

The Impact of Vaccine Activated Immunity Enhancement on SARS-CoV-2 Spread Dynamics in India and IgG Antibodies Prevalence in Japan Population

Zameer Shervani^{1,*}, Intazam Khan², Deepali Bhardwaj³, Muhammad Jehanzeb Khan¹, Venkata Phani Sai Reddy Vuyyuru⁴, Adil Ahmed Khan⁵, Diwakar Madan Kumar⁶, and Aisha Mahmood⁷

ABSTRACT

We reported the percentage of SARS-CoV-2 IgG antibodies generated in the Indian population from natural infection and vaccination. The waning of the antibodies over time has also been worked out. The article discusses the overall findings in India, the states (Tamil Nadu, Haryana, and Odisha), and Delhi. The abstract covers the Tamil Nadu's data pattern only, the main part of the paper has similar data from other states (Haryana and Odisha), the city of Delhi, and overall, India. Seroprevalence in Tamil Nadu increased to 87% in the fourth survey conducted in December 2021 from 70% in the third survey undertaken in July 2021. As of April 2021, 29% of residents were seropositive, but by July–August 2021, there was a steep rise to 70% in the third survey. By August 1, 2021, 22% and 6.2% of the state's total population had received single- and two-dose vaccinations respectively. The third serosurvey, which spanned until August, suggested that vaccination might have contributed to the seroprevalence in Tamil Nadu. Considering the third and fourth surveys' full vaccination figures of the state, 22.1% antibody enhancement had to have happened. However, only a 17% increase was reported, a decline of 5.1%. Whereas, considering the eligible population, the percentage reduction in seroprevalence (waning of antibodies) was higher at 11.7% that occurred in 4–5 months. In August 2020, the monthly caseload of Tamil Nadu reached a plateau of 182,182 during the original Wuhan (first) wave. When the first wave receded, baseline cases were the lowest at 21,263 in January 2021. Cases peaked at 929,760 in May 2021 and fell to 21,128 in December 2021, during the second Delta wave that hit Tamil Nadu. In January 2022, the Omicron surge (third wave) reached a plateau with 597,175 cases. Cases decreased in February 2022, with the lowest monthly caseloads recorded in April and May at 1542 and 1107, respectively. Seropositivity of 32.0% measured in the first survey (October and November 2020) and 29% seroprevalence reported in the second survey (April 2021) were due to the first original Wuhan wave that hit the state and peaked in August 2020. As a result of the strong Delta wave, which peaked in May 2021, and vaccination (22% partial, 6.2% full) done in the state, the seroprevalence increased to 70% in the third survey (July–August 2021). A monthly caseload of 597,175 cases in January 2022 (Omicron wave) led to an 87% seropositivity rate (fourth survey), which also includes vaccine-generated immunity as 28.3% of the total population and 36.8% of those who were eligible vaccinated to contribute to the survey done in Tamil Nadu. A small section of the paper examines the seroprevalence (%) in the Japanese population. We covered Okinawa's main and remote islands and the city of Kobe.

Keywords: Immunity waning, One-dose vaccination, Seroprevalence, Two-dose vaccination.

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¹ Food & Energy Security Research & Product Centre, Sendai, Japan.

² Progressive Neurology-Astoria, New York, USA.

³ Centre for Skin and Hair Pvt. Ltd., New Delhi, India.

⁴ Citizens Speciality Hospital and American Oncology Institute, Hyderabad, India.

⁵ All India Institute of Medical Sciences (AIIMS), Rishikesh, India.

⁶ Ragas Dental College and Hospital, Chennai, India.

⁷ King George's Medical University, Lucknow, India.

* Corresponding Author:

e-mail: shervani.nanotek@gmail.com

1. INTRODUCTION

Many COVID-19-infected people continued to experience symptoms over six months after the initial diagnosis, according to a study conducted in Japan [1]. The most prevalent symptom (20%) was fatigue. However, at the beginning of the infection, fever was the most common (78%) symptom. After six months, the percentage of individuals who had fever reduced to just 5%. The research was conducted under the direction of Professor Fukunaga Kōichi of Keio University (Japan), and the Ministry of Health, Labor, and Welfare (Government of Japan). Among the residual symptoms, breathing difficulty, sleep disturbance, and reduction in thinking or concentration were common and accounted for 13%, 11%, and 11%, respectively. Even a single persistent symptom can trigger anxiety or dejection, causing serious health issues and sleep disorders in general. A total of 522 affected hospitalized individuals were covered in the survey. The survey period spanned from January 2020 to February 2021, including the first three waves that hit Japan, the fourth wave and the fifth Delta wave were not part of the study. Another report [1], authored by Professor Akihito Yokoyama of Kochi University (Japan) and submitted to the above ministry, found that among critically ill hospitalized patients, half (50%) experienced shortness of breath, and 77.3% of them had muscle weakness after a three-month follow-up. However, fatigue persisted in 30.2% of the patients.

The lifting of the state of emergency (coronavirus) on June 20, 2021, in Japan might have contributed to the spike in new infections that began to occur during the last week of June 2021. The organizing committee's advisors recommended a 50% reduction in the number of seats available for the July–August 2021 Olympics in Tokyo, to reduce the risk of the virus spreading. A tertiary academic hospital in Japan has analyzed the symptoms of COVID-19 patients who visited the CAC (COVID-19 aftercare clinic) between February 15 and September 17, 2021, which included the first 4 waves but no delta wave [2]. Aftereffects symptoms were recorded, along with the patient's clinical and habitual backgrounds. In the survey, 87 infected Japanese individuals with a median age of 40 years were included, 52.9% of whom were female. A total of 79 days passed between the onset of the infection and the clinic visit. Among the symptoms recorded, fatigue was most common (50.4%), followed by dysosmia, dysgeusia, hair loss, headache, dyspnea, and dyssomnia in the proportion of 28.7%, 26.4%, 18.4%, 17.2%, 16.1%, and 13.1%, respectively. During the above study period, February–September 2021, and 79 days after the onset of the infection, the Delta wave was not included. Various symptoms of weight loss, fever, general fatigue, cough, sore throat, dyspnea, loss of appetite, dysgeusia, dysosmia, headache, dyssomnia, and anxiety have been investigated over time after infection onset. In addition, the percentage of these overall symptoms present over the entire period has been worked out. An OPC (outpatient clinic) specializing in PASC (post-acute sequelae of SARS CoV-2

