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Age- & sex-specific infection fatality ratios for COVID-19 estimated from two serially conducted community-based serosurveys, Chennai, India, 2020

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***Background & objectives*: Infection fatality ratio (IFR) is considered a more robust and reliable indicator than case fatality ratio for severity of SARS-CoV-2 infection. Age- and sex-stratified IFRs are crucial to guide public health response. Infections estimated through representative community-based serosurveys would gauge more accurate IFRs than through modelling studies. We describe age- and sex-stratified IFR for COVID-19 estimated through serosurveys conducted in Chennai, India.**

***Methods*: Two community-based serosurveys were conducted among individuals aged ≥10 yr during July and October 2020 in 51 of the 200 wards spread across 15 zones of Chennai. Total number of SARS-CoV-2 infections were estimated by multiplying the total population of the city aged ≥10 yr with the weighted seroprevalence and IFR was calculated by dividing the number of deaths with the estimated number of infections.**

***Results*: IFR was 17.3 [95% confidence interval (CI): 14.1-21.6] and 16.6 (95% CI: 13.8-20.2) deaths/10,000 infections during July and October 2020, respectively. Individuals aged 10-19 years had the lowest IFR [first serosurvey (R1): 0.2/10,000, 95% CI: 0.2-0.3 and second serosurvey (R2): 0.2/10,000, 95% CI: 0.1-0.2], and it increased with age and was highest among individuals aged above 60 yr (R1: 140.0/10,000, 95% CI: 107.0-183.8 and R2: 111.2/10,000, 95% CI: 89.2-142.0).**

***Interpretation & conclusions*: Our findings suggested that the IFR increased with age and was high among the elderly. Therefore, elderly population need to be prioritized for public health interventions including vaccination, frequent testing in long-term care facilities and old age homes, close clinical monitoring of the infected and promoting strict adherence to non-pharmaceutical interventions.**

Key words Case fatality ratio - COVID-19 - infection fatality ratio -seroprevalence

Till May 25, 2021, globally >3.4 million people have died due to coronavirus disease 2019 (COVID-19)[1]. Case fatality ratio (CFR), a ratio of number of deaths with cases, reflects disease severity. COVID-19 CFRs vary between and within nations[2]. With 28,047,000 COVID-19 cases (including

2,022,008 active cases) and 329,128 deaths reported till May 30, 2021, CFR in India was 1.17 per cent considering all reported cases as denominator and 1.26 per cent considering non-active cases as denominator[3]. CFR is influenced by several factors including extent of testing, test performance as well as completeness of reporting of deaths. Furthermore, asymptomatic infections are less likely to be included in the denominator[4]. Infection fatality ratio (IFR), which is the proportion of infections with fatal outcome, is considered a more robust and reliable indicator for severity of infection[4]. Age- and sex-stratified IFRs are crucial to guide public health response. Infections estimated through representative community-based serosurveys are considered to provide more accurate IFRs than through modelling studies[5]. Very few published reports are available about estimates of IFR in India[6]. Here, we describe age- and sex-stratified IFR estimated through two serial community-based serosurveys conducted in Chennai, Tamil Nadu, India.

Material & Methods

Chennai has reported >500,000 cases as on May 30, 2021[7]. Along with the local health administration [Greater Chennai Corporation (GCC)], two community-based surveys were conducted among individuals aged ≥10 yr during July and October 2020 in 51 of the 200 wards spread across 15 zones of Chennai to estimate the age- and sex-specific prevalence of SARS-CoV-2 infection. Both surveys were conducted in the same wards to monitor the trend of seroprevalence. Multistage cluster sampling method was used. A total of 51 wards were selected using probability proportion to population size method and six streets in the first and three streets in the second serosurvey were randomly selected from each ward from the list of streets available with GCC. The survey team selected a random starting point in each street, and visited contiguous households to enrol a minimum of 40 consenting individuals aged 10 yr and above residing in the house as described elsewhere[8]. When the house was locked or household members were unavailable, the team proceeded to the next house and completed the survey until the required number of individuals were enrolled. Trained phlebotomists collected 3-5 ml of venous blood from each participant and information was obtained about sociodemographic details, exposure to laboratory-confirmed COVID-19 case, history of symptoms suggestive of COVID-19 in the last three months and COVID-19 testing status. The study protocol was approved by the Institutional Human Ethics Committee of ICMR-National Institute of Epidemiology, Chennai. Written informed consent was obtained from individuals aged 18 yr and above and assent along with parental informed consent was taken for children aged between 10 and 17 yrs.

