Dynamic Change of COVID-19 Seroprevalence among Asymptomatic Population in Tokyo during the Second Wave

Sawako Hibino MD Ph.D.[1], Kazutaka Hayashida MD Ph.D.[2], Andrew C, Ahn, MD, MPH[3], Yasutaka Hayashida MD Ph.D.[1]

1. Y's Science Clinic Hiroo, Medical Corporation Koshikai, Tokyo, Japan.
2. Division of pulmonary medicine, Boston Children's Hospital, Boston. USA
3. Division of General Medicine and Primary Care, Beth Israel Deaconess Medical School, Boston, USA

Abstract

Importance: Fatality rates related to COVID-19 in Japan have been low compared to Western Countries and have decreased despite the absence of lockdown. Serological tests monitored across the course of the second wave can provide insights into the population-level prevalence and dynamic patterns of COVID-19 infection.

Objective: To assess changes in COVID-19 seroprevalence among asymptomatic employees working in Tokyo during the second wave.

Design: We conducted an observational cohort study. Healthy volunteers working for a Japanese company in Tokyo were enrolled from disparate locations to determine seropositivity against COVID19 from May 26 to August 25, 2020. COVID-19 IgM and IgG antibodies were determined by a rapid COVID19 IgM/IgG test kit using fingertip blood. Across the company, tests were performed and acquired weekly. For each participant, serology tests were offered twice, separated by approximately a month, to provide self-reference of test results and to assess for seroconversion and seroreversion.

Setting: Workplace setting within a large company.

Participants: Healthy volunteers from 1877 employees of a large Japanese company were recruited to the study from 11 disparate locations across Tokyo. Participants having fever, cough, or shortness of breath at the time of testing were excluded.

Main Outcome(s) and Measure(s): Seropositivity rate (SPR) was calculated by pooled data from each two-weeks window across the cohort. Either IgM or IgG positivity was defined as seropositive. Changes in immunological status against SARS-CoV-2 were determined by comparing results between two tests obtained from the same individual.

Results: Six hundred fifteen healthy volunteers (mean + SD 40.8 + 10.0; range 19 - 69; 45.7 % female) received at least one test. Seroprevalence increased from 5.8 % to 46.8 % over the course of the summer. The most dramatic increase in SPR occurred in late June and early July, paralleling the rise in daily confirmed cases within Tokyo, which peaked on August 4. Out of the 350 individuals (mean + SD 42.5 + 10.0; range 19 - 69; 46.0 % female) who completed both offered tests, 21.4 % of those individuals who tested seronegative became seropositive and seroreversion was found in 12.2 % of initially seropositive participants. 81.1% of IgM positive cases at first testing became IgM negative in approximately one month.

Conclusions and Relevance: COVID-19 infection may have spread widely across the general population of Tokyo despite the very low fatality rate. Given the temporal correlation between the rise in seropositivity and the decrease in reported COVID-19 cases that occurred without a shut-down, herd immunity may be implicated. Sequential testing for serological response against COVID-19 is useful for understanding the dynamics of COVID-19 infection at the population-level.

Introduction

Mortality from COVID-19 has been low in Japan as compared to the United States and European countries[1]. The reasons for the low number of deaths are unknown and may relate to either low prevalence of SARS-CoV-2 infections in the general population or diminished fatality rates among those infected. Distinguishing which of these factors come into play requires data on the total prevalence of SARS-CoV-2, particularly among the asymptomatic general population. To estimate the incidence of COVID-19, serology tests were obtained in asymptomatic individuals throughout the summer of the year 2020, incorporating the time before, during, and after the well-documented "second-wave" of COVID-19 infection in Japan. For each participant, serology tests were offered twice, separated by approximately a month, to provide self-references of test results, to identify cases of both seroconversion and seroreversion, and to estimate the seroprevalence of the general population in Tokyo over time.