or Long COVID effects has analyzed the clinical characteristics of Japanese patients in the above-mentioned article. The Long COVID aftereffects recorded in different countries in Europe, the US, China, and Japan have been thoroughly analyzed in several review studies [2]. One-third to half of COVID-19 patients experienced lingering symptoms for a long time, up to several months. The data of COVID-19-infected patients who visited the COVID-19 aftercare clinic (CAC) at Okayama University Hospital (Japan) for post-COVID symptoms between February and December 2021 were analyzed [3]. The period included the entire Delta wave because the wave ended before October 2021. Medical records of 186 patients were examined. The patient's primary complaint was general fatigue, but they also reported hair loss, headaches, dyspnea, dysosmia or dysgeusia, and sleep disorders. Long COVID refers to aftereffect symptoms that persist for more than a month after the COVID-19 infection. The aforementioned study considered the following medical records: age, gender, body mass index (BMI), underlying conditions (alcohol consumption and smoking), hospitalization due to COVID-19 infection, oxygen support or medication taken, number of days between infection onset and the visit to the CAC clinic, severity of the COVID-19 infection, COVID-19 vaccination record, and type of clinical aftereffect symptoms. Of the total number of patients, 40% were men and 60% were women. The individuals' median age was 40. Of the total patients, 41% and 43%, respectively, were smokers and drinkers. Hospitalization rates for COVID-19 were 29% and 17% for patients who received oxygen or steroid therapy, respectively. There were 76%, 22%, and 2% of individuals with mild, moderate, and severe symptoms, respectively. A proportion of 24% of the individuals had received full vaccination, whereas 12% had only one dosage. The vaccines used were either BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna). A significant number (64%) of individuals were unvaccinated. The average time between the onset of the infection and the CAC clinic visit was 83 days. During the first visit, patients reported more than ten symptoms, with the five most common being general fatigue (52.2%), followed by dysosmia or dysgeusia (43.0%), hair loss (24.7%), headache (19.9%), dyspnea (15.6%), and insomnia (14.5%).

The study [4] was done on the first four non-delta waves that hit Japan. More than 60% (61%) of COVID-19 hospitalized or convalescent patients lost their ability to taste or smell. Over a month, 60% and 84% of the individuals showed a drop in the altered smell and taste, respectively. In the study, 251 infected individuals were included. The data showed the pathogenic nature of the original Wuhan variant. It did not include the Delta wave and the waves after. In a study [5] post-COVID, Professor Hideki Ueno of Kyoto University (Japan) found that women were more likely to suffer from coughing, hair loss, and taste abnormalities. According to the study, the "T cells" that the human body produces to fight viruses are what give men's and women's immune systems their differences. The

immune response system produces “T cells” when a virus infiltrates. The aftereffects are caused by the production of T cells that deviate from the normal count, either too much or too little. A total of 70 COVID-19 patients who had aftereffects symptoms, including those infected during the Delta wave, had their blood samples examined. The type and amount of T cells produced by the immune system to eliminate the virus determine the symptoms that occur. T cells that eliminate viruses and suppress excessive immune activity were found to be high in women exhibiting severe symptoms of breathlessness and heart pounding. The symptoms occurred and lasted because of the disturbed and out-of-control immune system. The above reactions were less common in men. Similarly, patients with lower total T cell numbers also experienced severe difficulty in concentrating and complained of depression. The fragments of the virus that remain in the various organs due to the lowered T cell count are believed to be the cause of the lingering symptoms. Since the aftereffects of Omicron decay faster than that of the Wuhan and Delta variants, the immunological response may be different for Omicron variant symptoms. Additional research focusing on T cells can be done if it is established that they play a role in controlling and causing post-COVID symptoms. The difference in COVID-19 aftereffects between men and women was also confirmed by a large-scale survey (1,000 patients) conducted by a research team working for the Japanese Ministry of Health. The survey examined the patients hospitalized between January 2020 and February 2021, when the first three non-Delta waves hit Japan. Three months following diagnosis, 43.5% of men and 51.2% of women reported improvement in their symptoms. This represents a gender-based decline in symptoms. After three months, the symptoms in women improved less dramatically. In one year, the gap shrank to 32.1% for men and 34.5% for women who continued to suffer from after effects.

2. METHODS

The ICMR (Indian Council of Medical Research) carried out India’s fourth national serological survey in June and July 2021. A total of 28,975 members of the general public and 7252 healthcare personnel or workers were covered. The study also covered 8691 adolescents in total. It was carried out in 21 states and 70 districts throughout India. Before the Omicron wave hit the state, the Tamil Nadu Directorate of Public Health and Preventive Medicine conducted the fourth cross-sectional survey in all 38 districts of the state. It included 32,245 people in cohorts older than ten years. The state conducted the first, second, third, and fourth surveys in October and November 2020, April 2021, July and August 2021, and December 2021, respectively. Individuals were observed for three and five to six months to register the decline in the antibodies. In the study, 10,427 people participated. The participants were the Council for Scientific and Industrial Research (CSIR) employees, family members, and students from India’s 17 states and union territories. The Health Department and the Department of Community Medicine (Post Graduate Institute of Medical Sciences, Rohtak) surveyed Haryana. For the first and second surveys, the sample sizes were

18,700 and 15,840, respectively. The number of people assessed for the third round was 36,520. The samples were taken from all 22 districts of the state. The Regional Medical Research Centre (RMRC), Bhubaneswar (Odisha), conducted the serosurvey in Odisha. The serosurvey in 12 of Odisha’s 30 districts was done between August 29 and September 15, 2021. Of the total 5,796 samples collected, 4247 were positive for COVID-19 antibodies. HCWs’ samples were analyzed separately, out of the 1,312 HCWs, 1232 had antibodies. In Delhi, the survey was conducted in 272 wards spread across all 11 districts. The survey was conducted between January 15–23, 2021, and the sample size was 28,000. In the sixth serosurvey, which was conducted in September and October 2021, 28,000 blood samples from 280 wards were examined. Samples were taken from all socioeconomic classes.

3. RESULTS AND DISCUSSION

3.1. Antibodies’ Prevalence and Spread Dynamics in India’s Population and States

In this section, the seroprevalence (IgG antibodies) generated by natural infection and vaccination in Indian states and overall, has been described. In Section 3.2, the percentage of seroprevalence in the Japanese population is presented.

