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SARS-CoV-2 antibody seroprevalence in India, August–September, 2020: findings from the second nationwide household serosurvey



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Summary

Background The first national severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serosurvey in India, done in May–June, 2020, among adults aged 18 years or older from 21 states, found a SARS-CoV-2 IgG antibody seroprevalence of 0·73% (95% CI 0·34–1·13). We aimed to assess the more recent nationwide seroprevalence in the general population in India.

Methods We did a second household serosurvey among individuals aged 10 years or older in the same 700 villages or wards within 70 districts in India that were included in the first serosurvey. Individuals aged younger than 10 years and households that did not respond at the time of survey were excluded. Participants were interviewed to collect information on sociodemographics, symptoms suggestive of COVID-19, exposure history to laboratory-confirmed COVID-19 cases, and history of COVID-19 illness. 3–5 mL of venous blood was collected from each participant and blood samples were tested using the Abbott SARS-CoV-2 IgG assay. Seroprevalence was estimated after applying the sampling weights and adjusting for clustering and assay characteristics. We randomly selected one adult serum sample from each household to compare the seroprevalence among adults between the two serosurveys.

Findings Between Aug 18 and Sept 20, 2020, we enrolled and collected serum samples from 29 082 individuals from 15 613 households. The weighted and adjusted seroprevalence of SARS-CoV-2 IgG antibodies in individuals aged 10 years or older was 6·6% (95% CI 5·8–7·4). Among 15 084 randomly selected adults (one per household), the weighted and adjusted seroprevalence was 7·1% (6·2–8·2). Seroprevalence was similar across age groups, sexes, and occupations. Seroprevalence was highest in urban slum areas followed by urban non-slum and rural areas. We estimated a cumulative 74·3 million infections in the country by Aug 18, 2020, with 26–32 infections for every reported COVID-19 case.

Interpretation Approximately one in 15 individuals aged 10 years or older in India had SARS-CoV-2 infection by Aug 18, 2020. The adult seroprevalence increased approximately tenfold between May and August, 2020. Lower infection-to-case ratio in August than in May reflects a substantial increase in testing across the country.

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Introduction

As of Sept 30, 2020, India reported the second highest number of COVID-19 cases in the world, amounting to nearly 6·3 million cases and more than 97 000 deaths.¹ Case reporting is influenced by strategies implemented for case finding, testing, and contact tracing, and might underestimate the true burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

infection. Population-based data can supplement case-based surveillance to inform public health measures. Population-based seroepidemiological studies are useful to measure the extent of SARS-CoV-2 infection and the effect of ongoing public health responses in controlling the pandemic.²

The first nationwide SARS-CoV-2 serosurvey in India was done in May–June, 2020, when the entire country

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See Online for appendix

Research in context

Evidence before this study

The seroprevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies is important to understand the transmission dynamics of the virus; estimate total infections, including mild and asymptomatic individuals who might not receive testing; and inform the possibility of transmission interruption through the depletion of susceptible individuals, if seroconversion is associated with robust immunity. We reviewed the evidence for the seroprevalence of SARS-CoV-2 available as of Sept 30, 2020, by searching the National Library of Medicine article database and *medRxiv* for preprint publications, published in English, using the terms “serology”, “seroconversion”, “serosurveillance”, “seroepidemiology”, “seroprevalence”, “seropositivity”, “SARS-CoV-2”, and “COVID-19”. Several studies describing the seroprevalence of SARS-CoV-2 had been done across various geographical areas, using different sampling and recruitment strategies, as well as a range of testing approaches. Most studies were limited to smaller subnational areas, few were representative of the population as a whole, and potential sources of bias included the method of participant selection, non-response rates, and misclassification resulting from test specificity, particularly when the prevalence was low. The first national SARS-CoV-2 serosurvey in India indicated an overall low seroprevalence among adults by May, 2020, and the majority of infections were in people living in urban areas, with an estimated 82–130 infections for every reported COVID-19 case.

