Dynamic change of COVID-19 seroprevalence among asymptomatic office workers in Tokyo from May through Dec 2020 during the second waves of COVID-19.

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Abstract

Background COVID-19 deaths per capita in Japan have been low compared to Western Countries despite the absence of the lockdown. It is still unclear either the less spreading of the virus or, the less progression to the severe illness. Therefore, it is crucial to determine the seropositivity rates (SPR) in the general population. We determined SPR in healthy office workers in Tokyo with validation of results by comparing two test results from the same individual a month apart.

Method Healthy office workers for a Japanese company in Tokyo were determined seropositivity against COVID19 weekly from May 26 to August 25, 2020, by a rapid COVID19 IgM/IgG test kit using fingertip blood. SPR was calculated by pooled data from each two-week window. For each participant, tests were offered twice, separated by a month, to provide self-reference to validate the results. The seropositive individuals were offered a follow-up test on Dec 8th or 15th, 2020, when the third wave loomed in Tokyo, to determine the persistence of the seropositivity.

Results 615 volunteers (mean + SD 40.8 + 10.0; 45.7 % female) from 11 discrete locations received at least one test. 350 individuals completed two tests a month apart. The comparison showed that 93.2 % showed reasonable status changes and no instances with physiologically unexpected changes (e.g., IgG (+) turns IgM(+) in a month). Seroprevalence increased from 5.8 % to 46.8 %, paralleling the rise of the cases in Tokyo. Among 152 seropositive participants, 74 participants underwent the follow-up test in Dec 2020. 40.5 % turned seronegative in four months (mean $\pm$ S.D. 120 $\pm$ 17 days).

Conclusion COVID-19 infection may have spread widely in Tokyo despite the low fatality. Given the temporal correlation between the rise in seropositivity and the peak out of COVID-19 cases without a lockdown, temporary herd immunity might be achieved. However, the relatively short-lived antibodies among the asymptomatic individuals may explain why the herd immunity strategy has not succeeded, and COVID-19 resurgence happens every several months. Moreover, 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 countries¹. Although the reasons for the low number of deaths are unknown, either lower spreading of the virus or lower risk to develop severe illness can contribute to it. The fewer confirmed case numbers suggest that SARS-CoV-2 does not spread in Japan. However, the differences are much bigger than that expected by racial background². Moreover, they did not take any strict lockdown measures, which other countries took to mitigate the spreading. It is hard to understand that such a loose restriction can minimize the virus spreading more efficiently than in other countries. Therefore, the actual prevalence of COVID-19 in the community may be much bigger than expected from the case numbers. Serology tests should be a key to determine the viral load in the community. However, there is a big caveat with the

serology tests for asymptomatic individuals because there are no other methods to identify the person who contracted the virus without any symptoms for confirmation of the results.

Instead, we could validate the results of asymptomatic individuals by comparing the "paired sera". Detecting the change of antibody status/titer over time will find the results are valid. We used this approach to determine the seroprevalence among asymptomatic office workers in Tokyo during the summer of 2020, before, during, and after the 2nd wave of COVID-19.

Since it is unclear whether the antibodies can be persistent in the infected individuals even when they did not develop symptoms, we also performed the follow-up serological tests on the seropositive individuals in Dec 2020, when the 3rd wave of COVID-19 loomed in Tokyo.

Methods

We offered COVID-19 antibody test to 1877 employees of a Japanese company. Six hundred fifteen healthy volunteers (mean $\pm$ SD 40.8 $\pm$ 10.0, range 19–69; 45.7 % female) from 11 disparate locations across Tokyo participated the study. As is the general practice in Japan, participants commuted daily to their workplace: remote working was not common. First, each participant was offered two tests about one month apart. These 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 COVID19 IgM/IgG rapid test kit (Aurora Biomed, Vancouver, Canada) to detect antibodies. The seropositive case numbers were combined every two weeks, and Seropositivity Rates (SPR) were calculated. The SPR 95 % confident interval (95% C.I.) was calculated by binomial distribution [$\pm 1.96 \times \sqrt{(p(1-p)/n)}$]. We compared the first two test results a month apart for the self-reference to validate the results. Further, those who had positive test results were offered the follow-up test on Dec 8 or 15. An outside ethical committee reviewed and approved the protocol. All procedures were conducted in accordance with the approved protocol. Informed consent was obtained from all participants in this study in the written form.

Results

The demographic characteristics of the participants were composited every two weeks and summarized in Table 1. Seroprevalence increased from 5.8 % to 46.8 % throughout the summer (Fig. 1). The most dramatic increase in SPR occurred in late June and early July, paralleling the rise in daily confirmed cases within Tokyo³, which peaked on August 4. Out of the 615 participants, 350 individuals (mean $\pm$ SD 42.5 $\pm$ 10.0; range 19–69; 46.0 % female) completed the initial two tests. The interval between these tests was 30.5 $\pm$ 5.6 days (Mean $\pm$ S.D.). Among 350 individuals, 152 had seropositive results. 93.2 % (142/152) of these seropositive individuals showed some status change between the two tests (e.g., seronegative to positive, or seroconversion) (Table 2). 12.2 % (12/98) of the seropositive participants at the first test became seronegative at the second test (Table 2). There were no instances where the two tests a month apart revealed physiologically unexpected changes – for example, a case where IgM negativity and IgG

positivity became IgM positive in a month. Among 152 seropositive participants, 74 participants (52%: women, median age: 44 years, range: 23–69 years) underwent the follow-up test. The interval between the test showing positive results and the third test was approximately four months (mean $\pm$ S.D. 120 ± 17 days). Thirty of 74 participants (41 %) were seronegative at the third test (Table 3).