3.1.1. Serosurvey in Tamil Nadu, Vaccination, Hybrid Immunity, and Spread Dynamics

In the fourth serosurvey conducted in December 2021 in the Indian state of Tamil Nadu, an overall seroprevalence of 87% was found [6]. In a research paper [6], all four surveys conducted in the state have been analyzed in detail. The references [7]–[13] provided a systematic description of all four surveys and the contribution of vaccination to the percentage of total antibodies reported. The results of all four of Tamil Nadu’s serological surveys have been given in Table I. The first serosurvey (October–November 2020) reported that 32% of the Tamil Nadu population developed IgG antibodies against the virus. The second survey (April 2021) registered a slight decrease in seropositivity at 29%, whereas the third survey (July–August 2021) showed a steep rise in seropositivity to 70%. The fourth and last survey (December 2021) found that 87% of the population developed antibodies. A proportion of 68% of the 11–18 age group, who were not vaccinated, developed SARS-CoV-2 antibodies. There was 89.5% seropositive in the 18–44 cohort. The seroprevalence rate was 88.6% in the 45–59 cohort and 84.5% in the over 60 group as registered in the fourth survey in Tamil Nadu. The first and second surveys do not show a major contribution from vaccination, as of April 1, 2021, only 3.1% of the state’s residents had at least one dose, and just 0.6% were fully vaccinated. The seropositivity developed was mostly due to exposure to the natural infection. As of August 1, 2021, 22% and 6.2% of the state population (full population) were vaccinated for single- and two-dose regimens, respectively [14]. The third serosurvey, spanning until August 2021, had a contribution from vaccination. The combined effect of the severe Delta wave and vaccination led to a

TABLE I: THE SEROPOSITIVITY IN TAMIL NADU POPULATION

Survey number	First	Second	Third	Fourth
Month/Year	October–November 2020	April 2021	July–August 2021	December 2021
Seroprevalence (%)	32.0%	29.0%	70.0%	87.0%

steep rise in the seroprevalence, at 70%, as shown in Table I. The results of the survey done in December 2021 (the fourth survey), showed that 87% (9 out of 10 persons) developed antibodies against the virus. By November 2021, 53.5% and 28.3% of the population (full) had at least one dose and two-dose vaccination, respectively. Comparing the seroprevalence among unvaccinated residents in the third (63.8%) and fourth (58.7%) surveys, the seropositivity waned by 5.1% in 4–5 months. During the 4–5 months gap between the two surveys, the viral load did not increase in the state that ruled out infection generated antibody changes. Considering the two-dose vaccination data from the third and fourth surveys, 22.1% antibody enhancement must have occurred. But it only rose by 17%, a decrease of 5.1% was noticed. The same observation reported by taking unvaccinated data into account. Waning of the hybrid or natural immunity in 4–5 months among 5.1% of residents occurred considering the state’s full population. Whereas, taking into account the eligible population, the percentage reduction in seroprevalence was 11.7%.

The monthly caseload during all three waves (Wuhan, Delta, and Omicron) was worked out from the COVID-19 dashboard [14]. In August 2020, the monthly caseload of Tamil Nadu reached a plateau of 182,182 during the original Wuhan (first) wave. On receding the first wave, baseline cases were the lowest at 21,263 in January 2021. During the second (Delta surge) wave, monthly cases peaked at 929,760 in May 2021 and decreased to 21,128 in December 2021. Cases plateaued during the Omicron spurt (third wave) at 597,175 in January 2022. In February, cases declined, and the lowest caseload was recorded at 1,107 and 1,542 in April and May, respectively. Seropositivity of 32% was reported in October 2020, owing to the high viral load (182,182 monthly cases) registered in August 2020. In April 2021, seropositivity declined to 29% as the Wuhan wave receded to a low caseload of 21,263 reported in January 2021. Seroprevalence increased again in July 2021 to 70% and 87% in December 2021 due to higher caseload during the Delta and Omicron spurts in May 2021 and January 2022, respectively. In December 2021, the fourth survey revealed a high seroprevalence of 87%. This was due to hybrid immunity from natural infection (caseload) and the vaccination drive, which reached 28.3% of the total population and 36.8% of the eligible population in the state fully vaccinated, respectively. The loss of immunity reported in the Tamil Nadu population (discussed earlier) was similar to the Institute of Genomics and Integrative Biology (IGIB, India) findings that were done in India (overall data) and found that in 6 months, 20%–30% of the infected population lost virus-neutralizing activity [15].

3.1.2. Seroprevalence, Vaccination, Hybrid Immunity, and Spread Dynamics in Haryana

Seroprevalence increased over time in another Indian state, Haryana. The first, second, and third surveys conducted by the Haryana government in August, October 2020, and September 2021 registered 8%, 14.8%, and 76.3% seropositivity, respectively [16]–[21]. In June 2021, the central Indian Government agency (ICMR) conducted the fourth national serosurvey, which reported a seroprevalence of 60% in Haryana [21]. Seroprevalence increased monotonously with time, suggesting the virus spread was continuous. Three non- Omicron waves that hit the state and peaked in September 2020, November 2020, and May 2021 resulted in 76.3% seropositivity, according to the last survey conducted in September 2021 [22], [23]. Every three persons out of four (76.3%) in Haryana developed SARS-CoV-2 antibodies as of September 2021, with 81.6% of the population producing antibodies by vaccination and natural infection combined, whereas 75.5% developed due to virus infection. The vaccination resulted in a net 6.1% enhancement. Individuals who received a two-dose vaccine regimen were 84% seropositive, whereas among one-dose recipients, 79.5% had developed antibodies. We previously published district-wise seropositivity data for all of Haryana’s districts [21]. Kurukshetra district had the highest (85%), and Faridabad had the lowest (64.2%) among all 22 districts. Urban areas of the state had a marginally higher seroprevalence (78.1%) as compared to rural areas (75.1%). Seroprevalence was 75.3% among males, whereas it was slightly higher (77.1%) among females. The cohort of 6–9 years had seroprevalence at 69.8%, and the age group 10–17 reported 73.2% seroprevalence. In terms of vaccination, Haryana administered 16.3 million doses as of August 31, 2021. Considering the entire population, 16.5% underwent full vaccination, while 39.5% received at least one dose. The vaccine-generated antibodies, produced by the above proportion of the doses, will contribute to the seropositivity among the vaccinated individuals. The seroprevalence measured in the fourth national serosurvey of the Indian states reported 60% seroprevalence in the Haryana population in June 2021. From the virus spread dynamics viewpoint, 8% seropositivity reported in Haryana in August 2020 was the result of the initial Wuhan variant wave that peaked on September 17, 2020, with a 7-day daily average caseload of 2567 (88.5 cases per million) [22], [23]. Seroprevalence in October 2020 was 14.8%, resulting from another wave that peaked in November 2020 with a daily new caseload of 2563 (88.4 per million). The two other serosurveys conducted in Haryana in June–July 2021 (the fourth national survey) and September 2021 showed seropositivity at 60% and 76.3%, respectively, due to the strong Delta wave that hit the state and peaked on May 10, 2021, with a daily caseload of 14,430 (497.5 cases per million). The Delta wave receded in the last week of June 2021, and the caseload (7-day average daily)