Added value of this study

India represents one of the largest populations at risk of COVID-19 and as of Sept 30, 2020, had reported the second

highest number of confirmed cases globally. Because of India's large size, geographical diversity, and population heterogeneity, it is difficult to understand the extent of transmission of SARS-CoV-2 using case-based surveillance data alone. Furthermore, Indian cities represent challenging conditions for COVID-19 control, with some of the world's highest population densities and contact rates. This population-based study represents seroprevalence at the national level, covering many areas across India's large expanse. Our findings indicate an overall seroprevalence of around 7% among individuals aged 10 years or older, with a tenfold increase in adult seroprevalence between May and August, 2020. We estimated that for every reported case of COVID-19 there were 26–32 infections, and the infection-fatality ratio in surveyed districts was 0.09–0.11%. We found no difference in seropositivity by age group, sex, or occupation. Our findings indicate a substantial transmission in rural areas, although seroprevalence continues to be higher in urban slum and non-slum areas. We also found evidence of seroconversion among those without symptoms or known exposure, highlighting the limitations of symptom-directed or exposure-directed testing.

was under stringent lockdown, with the exception of conditional relaxation in areas deemed to be minimally affected.³ It found a low seroprevalence of 0.73% (95% CI 0.34–1.13) among the general adult population aged 18 years or older.⁴ Notably, this serosurvey found a high infection-to-case ratio (81.6–130.1 infections per reported COVID-19 case), suggesting the need for a further expansion of testing, and a low infection-fatality ratio (0.27–15.04 deaths per 10 000 infections). From June, 2020, onwards, India had various phases of relaxation of lockdown measures that varied across the states, depending on the local epidemic situation.³ We aimed to do a second national household serosurvey to measure changes in the epidemiology of SARS-CoV-2 infection, compare changes in population-based indicators for infection, and assess the effect of the public health response to the epidemic in India. The objectives of the second serosurvey were to estimate the nationwide seroprevalence of SARS-CoV-2 antibodies in the general population, including by age group, sex, area of residence, occupation, and COVID-19-related characteristics, and

determine the trends in infections since the previous serosurvey.

Implications of all the available evidence

The increasing national seroprevalence in India suggests a growing epidemic moving from urban to rural areas, but most of the population remain susceptible to infection. Continued expansion of testing capacity and stringent application of infection control measures remain warranted. Further rounds of the national serosurvey are planned and should provide crucial information on the rate of seroconversion, informing overall public health strategy and action.

determine the trends in infections since the previous serosurvey.

Methods

Study design and participants

We did a cross-sectional serosurvey in the same 700 clusters (villages in rural areas and wards in urban areas) from 70 districts in 21 states across India that were included in the first nationwide serosurvey (appendix pp 4–8), between Aug 18 and Sept 20, 2020. Within each of the selected clusters, four random locations were selected. In each location, the survey teams chose a random starting point and visited a minimum of four consecutive households. The survey teams listed all household members aged 10 years or older who were permanent residents, and all eligible individuals present in the household at the time of the survey team visit were invited to participate. Individuals aged younger than 10 years and households that did not respond at the time of survey were excluded. From each random location, at least ten individuals were enrolled

in the serosurvey. By selecting ten clusters per district, a minimum of 400 individuals were enrolled from each district.

We obtained written informed consent from individuals aged 18 years or older, or assent from children aged between 10 and 17 years, with written informed consent from their parents or guardians, before the survey. The study protocol was approved by the Central Ethics Committee of Health Research of the Indian Council of Medical Research (ICMR) and the Institutional Human Ethics Committee of the ICMR National Institute of Epidemiology, Chennai.

Procedures

Eligible participants were interviewed to collect information about sociodemographic details, symptoms suggestive of COVID-19 since March 1, 2020 (eg, fever, cough, shortness of breath, sore throat, new loss of taste or smell, fatigue), exposure history to laboratory-confirmed COVID-19 cases, and history of COVID-19 illness using the Open Data Kit mobile phone application. 3–5 mL of venous blood was collected from each participant, and centrifuged serum samples were transported to ICMR National Institute of Epidemiology, Chennai under cold chain.

Participant serum samples were tested for the presence of SARS-CoV-2 specific IgG antibodies on the Abbott Architect i2000SR automated analyser using the Abbott SARS-CoV-2 IgG assay (Abbott Park, IL, USA) as per the manufacturer's instructions. This assay detects IgG antibodies against the SARS-CoV-2 nucleocapsid protein, and has a sensitivity of 100·0% and specificity of 99·6%.⁵ The assay was calibrated with positive and negative quality controls before analyses. Assay results higher than or equal to the cutoff index value of 1·4 were interpreted as positive for SARS-CoV-2 antibodies. As a part of quality control, 10% of positive serum samples and an equal number of negative serum samples were re-tested using the same assay.

