-19 was 12.4% (95% CI 9.6–15.6) (Table 2). The age-and gender-adjusted seroprevalence was 8.5% (95% CI 6.9–10.8%) (Table 2). The unadjusted seroprevalence among participants with hypertension and diabetes was 16.3% (95% CI: 9.2–25.8) and 10.7% (95% CI: 5.5–18.3), respectively, but the association with seropositivity was not significant. Among seropositive individuals, one participant reported a history of a family member being positive in the past 3 months before the interview. The majority (92.0%) of the seropositive individuals did not report any symptom related to COVID-19 infection at the time of the study nor in the past.

We estimated that the cumulative number of SARS-CoV-2 infection in Dharmapuri district was 96,874 (95% CI 78638–123086) during 2 weeks before the beginning of the study (September 17–October 1, 2020). When we adjusted for sensitivity and specificity of the test kit, the seroprevalence was 6.1% (95% CI 4.02–8.17) and the cumulative number of infections was 69,521 (95% CI 45815–92315).

The cumulative number of RT-PCR confirmed cases until October 2 was 100.54 in Dharmapuri district. The study estimated 7 (96,854/100.54) undetected infected individuals for every RT-PCR confirmed case, that is, CIR of 1:7 and CIR could range from 1:4.5 to 1:9. Based on age-gender adjusted seroprevalence rate, the IFR was calculated as 12.38 per 100.00 infections as on October 22, 2020 in Dharmapuri district.

Table 1: Percentage of seroprevalence among different age groups, sex, and comorbid condition

Demographics	Variables	n	Percentage
Age group	≤20	18	3.5
	21–40	177	34.8
	41–60	208	40.9
	>60	106	20.8
Sex	Male	266	52.3
	Female	243	47.7
Co-morbidity	Diabetes	101	20.2
	Hypertension	82	15.8

DISCUSSION

Our study revealed that a large proportion of the rural population remains susceptible to infection and far from reaching the seroprevalence required for herd immunity. A serosurvey from Tamil Nadu during the same period (3–16 September) has reported a slightly higher seroprevalence of 15.2% in the same district.[21] The variation can be attributed to samples collected from multiple settings, including hospital settings and among the high-risk group. Our study estimated that there were 5–9 undetected infected individuals for every RT-PCR confirmed case. This shows that most of the infections were picked up the existing testing infrastructure.

We found age and comorbidities were not significantly associated with seropositivity. Although advanced age and comorbidities are associated with severe illness, there is limited data regarding increased COVID-19 susceptibility with mild asymptomatic cases.[22] The hospital-based study from Srinagar found that people between the age group of 30–69 years had higher odds of being seropositive (IgG) as compared to the younger population, but they did not find any gender difference in seropositivity.[10] However, the nationwide survey showed that male gender was significantly associated with seropositivity than females.[8] Age and gender have a profound influence on mobility and are varied across cultures. Hence, the susceptibility to infection can be attributed to the function of mobility rather than age and gender per se.

Although diabetes has been associated with increased mortality in COVID-19, the susceptibility to the infection may be same as the general population.[23] The same was reflected in our study. Although rural, this population had access to diagnosis and treatment of common comorbidities due to the outreach of the public-spirited hospital and the government health system. Access to chronic medications was facilitated even during the lockdown and intense resource reallocation following COVID-19, through our grass-root health workers who delivered medicines at home for people with chronic diseases to keep their diseases under control. We could imply that the efforts to sensitize the public regarding

Table 2: Category-wise seroprevalence with different age groups

Category	Male	Prevalence (95% CI)	Female	Prevalence (95% CI)	Total	Overall prevalence (95% CI)
Age						
≤20	10	10 (0.3–44.5)	8	0	18	5.6 (0.1–27.3)
21–40	86	10.5 (4.9–18.9)	91	16.5 (9.5–25.7)	177	13.6 (8.9–19.5)
41–60	120	13.1 (7.8–20.7)	88	11.4 (5.6–19.9)	208	12.5 (8.3–17.8)
>60	50	12.0 (4.5–24.3)	56	10.7 (4.0–21.0)	106	11.3 (6.0–18.9)
Total	266	12.0 (8.4–16.6)	243	12.0 (8.8–17.6)		12.4 (9.6–15.6)

COVID-19 by the government and private sectors in sensitization have played a valuable role.