was reduced to baseline cases at less than 40 daily (1.4 per million) cases until the Omicron surge started in the last week of December 2021. Strong vaccination drive and previous infection might have reduced the caseload during the highly contagious Omicron variant. For per-million calculations, we used Haryana's estimated population from the online population dashboard [24], [25]. During the Delta wave, the mortality rate in Haryana was high at 5.6 per million (7-day average) reported at the peak (163 deaths on May 11, 2021), while it reduced to just 0.6 per million (7-day average) at the peak (17 deaths on February 4, 2021) during the Omicron spurt. The less pathogenic nature of the latter variant led to nearly a ten-fold reduction in the mortality rate. Also, high seropositivity (76.3%) developed among the population, contributing to the decrease in mortality during the Omicron surge in the state.

3.1.3. Seroprevalence, Vaccination, Hybrid Immunity, and Spread Dynamics in Odisha

The seroprevalence in another state of India, Odisha, was recorded in August 2020, June 2021, and August 2021 and was found to be 20.8%, 68.1%, and 73%, respectively [21], [26]–[28]. By June 2021, 85% of HCWs had developed antibodies against the virus, while the general population reported 68.1% in the same period. The seropositivity rose to 93% among HCWs, while in the general population, it increased to 73% reported in August 2021. The increase in seroprevalence in June was due to the Delta wave that hit the state in April–June 2021. HCWs exposure to a higher viral load while attending to patients led to the higher seroprevalence. Age-wise analysis revealed 70%, 74%, 75%, 72%, and 66% of antibodies among cohorts 6–10, 11–18, 19–44, 45–60, and above 60 years of age, respectively [29]. The state's rural (72.7%) and urban (73.7%) areas showed no significant difference in seropositivity. Men and women had the same proportion of seroprevalence. According to Odisha state data [29], Covaxin and Covishield vaccines produced the same number of antibodies. A total of 22.0 million vaccine doses were administered all over the state as of August 31, 2021. Out of them, 16.7 million (35.5% of the full population) received at least one dose, and 5.3 million (11.3% of the full population) were fully inoculated. We used the current estimated state population and vaccination data from references [23], [30]–[34] to calculate the percentage of the vaccinated population. The original Wuhan wave (first wave) hit the state and peaked on September 27, 2020, with a caseload of 4,272 daily new infections (7-day average) (91.0 cases per million) that produced antibodies in 20.8% of the population, according to the first (August 2020) survey conducted in the state. The state experienced a strong Delta wave on May 26, 2021, resulting in seroprevalence of 68.1% and 73.0% in June and August 2021, respectively, with an average of 11,583 new infections per day (246.4 cases per million). Because of the high hybrid immunity (73.0%) that resulted from infection and vaccination, the subsequent Omicron wave remained slim and short (maximum daily 7-day average 10,837; January 21, 2022). Mortality during the Delta spurt was a maximum of 68 deaths (1.44 per million) (7-day average) reported on August 25, 2021, while it was much less, a 7-day average of 22 deaths (0.46 per million)

on February 12, 2022, were recorded during the Omicron surge.

3.1.4. Seroprevalence, Vaccination, Hybrid Immunity, and Spread Dynamics in Delhi

The SARS-CoV-2 IgG antibody detection method and statistical analysis have been described in an article [35]. A brief description of the survey has been given below. For the fifth serosurvey, residents aged five and older were selected for antibody testing. The survey was conducted in 272 wards spread across all 11 districts of Delhi. The survey was conducted in January 2021, and the sample size was 28,000 participants. In September–October 2021, the sixth serosurvey was done, testing 28,000 blood samples collected from 280 wards of Delhi. Serosurvey was done using CLIA technology, which was said to be more accurate and sensitive than ELISA technology. During the testing of samples, a uniform method was used to ensure the reproducibility of the data. Samples were collected from the individuals of all social and financial strata. The first pandemic wave appeared in Delhi, India's capital city, in June 2020, which triggered the transmission of the virus and caused two consecutive waves in September and November 2020. The infected individuals produced antibodies against the virus. The level of antibodies produced remained the same in the range of 22.9%–29.1% (Table II), as measured in the four different surveys conducted between June and October 2020 [36]. The transmission of the virus was slow, with no significant increase in seropositivity reported. In January 2021, the fifth serological survey reported a significant increase of 56.13% in individuals who developed antibodies [37]. More than half of the city's population was exposed to the virus [38]–[42]. The large monthly caseload, 8959 cases per million in November 2020, much higher than 387 cases per million recorded at the beginning of the pandemic in June 2020, was responsible for the high level of antibodies registered in the fifth survey. The current Delhi population was taken from the dashboard [43] to work out the per million caseloads. The wave that appeared in November 2020 caused the virus to spread faster, as could be seen in the fifth survey conducted in January 2021, which showed a seroprevalence of 56.1%. The Delta wave that hit the city in the first week of March 2021 and peaked in April 2021 was the biggest and nearly infected every person in the city, as the sixth serosurvey conducted in September–October 2021 showed 97% seroprevalence among the individuals [44]–[49]. The strong Delta wave, which hit the city with a viral load, peaked in April 2021 with 23,751 per million monthly cases. The high percentage of seropositivity (97%) was due to the net antibodies generated from infection, reinfection, vaccination, and breakthrough infections.