Statistical analysis

We described the characteristics of study participants as percentages, means, and SDs. We categorised the reported occupations into high-risk and low-risk categories, on the basis of the potential risk of exposure to a known or unknown COVID-19 case. For example, occupations such as health-care workers, police or security personnel, shopkeepers, bus or taxi drivers, or bank employees were considered as high-risk occupations; whereas, for example, farmers, retired employees, students, or information technology professionals were considered as being at lower risk of exposure. The information about occupation of the participants was captured as open-ended text and was categorised into high and low risk by the investigators. The data were analysed to estimate the seroprevalence of IgG antibodies against SARS-COV-2 with 95% CI, using a random-effects model

to account for cluster sampling. To estimate the weighted seroprevalence, we calculated sampling weights as a product of the inverse of the sampling fraction for the selection of districts and the selection of villages or wards from each district. The weighted seroprevalence was further adjusted for the sensitivity and specificity of the assay.⁶ We also calculated the seroprevalence by age group, sex, area of residence, and COVID-19-related characteristics of study participants. In the first serosurvey, only one adult aged 18 years or older was randomly selected from each household,⁴ whereas in this second serosurvey, all consenting individuals aged 10 years or older were sampled. To compare the seroprevalence between the first and second nationwide surveys, we randomly selected one adult per household from the survey database, and estimated the adjusted seroprevalence among these adults. We calculated the infection doubling time among adults using the observed seroprevalence, and difference in time between the median survey dates of the two serosurveys.⁷ We obtained a non-linear correlation coefficient by fitting polynomial curves for the IgG positivity and cumulative incidence of reported COVID-19 cases by districts.

To estimate the total number of SARS-CoV-2 infections among individuals aged 10 years or older, we multiplied the adjusted seroprevalence in the population aged 10 years or older in the selected 70 districts, by the total population of the entire country aged 10 years or older. We divided the estimated number of infections by the number of reported COVID-19 cases detected by RT-PCR or rapid antigen test, at 1 week (Aug 18, 2020) and 2 weeks (Aug 10, 2020) before the median survey date (Aug 25, 2020) to estimate the infection-to-case ratio. As the number of COVID-19 cases reported nationally are not specified by the type of tests (eg, positive by RT-PCR, positive by rapid antigen test, or negative by rapid antigen test but RT-PCR positive), it was not possible to adjust the total number of reported cases to account for the lower sensitivity of the rapid antigen test. We estimated the infection-to-case ratio at two different timepoints because studies indicate that IgG antibodies against SARS-CoV-2 start appearing between 7 and 14 days after symptom onset.⁸

We calculated the infection-fatality ratio for the 70 districts by dividing the number of deaths reported 3 weeks after symptom onset (assuming a 3 week lag time from infection to death),⁹ by the estimated number of SARS-CoV-2 infections in the selected 70 districts. The data were analysed using STATA version 16.1, and R version 3.5.1 (appendix p 2).

Role of the funding source

The funder of the study was involved in reviewing the study design, writing of the manuscript, and the decision to submit the paper for publication. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication.

For more on Open Data Kit see <https://getodk.org/>

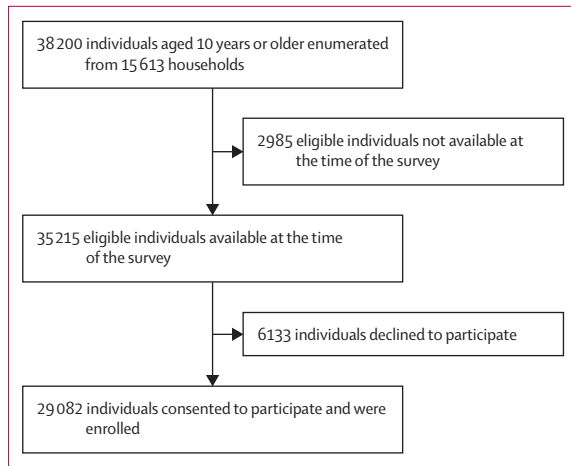


Figure 1: Flowchart of participant enrolment

Results

Between Aug 18 and Sept 20, 2020, we enumerated 38 200 individuals aged 10 years or older from 15 613 households in the 700 clusters. Approximately 26% of clusters were located in urban areas. 35 215 eligible individuals (92·2%) were available at the time of survey, of whom 29 082 (82·6%) consented to participate and were enrolled (figure 1).