Methods

Six hundred fifteen healthy volunteers (mean $\pm$ SD 40.8 $\pm$ 10.0, range 19 - 69; 45.7 % female) from 1877 employees of a large Japanese company were enrolled from 11 disparate locations across Tokyo. As is the general practice in Japan, participants commuted daily to their workplace: remote working was not practiced. Tests were performed weekly from May 26 to August 25 (except for 6/2, and 8/11; those designated to 8/11 were rescheduled to 8/18). Participants having fever, cough, or shortness of breath at the time of testing were excluded. Fingertip blood was applied onto the cassette of the COVID19 IgM/IgG rapid test kit (Aurora Biomed, Vancouver Canada) to detect antibodies. A second subsequent test was offered 3-5 weeks after the first. For each week, less than 150 participants received the tests across the study cohort. Data were combined every two weeks, and Seropositivity Rates (SPR) were calculated. Seropositivity was defined as having either IgM or IgG positive results. The SPR 95 % confident interval (95% C.I.) was calculated by binomial distribution [$\pm 1.96 \times \sqrt{(p(1-p)/n)}$]. An outside ethical committee reviewed and approved the protocol.

Results

The demographic characteristics of participants were composited every two weeks and summarized in Table 1. Seroprevalence increased from 5.8 % to 46.8 % throughout the summer (Figure). The most dramatic increase in SPR occurred in late June and early July, paralleling the rise in daily confirmed cases within Tokyo[1], which peaked on August 4.

Out of the 615 participants, 350 individuals (mean ± SD 42.5 ± 10.0; range 19 – 69; 46.0 % female) completed both offered tests. The interval between tests was 30.5 ± 5.6 days (Mean ± S.D.). From the subset of individuals who initially tested seronegative, 21.4 % (54/252) seroconverted to a seropositive result (Table 2). For the individuals who initially tested IgM positive, 81.1% (73/90) became IgM negative. Seroreversion was found in 12.2 % (12/98) of initially seropositive participants. There were no instances where serological tests revealed a physiologically unexpected result – for example, a case where IgM negativity and IgG positivity became IgM positive at the subsequent test. Out of all possible states, IgM+/IgG- was the least common, 0.4% (3/700 total tests), suggesting that the window when IgM is positive before the onset of IgG positivity is short in duration. None of the seroconverted individuals were hospitalized or had died.

Discussion

In this cohort, the SPR increased to an unexpectedly high 46.8 % by the end of the summer after the peak of the second-wave. This rate exceeds the estimated seroprevalence of COVID-19 in a known epicenter like New York City (20.2 %)[2]. Although our cohort was not selected from a broader, random sampling of Tokyo, this data may still be generalizable to the greater metropolitan area for a number of reasons: participants were sampled from multiple disparate locations across Tokyo; they had limited physical interactions with each other given the organizational structure of the company – limiting the role of clustering; participants were well-distributed across age and gender; and the initial SPR for this cohort started low at 5.9 % (95%CI [0,12.3%]) mirroring the pattern seen in Tokyo. Moreover, the exclusion of individuals with clinical symptoms may have led to an underestimation of total SPR. A high seropositivity rate in Tokyo may not be fully unexpected given its remarkably high population density, tight-spacing, the widespread use of public transportation, and no implementation of a "lock-down".

This study is unique in its utilization of sequential serological testing in a moderately sized cohort of asymptomatic individuals. The paired testing allows for an understanding of the temporal dynamics of the immunoglobulin response. First, the rapid tests did not yield any unreasonable answers: there were no illogical transitions (e.g., IgM-/IgG+ to IgM+/IgG-), and the overall SPR pattern remained stable over the course of testing (Figure). Second, IgM positivity is short-lived, typically turning negative over one month. Third, seroreversion was not infrequent, seen in 12% of participants over the one-month span between tests. This suggests that serological testing may significantly underestimate past COVID-19 infections, particularly when applied to an asymptomatic population.

These findings should also take into context the epidemiological dynamics seen during this COVID-19 wave. Japan took the atypical step of not instituting a mandatory lock-down. During this time, businesses, restaurants, and transportation were kept open, and public life continued relatively unabated. Nevertheless, the second wave peaked and subsided on its own. With the rise in SPR nearing 50% (Figure) within our cohort, matching the time when COVID-19 cases waned, the possibility of herd immunity should be considered, particularly in the highly-dense urban scenario like Tokyo. If this were true, then the remarkably low mortality related to COVID-19 should also be examined. Much like our cohort which had no reported hospitalizations, clinical severity in Tokyo was low. During the second surge, only 31 fatal cases (observed between June 22 and August 25) were reported in Tokyo, while the first surge (March 20 to May 20) claimed 244 lives. Assuming an infection rate of 40 % within the Tokyo urban population (14 million), the infection fatality rate (IFR) during this period could potentially be as low as 0.0006%, which is as low as the lowest IFR observed among teens in Switzerland[4]. Future studies may consider evaluating whether lifestyle/habits, viral strain, the widespread use of masks, and/or host factors such as immunological memory are responsible for the observed low fatality.