Table III shows the results [50] of seroprevalence among self-referred individuals in Delhi, conducted by the Thyrocare Laboratories under the project of the Canadian Institutes of Health Research and the University of Toronto, Canada. The seropositivity was 25.2%, 22.8%, 27.8%, 34.3%, 43.7%, and 54.9% in July, August, September, October, November, and December of 2020, respectively [51]. The seropositivity developed against the virus among the general population and self-referred

TABLE II: INCREASE IN SEROPREVALENCE IN DELHI POPULATION WITH TIME AMONG GENERAL POPULATION

Survey number	First	Second	Third	Fourth	Fifth	Sixth
Month/Year	June–July 2020	August 2020	September 2020	October 2020	January 2021	September–October 2021
Seroprevalence (%)	22.9%	29.1%	25.1%	25.5%	56.1%	97.0%

TABLE III: INCREASE IN SEROPREVALENCE IN DELHI POPULATION WITH TIME AMONG SELF-REFERRED INDIVIDUALS

Month/Year	July 2020	August 2020	September 2020	October 2020	November 2020	December 2020
Seroprevalence (%)	25.2%	22.8%	27.8%	34.3%	43.7%	54.9%

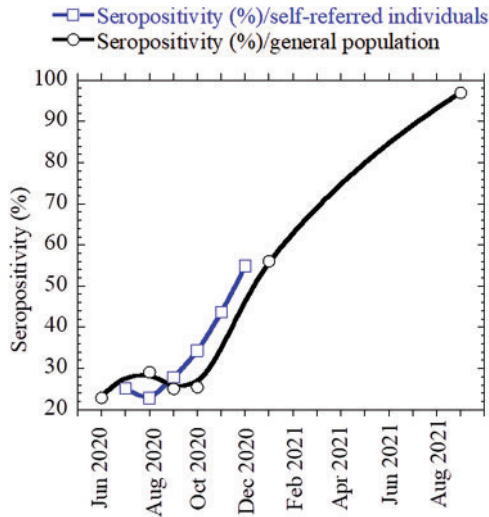


Fig. 1. Comparison of seropositivity (%) in Delhi among self-referred individuals and the general population.

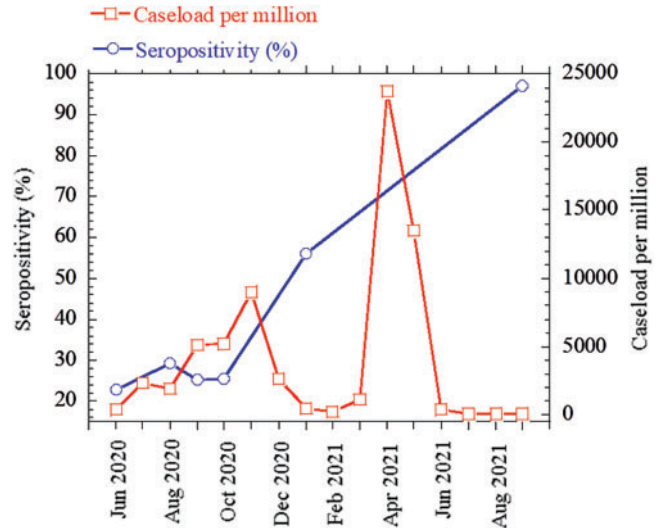


Fig. 2. Comparison of seropositivity (%) versus caseload (per million) in Delhi during Original Wuhan and Delta waves for the period June 2020 to September 2021.

wealthy individuals in Delhi is nearly the same as shown in Fig. 1. Table IV shows the gender- and age-wise seroprevalence recorded in the sixth survey. The seropositivity in women was slightly higher (90%) than in men (88%). The seroprevalence was the highest at 92% among the population above 50 years followed by 90% in the age cohort 18–49 and 82% in <18 years. The elderly generated more IgG antibodies against the virus than younger individuals. Table V shows the seropositivity recorded in Delhi among vaccinated and unvaccinated cohorts and other following details. The seropositivity between individuals <18 years and unvaccinated adults was the same at 82%. The proportion of antibodies among one-dose and two-dose regimen recipients was the same at 95%. Individuals who were inoculated with the Covishield (AstraZeneca-Oxford) vaccine manufactured at the Serum Institute of India (SII) developed 95% seropositivity, whereas the Covaxin (Bharat Biotech, India) generated marginally less, 93% seropositivity. The net enhancement (gain) in per cent seroprevalence registered on the ground in the real world under various conditions or cohorts has been shown in Table VI. Inoculation with one- or two-dose vaccine regimens resulted in a similar proportion of a 13% increase in seropositivity. Delhi’s population had an overall antibody threshold of 95%. The district-wise seroprevalence in Delhi city is shown in Table VII. In decreasing order of seropositivity, the districts were: East (99.8%), North East (99.7%), Central (99.5%), South (99%), North West (98.5%), South West (95.9%), South East (95.9%), New Delhi (95.7%), West (95.2%), North (95.1%), and Shahdara (94.3%).

After studying the net proportion (%) of antibodies remaining in real among the various cohorts taking into account of vaccination, reinfection, breakthrough infection, and the antibodies diminishing due to waning, the impact of the per cent seroprevalence on the caseload has been investigated as below. Fig. 2 shows the monthly caseload (per million) plot along with the percentage of seroprevalence reported in Delhi. The caseload (per million) reported in June 2020 was 387 which kept increasing till November (8959) and then showed a decrease in December 2020 (2682) reaching a minimum (204) in February 2021. The peak caseload reported in November 2020 was due to the original Wuhan variant, which spread worldwide in the early days of the COVID-19 pandemic. As the seropositivity plot shows, a decrease in value in September (25.1%) and October (25.5%) from a high (29.1%) in July was due to decreasing viral load in August (1909) from a higher load in July (2353). After the original Wuhan wave receded in December with a viral load of 2682 from a peak viral load reported in November (8,959) (plot part-year 2020), the seropositivity did not show a decrease because the virus kept spreading among the population of Delhi as the high viral load registered at the Wuhan lineage was enough to initiate the spreading. However, the viral load dipped to a low (204) in February 2021 before the Delta variant wave hit the city in March 2021 with the viral load (1128) and peaked in April 2021 with 23,751 per million monthly cases. This high viral load was enough to infect almost every individual in the city, with

TABLE IV: AGE- AND GENDER-WISE SEROPREVALENCE REPORTED IN SIXTH SURVEY (SEPTEMBER–OCTOBER 2021) IN DELHI POPULATION

Cohort	Below 18 years	18–49 years	Above 50 years	Males	Females
Seroprevalence (%)	82%	90%	92%	92%	88%

TABLE V: SEROPREVALENCE IN UNVACCINATED AND VACCINATED COHORTS IN DELHI POPULATION

Below 18 years	Unvaccinated	One-dose vaccination	Two-dose vaccination	Covishield	Covaxin
82%	82%	95%	95%	95%	93%

TABLE VI: ENHANCEMENT IN SEROPREVALENCE IN DELHI POPULATION BY VACCINATION UNDER DIFFERENT CONDITIONS AS REPORTED IN SIXTH SEROSURVEY

Cohort	1-dose vaccination	2-dose vaccination	Covishield	Covaxin
Gain of seroprevalence (%) due to vaccination	13%	13%	13%	11%

TABLE VII: DISTRICT-WISE SERO-PREVALENCE IN DELHI REGISTERED IN SIXTH SURVEY (SEPTEMBER–OCTOBER 2021)

District	East	North East	Central	South	North West	South West	South East	New Delhi	North	West	Shahdara
Seroprevalence (%)	99.8%	99.7%	99.5%	99%	98.5%	95.9%	95.9%	95.7%	95.1%	95.2%	94.3%

a seropositivity rate of 97% reported in the sixth survey in September–October 2021. The high seropositivity of 97% of the infected population may have contributed to the Delta wave's decline to the lowest recorded viral load in September 2021.