Of the 29 082 survey participants, 16 663 (57·3%) were in the age group 18–44 years, 6630 (22·8%) were aged 45–60 years, 3021 (10·4%) were aged 10–17 years, and 2768 (9·5%) were aged older than 60 years (table 1). 14 191 participants (48·8%) were female, 21 524 (74·0%) were residing in rural areas, and 4263 (14·7%) had an occupation with a high risk of exposure to people potentially infected with COVID-19. 546 participants (1·9%) reported symptoms suggestive of COVID-19 since March, 2020, of whom 191 (35·0%) reported seeking medical care. 747 individuals (2·6%) reported having been tested for SARS-CoV-2 previously, of whom 47 (6·3%) previously had a positive COVID-19 test.

Of the 29 082 participants, 3135 tested positive for the presence of IgG antibodies against SARS-CoV-2; resulting in an unweighted seroprevalence of 10·8% (95% CI 9·8–11·8; table 2). The seropositivity across districts ranged from 0·5% (Palakkad in Kerala; Kullu in Himachal Pradesh) to 42·6% (Ganjam in Odisha; appendix pp 4–8). The weighted seroprevalence adjusted for test performance was 6·6% (95% CI 5·8–7·4).

Seroprevalence was lowest among children aged 10–17 years (5·4% [95% CI 4·5–6·4]), and highest among adults aged 18–44 years (6·9% [6·1–7·7]), but did not differ significantly between age groups, and was similar among males (6·7% [5·9–7·5]) and females (6·5% [5·7–7·3]; table 2). Seroprevalence was higher in urban slums (16·9% [12·9–21·7]) and urban non-slum areas (9·0% [7·1–11·3]) than in rural areas (5·2% [4·6–6·0]). There was no difference in seroprevalence between occupations

	Participants (n=29 082)
Age, years	
10–17	3021 (10·4%)
18–44	16 663 (57·3%)
45–60	6630 (22·8%)
>60	2768 (9·5%)
Mean age, years (SD)	37·0 (16·4)
Sex	
Male	14 870 (51·1%)
Female	14 191 (48·8%)
Other	21 (0·1%)
Area of residence	
Rural	21 524 (74·0%)
Urban non-slum	4932 (17·0%)
Urban slum	2626 (9·0%)
Occupation with high risk of exposure to COVID-19 (n=29 033)	4263 (14·7%)
History of COVID-19-related symptoms since March 1, 2020	546 (1·9%)
Symptomatic individuals who sought medical care (n=545)	191 (35·0%)
Symptomatic individuals who were hospitalised (n=191)	31 (16·2%)
History of contact with a known COVID-19 case (n=29 044)	215 (0·7%)
Previously tested for COVID-19 (n=29 044)	747 (2·6%)
Previous positive COVID-19 test (n=747)	47 (6·3%)
Data are n (%) unless otherwise stated.	
Table 1: Participant characteristics	

categorised as high or low risk based on potential exposure to COVID-19. Among individuals who reported a history of symptoms suggestive of COVID-19, seroprevalence was 11·2% (8·8–14·3), compared with 6·5% (5·8–7·3) among individuals who did not report symptoms suggestive of COVID-19. However, among seropositive individuals, 99 (3·2%) reported a history of symptoms consistent with COVID-19 but 3029 (96·6%) reported no symptoms. Seroprevalence was higher among those who reported history of contact with a laboratory-confirmed COVID-19 case (12·7% [9·5–16·8]) and among those who had previously been tested for SARS-CoV-2 (11·8% [9·6–14·6]).

Individuals who were positive on previous SARS-CoV-2 testing had a higher seroprevalence (80·9% [64·5–90·7]) than those who tested negative (19·9% [15·4–25·2]) or were not aware of their result (8·6% [2·4–26·7]; table 2). Of the nine individuals with laboratory-confirmed SARS-CoV-2 infection but who were seronegative, the duration between PCR and serology testing was 1 day for two individuals, 8 days for one, 20–40 days for four, and more than 90 days for two. After excluding the three individuals with an interval of less than 2 weeks (to account for up to 2 weeks' delay in the development

of IgG antibodies between the date of laboratory confirmation and serological testing), 38 (86%) of 44 previous COVID-19 patients had IgG antibodies. The remaining six seronegative individuals were tested for COVID-19 because of their contact with a confirmed case, and none of them reported symptoms during illness. For two (33%) of these six seronegative individuals, the duration between laboratory confirmation and serological testing was more than 90 days.