Discussion

The seroprevalence of COVID-19 has been determined in various groups or regions. Those figures are mostly less than 20 %, which is far below the level for herd immunity. However, every surge of COVID-19 spontaneously peaks out. Although many factors should be involved for the peak-out, we must consider possible herd immunity, even if it is temporary. We observed a considerable jump in the seroprevalence from 5.8% up to 46.8 %, which is extremely high compared to other reports in Japan^{3,4}. However, the jump was parallel to the surge of the 2nd wave in Tokyo⁵. Soon after our cohort SPR reached 40 %, the second wave peaked (Fig. 1). Moreover, 40.5 % of seropositive individuals turned negative in four months, when the 3rd wave in Tokyo loomed⁵.

The seroprevalence in our cohort changed the same way to the daily new case numbers in Tokyo, and substantial seronegative conversion was observed at the early stage of the 3rd wave. Comparing the paired samples also confirmed that almost all seropositive individuals showed antibody status change and no illogical transitions. These findings strongly indicate that our results are valid and calculated SPR is not overestimated. Furthermore, SPR as high as 46.8% could explain why the 2nd surge peaked, probably due to temporary herd immunity if SPR in the general population in Tokyo also reached beyond 40 %. Although herd immunity is generally believed to require more than 70% SPR, our data suggest that a substantial fraction of the population contracted the virus silently, which was enough to achieve temporary herd immunity.

We used the first-generation rapid antibody test kit from Aurora Biomed. Generally, the lateral flow type antibody test is considered less reliable and more likely to give false-positive results⁶. However, to calculate the false positive rate in people with COVID-19 unknown status, we need some assumptions of COVID-19 infection prevalence in the community. Therefore, the direct validation of the results in asymptomatic individuals is still lacking. Indeed, the principle of antibody test is straightforward where the viral antigen and human immunoglobulin detecting reagents are required. Thus, the quality of reagents should not matter too much. The variations between kits probably arise from the difference in thresholds for the positive results among individual test kits. Therefore, if we use it for asymptomatic people, the cut-off point should be validated separately.

We do not know why our kit provides such high SPRs. They use a mixture of COVID-19 S and N antigens for antibody capture, while many other kits use a single antigen. It probably helps to increase the detectability or may have a lower threshold. Our data may indicate that the previously reported seroprevalences were underestimated. Especially for asymptomatic individuals, who should have a lower level of antibodies, we may need to use the lower threshold.

In the follow-up study, more than 40 % of seropositive individuals turned seronegative in four months. Thus, this observation suggests the antibodies induced in asymptomatic individuals are short-lived, even though half of the seropositive individuals in our cohort dropped off before the 3rd test. Given that most infected people are asymptomatic or with very mild symptoms, the short duration of the antibody persistence in the asymptomatic population will explain why the herd immunity strategy has not succeeded and why we have a resurgence of COVID19 every several months. In contrast, the vaccination provides persistent and higher antibody titers even after six months⁷. Therefore, extensive coverage of the general population by vaccination should be critical to eradicating COVID-19 from the community.

This study has some limitations. First, the cohort was a sampling of a single large company in Tokyo and not the general population. Therefore, the seroprevalence may reflect the local virus spreading among the employees. However, we did not have any cluster COVID-19 infection in our cohort, and participants were widely recruited from 11 discrete locations. Thus, the high SPR is unlikely to attribute to a cluster of COVID-19 infection at a single site. Second, detailed medical histories and behavioral patterns of each employee were not obtained. They do not usually visit different locations, but the role of cross-exposure between employees cannot be excluded. Third, our antibody test is qualitative and not quantitative. Therefore, negative results indicate the complete loss of neither antibody nor immune memory. Further studies using a quantitative antibody measurement are required.

Our data suggest COVID-19 spreads widely among people disproportionally with low mortality (137/1M at 5/9/2021) in Tokyo. If our data is confirmed, there must be some factors (social, behavioral, or biological) preventing people from developing severe illnesses. Further studies should be guaranteed to determine what makes the difference.

Sequential testing for serological response against COVID-19 will help validate the results and understand the dynamics of COVID-19 infection at the population level, especially when we determine the viral load among asymptomatic individuals.

Declarations

Ethics approval and consent to participate

The protocol was reviewed and approved by a third-party ethics committee (Tokyo Cancer Clinic ethics committee, case number TCC2020-01). All procedures were conducted in accordance with the approved protocol. Informed consent was obtained from all participants in this study in the written form.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Consent for publication

All authors agreed to publish this study.

Conflict of interest disclosure

Nothing to disclose for all authors

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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: S 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: S Hibino, Y Hayashida

Supervision: All authors.

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Role of the donor

The donor of the kits 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.

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Tables

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Figures

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.

Figure 1

The seropositivity rate and 7 days moving average of daily confirmed new cases of COVID-19 during the second wave

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [COVID19seroprevalencetable1.pdf](#)
- [Covid19seroprevalencetable2.pdf](#)
- [Covid19seroprevalencetable3.pdf](#)