Table VIII compares the various health incidents and occurrences during the Delta and Omicron waves that hit Delhi. On April 24, 2021, Delhi reported a 7-day average daily caseload of 25,255 at the peak of the Delta wave. In terms of per million, there were 1,174 daily new cases. The daily caseload at the peak of the highly transmissible Omicron wave (January 16, 2022) was 23,530, and in terms of per million, it worked out to be 1094 cases. Considering the mortality rate, the 7-day average mortality rate at the peak during the Delta wave was 18.5 per million, or 1.57% of the total infections. On May 4, 2021, 398 deaths were registered in Delhi. During the Omicron wave on January 25, 2022, there were only 38 reported deaths, accounting for 1.76 per million and 0.16%, nearly tenfold lower compared to the Delta wave. The generation of strong hybrid immunity, as evidenced by 97% of the city's population having IgG antibodies against the virus (sixth survey, September–October 2022), contributed to a relatively low daily caseload and significantly lower mortalities during the Omicron wave compared to the Delta wave.

3.1.5. Seroprevalence, Vaccination, Hybrid Immunity, and Spread Dynamics in Overall India

The ICMR collected the samples in May 2020 for the first national serological survey to detect the prevalence of the viral disease (COVID-19) in all of India [52]. The first nationwide seroprevalence was 0.73%. Among those seropositive for SARS-CoV-2 infection, 43.3% were aged

18–45. The age group 46–60 years accounted for 39.5% of the total samples. The study included a total of 28,000 participants. A proportion of 0.5% (151 individuals) contracted the virus from COVID-19 patients, and 0.3% (70 persons) tested positive before the survey. Individuals residing in urban slums faced a higher risk of exposure to infected persons. A cumulative total of 6.4 million adult infections were estimated in India by early May 2020, and the survey's results were reported in June. Samples were collected from 700 villages in 21 states across India, spanning 70 districts. The ICMR study revealed that the formation of antibodies (IgG) begins one week after the onset of symptoms and reaches the detection limit in two weeks. Following is the comparison of the first, second, third, and fourth national serosurveys of India conducted by the ICMR. The results of all four national surveys have been described in references [53]–[56]. In brief, the first serosurvey (May–June 2020) revealed that 0.73% of the adult population had IgG antibodies against the virus. The second survey, which took place between August and September 2020, revealed an increase in seropositivity to 7.1%. The third survey, which took place from December 17, 2020, to January 8, 2021, revealed a further rise in seroprevalence to 24.1%. A proportion of 24.1% of individuals who were seropositive developed antibodies merely due to infection, as vaccination in India started in mid-January 2021 [54]. Between June and July 2021, the fourth national survey revealed that 67.6% (two-thirds) [55]–[58] of the population had antibodies against the SARS-CoV-2 virus. The first survey covered only adults. Children aged 10 years and older were included in the third survey, while children of the cohort aged 6 years and older were tested in the fourth survey. The fourth survey reported hybrid

TABLE VIII: COMPARISON OF DIFFERENT INCIDENCES OR OCCURRENCES BETWEEN DELTA AND OMICRON WAVES IN DELHI

Wave	7-day average daily caseload per million at the peak	7-day average daily mortalities per million at the peak	Mortalities (%)
Delta wave	1174	18.5	1.57%
Omicron wave	1094	1.76	0.16%

TABLE IX: COMPARISON OF SEROPREVALENCE BETWEEN OKINAWA (JAPAN) MAIN ISLAND AND REMOTE ISLANDS AT THREE DIFFERENT PERIODS BETWEEN JULY 2020 AND FEBRUARY 2021

Survey number/Date	Seroprevalence (%)		Case detection (%)	
	Main island	Remote island	Main island	Remote island
First (July 1–July 31, 2020)	0.0%			
Second (October 1–December 31, 2020)	0.6%	0.0%		
Third (February 1–February 28, 2021)	1.4%	1.6%	2.7%	2.8%

TABLE X: EFFECT OF VACCINATION ON INCREASING NEUTRALIZING ACTIVITY

Survey date	% IgG against		Neutralization activity (%) against	
	N-protein	S-protein	Delta variant	Omicron variant
August 2021	2.1%	38.7%		
December 2021	3.9%	90.8%	78.7%	36.6%

immunity, seroprevalence reported resulted from the combination of vaccination and infection. At the time of the fourth survey, 13% of the Indian population had received full vaccinations, while 24% were partially vaccinated. The fourth survey reported that the high viral load during the Delta surge in May 2021 accelerated the virus spread in its later stages. According to state-wise seropositivity data, 66.6% of the population in 11 Indian states developed antibodies against the virus [57]. A report [57] listed the percentage of antibodies formed in 21 states of India. Madhya Pradesh, with 79% seroprevalence, had the highest infection rate, whereas Kerala had the lowest (44.4%). Age-wise seropositivity was found in the cohorts of 6–9, 10–17, 18–44, 45–60, and above 60 years in the order: 57.2%, 61.6%, 66.7%, 77.6%, and 76.7%, respectively. The fourth survey of India's population recorded the following vaccine-generated antibody data: the unvaccinated cohort had a 62% seroprevalence, followed by one-dose (81%), and two-dose (90%). According to a review paper [53], 24% of the population who received a single vaccine dose showed a 19% increase in seropositivity. In comparison, when 13% of the population received two vaccination doses, their seropositivity increased by 28%. HCWs had a seropositivity of 85%, which was lower than the two-dose vaccinated general population (90%) because 10% of HCWs had not received vaccination. As recorded in Delhi, the seroprevalence among the Indian population can be as high as 97%. Hybrid immunity from virus infection and vaccination, resulting in seropositivity of 80%–97%, has prevented the recurrence of many subsequent waves and fatalities in India. In other parts of the world, the virus caused more damage than in India. The fourth serological survey showed that one in three Indians did not have IgG antibodies. As a result, there were still approximately 400 million people at risk of getting infected with SARS-CoV-2 [58], [59].