Among 15 084 randomly selected adults (one from each household), 1696 were seropositive for SARS-CoV-2 IgG antibodies, resulting in an unweighted seroprevalence of 11.2% (95% CI 10.2–12.4). The weighted and adjusted seroprevalence among adults was 7.1% (6.2–8.2). Using an interval of 99 days between the two nationwide surveys, the infection doubling time was 30.2 days (95% CI 23.6–34.6).

We estimated that, among individuals aged 10 years or older, a cumulative 10 663 677 infections (95% CI 9 371 110–11 956 244) had occurred by Aug 18, 2020, in the selected 70 districts. Extrapolation to the entire country resulted in an estimation of 74 326 463 infections (65 317 195–83 335 732). Considering there were 2 339 112 reported COVID-19 cases by Aug 10, 2020, and 2 856 248 by Aug 18, 2020, we estimated there were 31.8 (95% CI 27.9–35.6) and 26.0 (22.9–29.2) infections per reported case by these respective dates. Among the 70 surveyed districts, there were 10 058 COVID-19 deaths by Aug, 31, 2020, and 11 358 deaths by Sept 8, 2020, with an infection-fatality ratio ranging from 9.43 (95% CI 8.41–10.73) to 10.65 (9.50–12.12) COVID-19 deaths per 10 000 infections. The seroprevalence had a positive non-linear correlation with the cumulative incidence of reported COVID-19 cases (correlation coefficient 0.702) in the selected 70 districts (figure 2).

Discussion

Our findings from the second nationwide serosurvey indicate that nearly 7% of India's population aged 10 years or older had been exposed to SARS-CoV-2 infection by August, 2020, with an estimated 74 million infections. Seroprevalence did not differ by age group or sex, but was higher in urban areas, especially in the slums, than in rural areas.

Seroprevalence among adults increased by about ten times, from 0.7% in May, 2020, to 7.1% in August, 2020. All 70 surveyed districts showed a rise in IgG seropositivity between the two serosurveys, although the change was highly variable. Despite the study not being powered to provide reliable district-level estimates, some of the variation observed between districts matches the known context. For example, the largest increase in seropositivity was recorded in the Ganjam district, which also reported the highest number of COVID-19 cases in Odisha State, subsequent to migration of interstate and intrastate informal workers, and challenges in facility-based

	Participants tested, n	Seropositive participants, n	Unweighted seroprevalence, % (95% CI)*	Weighted seroprevalence, % (95% CI)†	Weighted seroprevalence adjusted for test performance, % (95% CI)‡
Overall	29 082	3135	10.8% (9.8–11.8)	7.0% (6.2–7.8)	6.6% (5.8–7.4)
Sex					
Male	14 870	1673	11.2% (10.2–12.4)	7.1% (6.3–7.9)	6.7% (5.9–7.5)
Female	14 191	1462	10.3% (9.3–11.4)	6.9% (6.1–7.7)	6.5% (5.7–7.3)
Other	21	0
Age, years					
10–17	3021	271	9.0% (7.7–10.5)	5.8% (4.9–6.8)	5.4% (4.5–6.4)
18–44	16 663	1820	10.9% (9.9–12.0)	7.3% (6.5–8.1)	6.9% (6.1–7.7)
45–60	6630	753	11.4% (10.1–12.7)	6.9% (6.1–7.9)	6.5% (5.7–7.5)
>60	2768	291	10.5% (9.0–12.3)	6.6% (5.6–7.7)	6.2% (5.2–7.3)
Area of residence					
Rural	21 524	1889	8.8% (7.8–9.8)	5.6% (5.0–6.4)	5.2% (4.6–6.0)
Urban non-slum	4932	672	13.6% (11.4–16.2)	9.4% (7.5–11.7)	9.0% (7.1–11.3)
Urban slum	2626	574	21.9% (17.7–26.6)	17.2% (13.2–22.0)	16.9% (12.9–21.7)
Occupation with high risk of exposure to COVID-19 (n=29 033)					
Yes	4263	519	12.2% (10.4–14.2)	6.9% (6.0–8.0)	6.5% (5.6–7.6)
No	24 770	2608	10.5% (9.6–11.5)	7.0% (6.2–7.8)	6.6% (5.8–7.4)
History of COVID-19-related symptoms since March 1, 2020 (n=29 045)					
Yes	546	99	18.1% (14.1–23.0)	11.6% (9.2–14.6)	11.2% (8.8–14.3)
No	28 499	3029	10.6% (9.7–11.6)	6.9% (6.2–7.7)	6.5% (5.8–7.3)
History of contact with a known COVID-19 case (n=29 044)					
Yes	215	57	26.5% (18.4–36.6)	13.0% (9.9–17.1)	12.7% (9.5–16.8)
No	25 013	2690	10.8% (9.8–11.8)	6.7% (6.0–7.5)	6.3% (5.6–7.1)
Not known	3816	381	10.0% (8.1–12.2)	8.3% (6.9–9.9)	7.9% (6.5–9.5)
Previously tested for COVID-19 (n=29 044)					
Yes	747	173	23.2% (18.5–28.6)	12.2% (10.0–14.9)	11.8% (9.6–14.6)
No	28 297	2955	10.4% (9.5–11.4)	6.2% (5.5–7.0)	5.8% (5.1–6.6)
Previous COVID-19 test result (n=747)§					
Positive	47	38	80.9% (64.5–90.7)
Negative	665	132	19.9% (15.4–25.2)
Not known	35	3	8.6% (2.4–26.7)