This study has several limitations. First, the cohort was a sampling of a single large company in Tokyo and not of the population, in general. Second, detailed medical histories and behavioral patterns of each employee were not obtained. Such information would have been helpful in understanding the role of cross-exposure and the factors associated with reduced fatality. Third, paired testing was separated by a month. Closer intervals may have yielded more granular insights into the immunological responses to SARS-CoV-2 infection. Despite these limitations, this study is one of the first, to our knowledge, to obtain sequential COVID-19 serological testing in an asymptomatic population and also provides an explanation for why rates of COVID-19 had declined in Tokyo despite the absence of a public lock-down.

Reference:

1. "Coronavirus: Japan's mysteriously low virus death rate". 4, July 2020. dot: https://www.bbc.com/news/world-asia-53188847
2. Updates on COVID-19 in Tokyo (https://stopcovid19.metro.tokyo.lg.jp/en/)
3. Rosenberg ES, Tesoriero JM, Rosenthal EM, et al. Cumulative incidence and diagnosis of SARS-CoV-2 infection in New York. Ann Epidemiol. 2020; 48; 23-29 E4. doi: https://doi.org/10.1016/j.annepidem.2020.06.004
4. Perez-Saez FJ, Lauer SA, Guessous I, et al. Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland. The Lancet. 2020; 396 (10247); 313-319 DOI:10.1016/S1473-3099(20)30584-3

Figure Legend

Tests were performed at 5/26, 6/9, 6/16, 6/23, 6/30, 7/7, 7/14, 7/21,7/28, 8/4, 8/18 and 8/25. Data from every two weeks are combined, and SPR is calculated. SPR (closed circle) with 95 % confident interval (95% C.I.) is plotted on the graph. 7 days moving average of daily confirmed new case number in Tokyo on the indicated dates (closed triangle) is also shown. Seropositivity numbers and the total number of antibody tests performed for each two-weeks window are shown at the bottom of the graph.

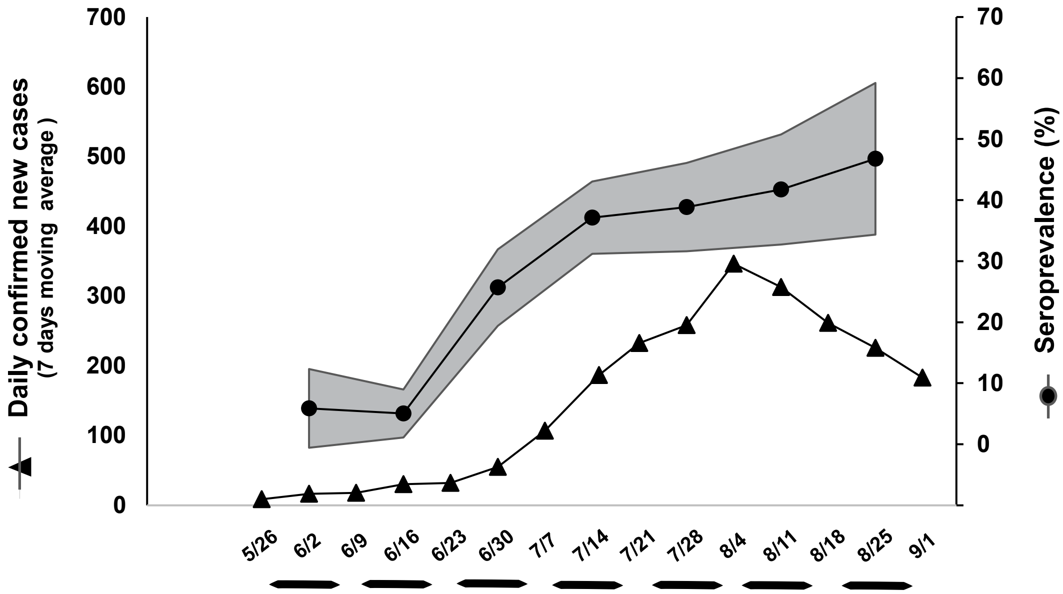
Table 1. Baseline background characteristic of the participants on each two-weeks window