3.2. Antibodies Prevalence and Spread Dynamics in Japan's Population

Batra et al. have explained [60] the different types of proteins present in the SARS-CoV-2 virus. Immunoglobulin G (IgG) antibodies that target the N-protein (nucleocapsid protein) located in the viral core of the SARS-CoV-2 virus are detectable in the serum of infected patients. In article [60], the percentage of IgG generated against N-protein

as a result of clinical outcomes of the COVID-19 virus has been described. The SARS-CoV-2 virus contains four key structural proteins: the S-Protein (Spike Protein), M-Protein (Matrix Protein), E-Protein (Envelope Protein), and N-Protein (Nucleocapsid Protein). The neutralizing antibodies IgG generated against the S-protein provide an immune response to the attacking virus. The primary target of the vaccines is the S-protein of the virus. Table IX presents a comparison of the seroprevalence between Okinawa's main and remote islands. The table illustrates the three periods of a cross-sectional survey [61], [62]. The survey was conducted during three periods: July 1–31, 2020, October 1–December 31, 2020, and February 1–28, 2021. Surveys were conducted in remote islands only during the second and third survey periods. The main island recorded a seroprevalence of 0.0%, 0.6%, and 1.4% in the first, second, and third surveys, respectively. During the second and third surveys, seroprevalence rates were recorded at 0.0% and 1.6%, respectively, in remote islands. The third survey revealed a 2.7% case detection ratio on the main island and 2.8% on remote islands. The case detection ratios indicated that the cumulative number of cases in Okinawa should be 2–3 times higher than those reported by routine RTPC or RAT testing surveillance. Regular serosurveys were necessary to determine the actual number of cases. Low seropositivity suggested that, until February 2021, the large-scale transmission had not occurred in Okinawa. The effect of the SARS-CoV-2 vaccination was assessed [63] through sera analysis of infected patients undergoing health checkups (Table X). In August, the N-seropositive rate was 2.1%, and in December 2021, it was 3.9%. The strong vaccination drive in Japan led to a steep rise in the S-seropositive rate, from 38.7% in August to 90.8% in December. Among the December 2021 cohort, 78.7% of the individuals exhibited neutralizing activity against the Delta variant, whereas only 36.6% showed such activity against the Omicron strain. In December 2021, a large number of people developed effective immunity against the Delta version of the virus, while booster or bivalent doses of the vaccine were required to contain the Omicron variant. In 90.9% of patients, neutralizing antibodies (NAbs) remained for 12 months after the primary infection [64]. However, the median titers decreased with time, as recorded at 2, 6, and 12-month intervals. The titers dropped to 56.2% after 12 months. The NAb titers

TABLE XI: VARIOUS INCIDENCES CAUSED BY INFECTIONS

Survey date	Clinic survey done	Sample size (Samples screened)	Positive sample for IgG and (%)	Age and sex adjusted positivity	Total number of people infected in Kobe (Non sex-adjusted)	Total number of people infected in Kobe (Sex-adjusted)	Population of Kobe city (Japan)	Caseload of Kobe city by PCR as of April 7, 2020
March 31–April 7, 2020	Kobe, Japan	1,000	33 (3.3%)	2.7%	50,123	41,000	1,518,870	69

TABLE XII: DIFFERENT INCIDENCES CAUSED BY INFECTION

Survey date	Clinic survey done	Sample size (Sample screened)	Kurabo immunochromatographic assay	Abbott CMIA	Total number of people infected in Kobe (Abbott assays)	Caseload in Kobe city as determined by PCR	Population of Kobe city (Japan)	Estimated caseload by sero survey higher than PCR (times)
May 26–June 7, 2020	Kobe, Japan	1,000	18 (1.8%)	2 (0.2%)	3,038	285	1,518,870	10.7

decreased to an undetectable level over 35.5 months after the onset of the infection, according to an exponential decay model. It was therefore suggested that the individuals need booster or bivalent vaccine shots within one year of the onset of the infection to be on the safe side, though an ample amount of NABs remained after one year.

Researchers have developed a method [65]–[67] to accurately estimate the prevalence of COVID-19 infection in Japan. Using 1000 outpatients who visited clinics in Kobe (Japan) between March 31 and April 7, 2020, 33 of the 1000 serum samples tested positive for IgG antibodies. Tables XI and XII provide estimations of various incidences or occurrences based on serological surveys and methods established in the above references. The number of infected individuals in the above table was estimated to be 396 to 858-fold more than the confirmed cases reported from PCR testing done in Kobe City. Out of 1000 samples scanned for the period May 26–June 7, 2020, in Kobe City (Kobe City Medical Center General Hospital designated for COVID-19 patients), 18 were positive using Kurabo immune-chromatographic assays, and only 2 were positive from Abbott CMIA. Thus, only two samples were positive for both of the above assays. The assay results showed discrepancies in 16 samples.

4. CONCLUSIONS

In Tamil Nadu, seroprevalence was 87% as recorded in the December 2021 survey (fourth survey), up from 70% reported in July 2021 (third survey). The age group 11–18 had 68% SARS-CoV-2 antibodies; they were unvaccinated individuals. Age group 18–44 had 89.5% seropositivity. In the 45–59 cohort, the seroprevalence rate was 88.6%, while among the cohort over 60, it was 84.5%. The first serosurvey (October 2020) reported 32% of the population developing SARS-CoV-2 IgG antibodies. The second survey (April 2021) revealed a slight decline (29%) in seropositivity. The third and fourth surveys revealed hybrid immunity against the virus, which was the result of natural infection and a strong vaccination drive in Tamil Nadu. In the first two surveys, the SARS-CoV-2 virus infection was the sole cause of seroprevalence due to the low vaccination

rate until the second survey. Given Tamil Nadu’s two-dose (full) vaccination data from the third and fourth surveys, 22.1% antibody enhancement must have occurred. However, only a 17% increase was observed with a 5.1% decline. Considering the unvaccinated data yielded a similar finding. Taking into account the entire population of the state (full population), 5.1% of residents saw a waning of hybrid or natural immunity in 4–5 months. The waning of the antibodies was 11.7% when only the eligible population was considered.