*Adjusted for clustering. †Weighted for sampling weights. ‡Adjusted for test performance as reported by manufacturer (sensitivity 100.0% and specificity 99.6%). §Weighted and adjusted seroprevalence not estimated because of small sample number.

Table 2: Seroprevalence by demographic characteristics

quarantine. Interstate migration of informal workers is also thought to explain the substantial rise in seroprevalence in all six districts in Bihar, and Kamrup Metropolitan district in Assam.¹⁰ The increase in seropositivity among adults between the first and second serosurveys also indicates widespread infection in all districts, except for Palakkad and Kullu.

The seroprevalence of SARS-CoV-2 infection did not differ by age group or sex, indicating similar exposure and susceptibility between these groups. This absence of a significant difference was despite school closures and other non-pharmaceutical infection-control interventions (eg, washing hands, wearing masks, physical

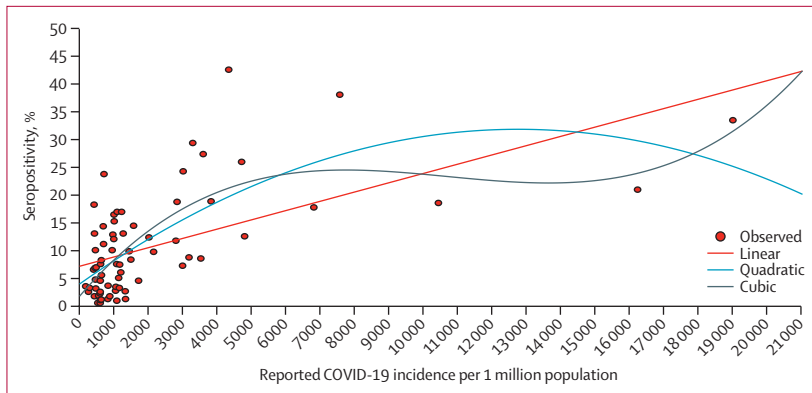


Figure 2: SARS-CoV-2 IgG seropositivity and incidence of reported COVID-19 cases per 1 million population by district, fitted with polynomial curves

Points on the graph represent the 70 surveyed districts. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

distancing) during the survey period, suggesting household-level exposure of children and adults aged older than 60 years to other household members who are more mobile, socially active, and perhaps non-adherent to the prescribed non-pharmaceutical measures. Seroprevalence was reported to be similar across age groups in Brazil (first survey),¹¹ and Spain,¹² with the seroprevalence among adults aged older than 65 years being lower than in those aged 5–65 years in Santa Clara County, CA, USA,⁹ and higher in older adults in Greece¹³ and Iceland.¹⁴ Children had a lower seroprevalence compared with adults aged younger than 60 years in the second survey in Brazil.¹¹ A similar seroprevalence by sex to that observed in our study has been reported from serosurveys in Santa Clara County⁹ and Spain,¹² but a serosurvey in Geneva, Switzerland¹⁵ showed a higher seroprevalence among males.