A total of 12,319 and 6366 participants were enrolled in the first and second surveys, respectively (Table I). The serum samples were tested for the presence of IgG antibodies against nucleocapsid protein using Abbott Architect i2000SR (Abbott Park, IL, USA) chemiluminescent immunoassay. The weighted seroprevalence of SARS-CoV-2 infection was estimated by using appropriate sampling weights (product of the inverse of the sampling fraction for the selection of wards and the selection of streets). The weighted seroprevalence was then adjusted for the sensitivity (100%) and specificity (99.6%) of the test[9]. We estimated total number of SARS-CoV-2 infections among individuals aged ≥10 yr by multiplying the weighted seroprevalence adjusted for assay characteristics with the 2020 population of Chennai aged ≥10 yr. Number of cases and deaths reported in the State bulletin was used to calculate CFR. For estimating IFR, the line list of cases with clinical outcomes reported by date of sample collection provided by GCC was used. IFRs along with 95 per cent confidence interval (CI) were calculated by dividing the number of deaths reported three weeks after infection with the estimated number of infections accounting for a three-week lag time from infection to death[10]. R software (version 4.0.2, R Foundation for

Table I. Demographic characteristics of study participants in the first and second serosurveys, Chennai

Characteristics	First serosurvey[8] (n=12,319), n (%)	Second serosurvey (n=6366), n (%)
Age (yr)		
10-19	1473 (12.0)	670 (10.5)
20-29	2105 (17.1)	1341 (21.1)
30-39	2353 (19.1)	1334 (21.0)
40-49	2353 (19.1)	1171 (18.4)
50-59	1927 (15.6)	933 (14.7)
Above 60	2108 (17.1)	917 (14.4)
Sex		
Male	5785 (47.0)	3338 (52.4)
Female	6493 (52.7)	3021 (47.5)
Transgender	41 (0.3)	7 (0.1)

Statistical Computing, Vienna, Austria) was used for the statistical analysis.

Results & Discussion

The weighted seroprevalence after adjusting for test performance among individuals aged ≥10 yr was 18.4 per cent (95% CI: 14.8-22.6%) in July (round 1, R1)[6] and 30.1 per cent (95% CI: 24.7-36.1%) in October (round 2, R2). The estimated infections during these periods were 1,295,908 (1,040,975-1,593,330) and 2,473,238 (2,029,534-2,966,242), respectively. Chennai had reported 2176 COVID-19 deaths and 102,985 cases by August 3, 2020 and 3580 deaths and 194,139 COVID-19 cases by October 23, 2020.This translates into the CFRs of 2.1 per cent by August and 1.8 per cent by October 2020.

There were 17.3 (95% CI: 14.1-21.6) and 16.6 (95% CI: 13.8-20.2) deaths estimated/10,000 infections during July and October, respectively. In both rounds, IFR was significantly higher (P<0.001) among males (Table II). Younger children had the lowest IFR (R1: 0.2/10,000, 95% CI: 0.2-0.3 and R2: 0.2/10,000, 95% CI 0.1-0.2). IFR increased with age and was highest among individuals aged above 60 yr (R1: 140.0/10,000, 95% CI: 107.0-183.8 and R2: 111.2/10,000, 95% CI: 89.2-142.0) (Table II). Overall IFR (0.16-0.17%) observed in Chennai was lower than IFR estimated through seroprevalence studies in Geneva (0.64%) and Spain (0.83%)[5,11]. The median overall IFR (0.27%, range: 0.09-0.57%) inferred from seroprevalence data across 51 locations[6] was also higher than estimated IFR in our study. Overall CFR in Chennai was 10-12 times higher than estimated IFR. Higher IFR among males seen in Chennai was consistent with other studies[11]. IFR in Chennai increased with age and a steep rise was observed in individuals above 50 yr. Many studies have identified older age and male gender as risk factors for progression to severe disease and death[12]. Most serosurveys in India including the first and second nationwide serosurveys conducted by the Indian Council of Medical Research, provided overall estimate of IFR[13,14]. With the availability of age distribution of COVID-19 deaths and fairly complete reporting of deaths (at least institutional), we calculated age-specific IFRs in Chennai.