The serological survey was conducted in Haryana, India. Over time, the seroprevalence rose. In August, October 2020, and September 2021, the Haryana government conducted its first, second, and third surveys and found that 8%, 14.8%, and 76.3% of the state’s population were seropositive, respectively. Indian government agency carried out the fourth nationwide serosurvey in June 2021, revealing a seroprevalence of 60% in Haryana. People in the state developed seropositivity in three waves that hit in September, November 2020, and May 2021. Vaccination enhanced a net seropositive of 6.1%. Overall, 84% of two-dose vaccine recipients developed antibodies, and 79.5% of one-dose recipients tested seropositive. During the Omicron spurt, Haryana’s mortality rate was barely 0.6 per million (7-day average), compared to a high of 5.6 per million (7-day average) at its peak (163 fatalities on May 11, 2021) during the Delta wave. The death rate was about ten times lower during the Omicron wave due to its less pathogenic character. Additionally, the population developed high hybrid seropositivity (76.3%), which helped to lower the state’s death rate during the Omicron surge. In August 2020, June 2021, and August 2021, the seroprevalence in Odisha, another state in India, was reported to be 20.8%, 68.1%, and 73%, respectively. By June 2021, 85% of HCWs had produced antibodies against the virus compared to 68.1% in the general population. In August 2021, the seropositive rate grew to 93% among HCWs and 73% in the general population. Seropositivity rates in Odisha’s rural (72.7%) and urban (73.7%) areas did not differ significantly. The seroprevalence proportion was the same for males and females. According to Odisha state data, the number of antibodies produced by the Covaxin

and Covishield vaccines was equal. The original Wuhan wave (first wave) struck the state (Odisha) and peaked on September 27, 2020, with a caseload of 4,272 daily new infections (7-day average) (91.0 cases per million) that developed antibodies in 20.8% of the population. Strong Delta waves struck the state on May 26, 2021, with an average of 11,583 new infections per day (246.4 cases per million) and seroprevalences of 68.1% and 73.0% in June and August 2021, respectively was reported. The Omicron wave was narrow and short because to the strong hybrid immunity (73.0%) that came from infection and immunization. Reports showed a maximum daily 7-day average of 10,837 cases on January 21, 2022. Maximum mortality during the Delta surge was 68 fatalities (1.44 per million) (7-day average) reported on August 25, 2021. However, substantially lower mortality was recorded on February 12, 2022, with a 7-day average of 22 deaths (0.46 per million) at the peak of Omicron surge.

The virus began to spread in June 2020, when the first pandemic wave emerged in Delhi, the capital city of India. This led to two additional waves in September and November of 2020. The level of antibodies generated, as determined by four separate surveys carried out between June and October 2020, remained within the range of 22.9%–29.1%. The virus spread slowly, and there was no noticeable rise in seropositive cases. In January 2021, the fifth serological survey indicated a significant increase in the percentage of individuals who developed antibodies, reaching 56.13%. The fifth survey revealed a high level of antibodies due to a large monthly caseload of 8959 cases per million in November 2020, significantly higher than the 387 cases per million recorded at the start of the pandemic in June 2020. The sixth serosurvey, which was carried out in September and October 2021, revealed a 97% seroprevalence among the people, indicating that the Delta wave, which struck the city Delhi in the first week of March 2021 and peaked in April 2021, was the largest and almost infected every person. The powerful Delta wave severely affected the city, peaking in April 2021 with a 23,751 monthly (per million) caseload.

The ICMR collected samples in May 2020 to conduct the nation's first nationwide serological survey to determine the prevalence of the COVID-19 virus infection. The production of antibodies (IgG) starts one week after symptoms appear and takes two weeks to reach the detection level. In August and September of 2020, the number of seropositive individuals increased to 7.1% in the second survey. Between December 17, 2020, and January 8, 2021, the third survey revealed an increase in the prevalence of infections to 24.1%. Infection alone was the cause of antibody formation in 24.1% of seropositive persons since vaccination campaigns in India began in mid-January 2021. The fourth national survey conducted between June and July 2021 found that 67.6% (two-thirds) of people had antibodies against the SARS-CoV-2 virus. The fourth survey identified a hybrid immunity seroprevalence resulting from a combination of infection and vaccination. On the completion of the fourth survey, 13% of Indians had received both the recommended doses, while 24% had only received a partial vaccination. The virus spread more quickly due to the high viral load during the Delta wave

that hit India in May 2021, as revealed in the fourth survey's results. State-wise data indicated that Madhya Pradesh had the highest infection rate (79%), while Kerala had the lowest (44.4%). For cohorts 6–9, 10–17, 18–44, 45–60, and over 60, seropositivity was 57.2%, 61.6%, 66.7%, 77.6%, and 76.7%, respectively. The fourth survey in India found 62% seroprevalence in unvaccinated group, 81% in one-dose cohort, and 90% in two-dose recipients.

The types of proteins found in the SARS-CoV-2 virus have been identified. Four essential structural proteins are present in the SARS-CoV-2 virus: the N-protein (nucleocapsid protein), the M-protein (matrix protein), the E-protein (envelope protein), and the S-protein (spike protein). The invading virus triggers an immunological response from the neutralizing antibodies (IgG) produced against the S-protein. The virus's S-protein is the main target of the vaccines. The seroprevalence rates of Okinawa's (Japan) main and distant islands were measured for the following three periods: July 1–31, 2020, October 1–December 31, 2020, and February 1–28, 2021. Only the second and third rounds included the remote islands. In the first, second, and third surveys (mentioned above), the seroprevalence on the main island was 0.0%, 0.6%, and 1.4%, respectively. The seroprevalence rates on the remote islands were 0.0% and 1.6% in the second and third surveys, respectively. On the main island, the third survey found a 2.7% case detection ratio, while on distant islands, it was 2.8%. The analysis of serosurvey data from India and Japan can provide important insights into pandemic management and the development of new drugs and medicines. The study of hybrid immunity resulting from infection and vaccination is important in the context of the gradual loss of immunity. Populations should be vaccinated periodically. There is a need to expedite the development of multivalent vaccines to protect citizens.

STATEMENTS

No experiments on animals, humans, or in the laboratory were conducted. The author, Zameer Shervani (ZS), Ph.D., is the Director General of the Food & Energy Security Research & Product Center located in Sendai, Japan. The article copyrights belong to the corresponding author (ZS). Coauthors contributed online. Authors have qualifications: Intazam Khan MD; Deepali Bhardwaj MBBS, MD, DVDL, M.Phil.; Muhammad Jehanzeb Khan Ph.D.; Venkata Phani Sai Reddy Vuyyuru MBBS; Adil Ahmed Khan MBBS; Parangimalai Diwakar Madan Kumar BDS, MDS; Aisha Mahmood MBBS.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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