During June–October, 2020, a number of serosurveys have been done in various Indian cities or states (appendix p 11). The higher seroprevalence in urban slum and non-slum areas observed in our study is consistent with that of other serosurveys in densely populated urban areas, where the prevalence ranged from 7·8% to 51·5%. The seroprevalence was also higher in slum areas of Mumbai (54·1%) compared with non-slum areas (16·1%).¹⁶ Although population density, coupled with high mobility and challenges in safe physical distancing and hand hygiene are the main drivers of spread of infection in urban areas, especially in urban slums,¹⁷ our findings also indicate substantial transmission among the rural population later in the epidemic, by contrast with the first serosurvey.⁴ Transmission is likely to increase further in these rural areas in the coming months, emphasising the need to implement non-pharmaceutical interventions, as well as strengthening health-care facilities for the effective management of infections.¹⁸

One in nine individuals who reported no COVID-19-related symptoms were seropositive for SARS-CoV-2 IgG

antibodies (adjusted seroprevalence 6·5% [95% CI 5·8–7·3]), indicating asymptomatic seroconversion among the general population in India. Seroconversion was also documented among individuals without a history of known contact with a COVID-19 case, and among those without any previous SARS-CoV-2 testing. These data support the expansion of testing strategies to include individuals who do not have known exposure or symptoms.¹⁹ Only 3% of seropositive individuals reported symptoms suggestive of COVID-19, highlighting the limitations of symptom-directed testing and the importance of universal prevention methods.

Among the laboratory-confirmed patients with COVID-19 identified in our survey, only 81% of patients had SARS-CoV-2 IgG antibodies. The reasons for absence of IgG antibodies in recovered COVID-19 individuals might be due to poor B-cell response,^{20,21} false-negative testing, or waning immunity over time.²²

The laboratory infrastructure for the diagnosis of COVID-19 has been rapidly built up from one laboratory in January, 2020, to 1511 laboratories by August, 2020.²³ With the addition of rapid point-of-care antigen-detection tests and the expansion of testing criteria, test capacity and use saw further growth, resulting in more than 34 million tests having been done as of Aug 21, 2020.^{23–25} The decrease in infection-to-case ratio from 82–131 in May, 2020, to 26–32 in August, 2020, is a consequence of the growth of testing outpacing the growth of infection rate. The ratio of estimated infections to reported cases in Brazil was 10·3, based on the serosurveys done in May–June, 2020.¹¹

Population-based seroprevalence data are useful in understanding the current and future course of the COVID-19 pandemic. The overall seroprevalence of less than 10% in India indicates that a large proportion of the population remains susceptible to SARS-CoV-2 infection. The transmission of infection is expected to continue in most states in India until the herd immunity threshold is achieved, either by natural infection or vaccination. Although this threshold is unknown, most estimates place it at higher than 50% of the population.²⁶ Heterogeneity in individual susceptibility or exposure to infection, pre-existing immunity in the population, and use of non-pharmaceutical infection-control interventions might alter the required prevalence for herd immunity.^{27–29} The infection doubling time at the national level was estimated to be 30·2 days (95% CI 23·6–34·6). Assuming the same rate of infection continued, the required herd immunity threshold could be estimated to be reached as of November–December, 2020. However, the duration of persistence of IgG antibodies¹⁴ and memory B cells, and the contribution and durability of cell-mediated immunity against SARS-CoV-2 is still uncertain.²⁹ It is pertinent to note that the reported number of COVID-19 cases in India has been declining since October, 2020.

The infection-fatality ratio indicates the probability of death among those infected. In our study, the infection-fatality ratio ranged from 0·09% to 0·11%. A systematic

review and meta-analysis of published studies on COVID-19 as of July, 2020, indicated an infection-fatality ratio of 0.68% (95% CI 0.53–0.82).³⁰ Another study based on the seroprevalence data from 51 locations indicated substantial variation in infection-fatality ratios, ranging from 0.00% to 1.54%, with a median of 0.23%.³¹ The lower infection-fatality ratio in our study could be accounted for by several factors, including the completeness of death reporting, variation in the prevalence of comorbidities, and the age structure of the population.^{32,33} Due to the absence of age-stratified death data from these 70 districts, and as the study was not powered for age-stratified seroprevalence, we could not calculate age-stratified infection-fatality ratios.