We could draw several implications from the findings of the study. First and foremost, rural areas succeeded in halting the spread of infection to a greater extent as compared to cities. However, rural areas are challenged by the poor health system and low cash economy, distancing itself from urbanization reaped overall health benefits to people in villages, in terms of the number of infections. This is a reminder that guarded urbanization preserving the natural ecosystem is an essential determinant of health.

Second, strict containment strategies like lockdown curbed infection without profound livelihood implication in this rural setting. This was possible due to the strength of the local economy and reduced inequities. The villages had enough seasonal grains (ragi, a millet), homegrown vegetables and dairy products for nourishment. Since the population density was less, there was enough water for the increased demand for handwashing, clean air to breathe, and physical distancing which was a practical possibility. Strong social connections, a powerful rural disposition, added value during COVID-19 infections. Neighborhoods took care of infected households with food and essential medicines and arranged for a referral if they need hospital support.

Third, low seroprevalence should be looked in two ways. One-way to look at this "achievement," is in terms of success in preventing the spread and the other way to look at it as "responsibility" due to individual susceptibility. Since we assume that other villages in India have similar or a slightly lesser seroprevalence, we need to keep in mind' huge susceptible burden' as 68.84% of India's population live in villages according to the census (2011).[24] This has potential to staggering peaks and gives a warning signal for policymakers about the possibilities of multiple waves of the pandemic. In this context, discussion on sustaining safety measures and access to vaccination is of paramount importance.

The study has potential biases. Although all the subdistricts were selected, and subsequently villages were randomly selected, we employed convenience sampling at the village level. Villages were apprehensive about the medical team from the city, and hence, we enrolled based on individual preference. This would have resulted in selection bias; however, we tried to reduce the bias by calculating age-gender adjusted seroprevalence. Another possibility is the occurrence of measurement bias in estimating seroprevalence. Since we have not done RT-PCR, we would have missed the current infection and underestimated the prevalence. Measurement bias can also be due to validity parameters of the test, in which we have addressed through test performance adjusted seroprevalence.

There are many strength to this study. This is one of the earliest population-based seroprevalence study conducted in a rural district of India harboring a million people. This contributes to the body of evidence regarding the virus, its spread and the future implications in the rural context. The study being conducted by researchers who know the population closely is an added advantage as the results are discussed in relation to the contextual realities.

Limitations of the study

We did not follow a strict probability sampling technique due to feasibility reasons. Another limitation is that we did not estimate the current infection using RT-PCR. Both these aspects have an effect on the true estimation of seroprevalence in this community. Although a 15 days recall period is generally recommended for eliciting morbidity, we have used a longer (3 months) recall. Our assumption was that people would recall their symptoms related to COVID for a longer period due to the unusually significant nature of this pandemic and the attention it had received from media. However, this could have resulted in recall bias. Another limitation is that we have limited our research to one rural district; hence, the generalization of the findings has to be done with caution.

CONCLUSION

We found a low seroprevalence of COVID-19 infection among rural population in a district of Tamil Nadu, 6 months after the index case. The age-old public health measures of low population density, good housing, adequate ventilation, and hygiene measures combined with the public, private, and local health leadership limited the spread of an infectious respiratory viral pathogen in this low resource setting. Since more than three fourth of the rural population remains susceptible to COVID-19, sustaining public health measures and promoting access to vaccination is of utmost importance to safeguard the health this population as severe COVID-19 can be overly burdensome due to poor tertiary healthcare landscape of the rural setting.

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KG- Concept and design of the study, prepared first draft of manuscript; **AP-** Interpreted the results; reviewed the literature and manuscript preparation; **NN-** Concept, coordination, statistical analysis and interpretation; **KRM**- Preparation of manuscript and revision of the manuscript.

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