The seroprevalence in Chennai increased from 18.4 to 30 per cent during the period July-October, 2020. However, there was wide variation in seroprevalence in the north, south and central regions between the two serosurveys. During the first serosurvey,

Table II. Age- and sex-stratified infection fatality ratios, August and October 2020, Chennai, India

Characteristics	First serosurvey (July17-28, 2020)			Second survey (October 8-15, 2020)		
	Number of COVID-19 deaths*	Number of COVID-19 infections (95% CI)	IFR per 10,000 infections (95% CI)	Number of COVID-19 deaths**	Number of COVID-19 infections (95% CI)	IFR per 10,000 infections (95% CI)
Overall	2246	1,295,908 (1,040,975-1,593,330)	17.3 (14.1-21.6)	3520	2,473,238 (2,029,534-2,966,242)	16.6 (13.8-20.2)
Sex						
Male	1556	574,859 (454,209-716,799)	27.1 (21.7-34.3)	2438	1,222,608 (999,565-1,474,564)	23.3 (19.3-28.5)
Female	690	713,657 (57,5872-879,706)	9.7 (7.8-12.0)	1082	1,250,409 (1.021,576-1,503,760)	10.0 (8.4-12.3)
Age (yr)						
10-19	5	234,050 (180,914-298,571)	0.2 (0.2-0.3)	5	320,058 (248,234-401,963)	0.2 (0.1-0.2)
20-29	26	333,664 (264,352-415,871)	0.8 (0.6-1.0)	33	463,976 (372,465-568,331)	0.7 (0.6-0.9)
30-39	82	264,175 (207,253-331,313)	3.1 (2.5-4.0)	104	465,181 (376,506-565,486)	2.2 (1.8-2.8)
40-49	209	220,481 (173,399-276,749)	9.5 (7.6-12.1)	292	383,154 (311,098-463,216)	7.6 (6.3-9.4)
50-59	447	156,962 (123,215-196,987)	28.5 (22.7-36.3)	640	240,755 (191,509-297,035)	26.6 (21.5-33.4)
≥60	1477	105,528 (80,364-137,998)	140.0 (107.0-183.8)	2446	219,914 (172,212-274,084)	111.2 (89.2-142.0)

*Deaths as on August 3, 2020, **Deaths as on October 23, 2020. CI, confidence interval; IFR, infection fatality ratio

prevalence was higher in the northern and adjoining parts of Central Chennai. Subsequently, the prevalence increased in most of the wards from Central (from 21.4 to 32.6%) and Southern Chennai (from 13.4 to 30.5%). Northern Chennai was affected first by the COVID-19 pandemic. Central and southern regions were relatively spared in the early phase of the pandemic.

Our study had certain limitations. First, antibodies decline over time[15] and hence the calculated seroprevalence might be an underestimate. This could have influenced the IFR in our study. Second, we might have underestimated the IFR due to incomplete reporting of deaths. It is also likely that all deaths, especially those occurred during the initial surge in cases, might not have been tested for SARS-CoV-2 infection. Third, children aged below 10 yr were not included in the serosurvey due to challenges in collecting venous blood from young children.

In conclusion, the IFR increased with age and was high among the elderly. The findings suggest that elderly population need to be prioritized for public health interventions including vaccination, frequent testing in long-term care facilities and old age homes, close clinical monitoring of the infected and promoting strict adherence to non-pharmaceutical interventions to protect them from exposure to infection from within and outside the household.

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***Conflicts of Interest*:** M. Jagadeesan and M.S. Hemalatha are employees of GCC. Others have no conflicts to declare.

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