Date	5/26-6/9	6/10-6/23	6/24-7/7	7/8-7/21	7/22-8/4	8/5-8/18	8/19-9/2
Age , mean (SD)	45.6 (9.1)	42.5 (8.7)	40.7 (9.5)	40.9 (10.3)	41.0 (10.5)	41.5 (9.7)	41.6 (12.2)
No. (%)							
Age groups, y							
30>	3 (5.9)	9 (7.6)	27 (14.4)	39 (15.2)	28 (16.0)	10 (8.7)	12 (19.4)
30-39	9 (17.6)	36 (30.3)	59 (31.6)	79 (30.9)	50 (28.6)	43 (37.4)	18 (29.0)
40-49	23 (45.1)	50 (42.0)	70 (37.4)	85 (33.2)	62 (35.4)	40 (34.8)	15 (24.2)
50-59	13 (25.5)	20 (16.8)	26 (13.9)	44 (17.2)	28 (16.0)	18 (15.7)	13 (21.0)
60 or older	3 (5.9)	4 (3.4)	5 (2.7)	9 (3.5)	7 (4.0)	4 (3.5)	4 (6.5)
Gender							
Male	43 (84.3)	74 (62.1)	104 (55.6)	137 (53.5)	82 (46.9)	59 (51.3)	23 (37.1)
Female	8 (15.7)	45 (37.8)	83 (44.4)	119 (46.5)	93 (53.1)	56 (48.7)	39 (52.9)

Table 2. The comparison of two antibody test results in the same individuals.

Second test \ First test	Seronegative	IgM(+)/IgG(-)	IgM(+)/IgG(+)	IgM(-)/IgG(+)	Total
Seronegative	198	0	7	5	210
IgM(+)/IgG(-)	0	0	0	0	0
IgM(+)/IgG(+)	17	2	8	1	28
IgM(-)/IgG(+)	37	1	72	2	112
Total	252	3	87	8	350

Figure. The seropositivity rate and 7 days moving average of daily confirmed new cases of COVID19 from 5/26 to 9/1



Positive no.	**3**	**6**	**48**	**95**	**68**	**48**	**29**
Tested no.	**51**	**119**	**187**	**256**	**175**	**115**	**62**

Tests were performed at 5/26, 6/9, 6/16, 6/23, 6/30, 7/7, 7/14, 7/21,7/28, 8/4, 8/18 and 8/25. Data from every two weeks are combined, and SPR is calculated. SPR (closed circle) with 95 % confident interval (95% C.I.) is plotted on the graph. 7 days moving average of daily confirmed new case number in Tokyo on the indicated dates (closed triangle) is also shown. Seropositivity numbers and the total number of antibody tests performed for each two-weeks window are shown at the bottom of the graph.

Article information

Corresponding Authors;

Kazutaka Hayashida, MD, Ph.D. Division of Pulmonary Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston MA 02115

(kazutaka.hayashida@childrens.harvard.edu)

Yasutaka Hayashida, MD, Ph.D. Y's Science Clinic Hiroo, Medical Corporation Koshikai, 5-15-27 Minami-Azabu, Minato-ku, Tokyo, Japan

(pandarinda@gmail.com)

Author Contributions:

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design*:* K Hayashida.

Acquisition of data*:* H Hibino, Y Hayashida

Analysis, or interpretation of data*:* K Hayashida, A Ahn

Drafting of the manuscript*:* K Hayashida, A Ahn.

Critical revision of the manuscript for important intellectual content*:* All authors.

Administrative, technical, or material support*:* H Hibino, Y Hayashida

Supervision*:* All authors.

Conflict of interest disclosure

Nothing to disclose for all authors

Funding/Support

No funding. The antibody test kits were generously donated from an anonymous donor.

Role of the Funder/Sponsor

The donor had no role or influence in the design and conduct of the study, analysis, and interpretation of the data, preparation, review, and submission for the publication of the manuscript.