Our study has several limitations. The representation of children aged 10–17 years in the surveyed sample was lower than the census-based age distribution in India. According to Census of India projections, about 14% of the population are aged 10–17 years,³⁴ whereas 10.4% of the study population were aged 10–17 years. The under-representation of children and over-representation of adults in the survey could lead to overestimation of the true seroprevalence, if we expect a real difference in the risk of exposure to SARS-CoV-2 across age groups. Although the required sample size was achieved, about 17% of the eligible population declined to participate in the survey. If this non-response was not at random, then this could introduce selection bias. Individuals who declined to participate were more likely to be male and younger than 60 years of age (appendix p 9). We adjusted our weighted seroprevalence estimate as per the manufacturer specified sensitivity (100.0%) and specificity (99.6%) of the Abbott SARS-CoV-2 IgG assay. According to an external evaluation, the sensitivity is reported as 92.7% and the specificity as 100.0%.³⁵ Adjusting for these figures, our estimated overall seroprevalence was 7.6% (95% CI 6.7–8.4; appendix p 10). In the first nationwide serosurvey, we used a laboratory assay which detected IgG antibodies against whole cell antigen, and positive serum samples were re-tested with an assay that detects antibodies against the S1 domain of the spike protein of SARS-CoV-2, to improve the specificity of testing.⁴ In this second serosurvey, we used a laboratory assay which detected IgG antibodies against the nucleocapsid protein of the virus. Although we used different assays in the two serosurveys, we adjusted the seroprevalence to account for each assay's sensitivity and specificity. Additionally, as antibodies to the nucleocapsid protein of SARS-CoV-2 virus have been shown to reduce over time,³⁶ we might have underestimated the seroprevalence and number of infections. For the same reason, we might have underestimated the true difference in seroprevalence between the two serosurveys, as we used antibody assays for different viral proteins. Finally, we might have overestimated the infection-to-case ratio by using COVID-19 cases reported at 1 week and 2 weeks

before the median date of survey for all clusters. About half of the 700 clusters were surveyed within the first 8 days of the study period. The remaining clusters were surveyed over the next 3 weeks, and the number of cases reported from these clusters at 1 or 2 weeks before the actual date of survey would have been higher.

In conclusion, our findings indicate that nearly one in 15 individuals aged 10 years or older were exposed to SARS-CoV-2 in India by Aug 18, 2020. Although the seroprevalence among adults increased approximately tenfold between May and August, 2020, a large proportion of the population remains susceptible to SARS-CoV-2. These findings, in combination with the first national serosurvey and other serosurvey data, give a clear picture of the epidemic in India; there is high seroprevalence in urban slums, as well as non-slum urban areas, and seroprevalence is now increasing in the vast rural areas of the country. Although the epidemic was successfully contained to the cities at the outset, the current general trend presents many forthcoming challenges. We recommend continued expansion of testing capacity to improve the infection-to-case ratio, especially in districts with high seroprevalence but low case reporting; continued application of interventions to control transmission of the virus; and health facility planning for increased caseloads throughout the country, with particular focus in rural areas. Finally, we recommend further rounds of the national serosurvey, to continue providing strategic insight into the epidemiology of the SARS-CoV-2 pandemic, and to inform public health action.

Contributors

TB, JWVT, and MSaK did the literature search. MVM, TB, KR, MSaK, NS, DCSR, and BB did the study design. SSe, RSa, SA, RB, SDB, AKB, JB, VC, DD, AKD, KR, GRD, SMSK, MSuK, AL, MM, AMa, SSM, CR, AT, DKB, ASC, FD, IH, AK, SK, JSK, GGJNL, AMi, ARN, GVP, MAQ, SeS, RKS, KS, VKS, PKS, PS, RaS, DSV, AV, and SP did the data collection. CPGK and KS did the laboratory investigations. VS, JWVT, MVM, TB, RSa, and MSaK did the data analysis. MVM, TB, KR, NS, DCSR, and BB did the data interpretation. MVM, TB, VS, JWVT, and MSaK accessed and verified the data. MVM, TB, JWVT, NS, VS, and MSaK wrote the first draft of the manuscript. All authors approved the final version of the manuscript.

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Declaration of interests

We declare no competing interests.

Data sharing

A subset of the key anonymised individual participant data collected during the study, along with a data dictionary, is available upon request to the corresponding author, after approval of a proposal with a signed data access agreement.

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