■Introduction

Hi, everyone!

Last year, the second and third-grade students of Izumo high school learned about COVID-19 online in May. (https://www.izumo-hs.ed.jp/information/28935). At that time, the school was closed due to the first emergency status, which affected the whole of Japan. Since then, Tokyo has experienced three more emergency statuses, while Shimane prefecture was spared. We have published some message from your online questionnaire (https://www.izumo-hs.ed.jp/information/29321). “Have you had any outbreak of COVID-19 in Izumo city or Shimane prefecture?” and “How many COVID-19 patients do you have, and what is the incidence?”

On July 23 the Tokyo 2020 Olympic and Paralympic Games are set to commence — if they are not canceled. On June 21, the IOC, Tokyo Metropolitan Government, central government, and related organizations released a joint statement informing that on July 12, a decision will be made on whether to declare a new emergency status or implement a semi-emergency status. The semi-emergency status will principally follow countermeasure policies such as no audience at events — do you think it is appropriate as a countermeasure policy? How would you evaluate these audience policies ex post? Let us learn more about COVID-19 again!

■Epidemiology

As of June 24, 2021, there were 787,988 confirmed infections in Japan - an incidence of approximately 0.5% = is this high or low compared to the rest of the world?

The Ministry of Health, Labour and Welfare has provided the online resource “Visualizing the data: information on COVID-19 infections” (https://covid19.mhlw.go.jp/en/), which comprises important COVID-19 epidemiological data. Examples of these are, “Trend in the number of newly confirmed cases (daily),” “Number of newly confirmed cases per 100,000 population,” and “Trends in the number of severe cases.” Keeping track of cases is important. Many severe cases risk exhausting healthcare capacities such as ICU beds and respirators; however, healthcare capacity does not need to be exceeded for the healthcare system to collapse. It happens when regular medical services that were provided before COVID-19 emerged cannot be provided anymore. The purpose of the countermeasure policy implemented in Japan was to prevent medical collapse.

Other data available are “Number of confirmed cases by sex and age (cumulative)” and “Deaths by sex and age (cumulative),” which provide information on the age distribution of the disease. Before the emergence of mutated strains, there were very few confirmed infections in persons younger than 20, and most of them were asymptomatic. While there are still relatively few young patients in Japan — with no severe cases — recent investigations have reported that the delta strain infects younger persons more frequently than the original strain. Therefore, we will have to examine the change in age distribution should the delta strain become dominant in Japan.

■Epidemiological curve

Last year, we learned the importance of the epidemiological curve, which indicates the number of patients by onset date. However, media have reported the number of new infections per day; additionally, the Ministry of Health, Labour and Welfare presents daily data in its figure (https://www.mhlw.go.jp/stf/covid-19/open-data.html) Since these data represent daily new COVID-19 patients confirmed with PCR tests — including asymptomatic patients -they do not describe the epidemiological curve. They are thus referred to as "newly confirmed positive cases." Onset date has not been reported in many cases; moreover, data of symptoms for each patient is missing. Therefore, we have to estimate the epidemiological curve from newly confirmed positive cases without any information about onset. Two data points are important to estimate the curve: reporting delay, the number of days from disease onset to it being reported, and the proportion of asymptomatic cases.

None of the patients have been required to visit a doctor immediately after onset; some patients stayed in bed for a few days, whereas others continued their daily activities before seeing a doctor and receiving a test. Moreover, PCR test results occasionally take a few days until they are returned; whenever a result is positive, it is reported to the public health center. Finally, the prefectural office summates the reported numbers from public health care centers and publishes them on their home page and through the media. On average, it takes approximately seven days from disease onset until it is reported to the public. Typically, reporting delays should be distributed over several days; however, to simplify, we ignore this requirement and use a fixed number of seven days for reporting delays.

It is important to consider that newly confirmed positive cases also include asymptomatic patients who do not have an onset date, by definition. These people were in close contact with confirmed cases and thus tested positive. Since they were identified by the public health center using different sampling procedures from symptomatic patients, we cannot aggregate them with symptomatic patients. The proportion of newly confirmed positive cases that were asymptomatic was stable at approximately 20%; hence, we can ignore them.

■Creating the epidemiological curves

We can draw epidemiological curves based on these assumptions using open data of newly confirmed positive cases provided by the Ministry of Health, Labour and Welfare. First, we exclude asymptomatic cases, which were approximately 20% of Xt, which was the number of newly confirmed positive cases on day t. In other words, 0.8Xt was estimated to show onset on day t-7. Therefore, the epidemiological curve, Yt, is simply $Yt=0.8X_{t+7}$.

■Rt（the effective reproduction number）

Then, we calculate Rt =the effective reproduction number = which we explained briefly last year, defined as the number of persons infected per symptomatic case on day t. If Rt is larger than one, the number of cases increases exponentially; conversely, the number of cases decreases if it is less than one. Thus, it is an important index for predicting the course of the outbreak. Rt is different from R_0, the basic reproduction number, and may probably depend on factors like climate conditions (such as temperature and humidity), personal countermeasures including wearing a mask and social distancing, countermeasure policies like emergency status declarations, and limiting the size of audiences at large events, and frequency of going out on day t. In addition, vaccination coverage was expected to reduce Rt because the virus has less access to un-vaccinated susceptible persons; similarly, the development of the outbreak also reduced Rt.

A common misconception is that Rt is a measure of the number of infections; however, Rt is an index of infectiousness on day t and does not indicate the number of infected individuals. Therefore, if Rt is high, such as 3 over a few days, it may not significantly affect the epidemiological curve. Conversely, if it were slightly higher than 1, such as 1.01, the epidemiological curve would increase explosively over several years. In this sense, the length of the period is as important as Rt to determine the epidemiological curve.

■Calculation of Rt

Now let's actually calculate Rt. The important data points needed to calculate Rt are the distribution of the incubation period, from infection to onset, and the virus shedding pattern for each day from onset.

Rt is indicated by “the number of people infected on the t day”/ “the number of people who have the ability to infect others on the t day.” First, calculate the “number of people infected on day t” of the numerator. In the model I propose to you, the incubation period is simply calculated as an average of 6 days. In addition, the incubation period of 6 days is set to 50%, and the incubation period of 5 or 7 days is set to 25%. The “number of people infected on day t” of the numerator is $0.5Y_{t+6}+0.25Y_{t+7}+0.25Y_{t+5}$ using the number of patients Y on the epidemiological curve calculated earlier. Second, let us calculate the denominator “the number of people who are infectious to others on the t day.” After the onset, the viral load shed from an affected person changes daily. In this model, we set the highest infectivity on the day of onset. Next, the infectivity on the 2nd and 3rd days decreases by 25%, and the infectivity on the 4th and subsequent days is assumed to be 0%. "The number of people who have infectivity to others on the t day" is $0.5Y_t+0.25Y_{t-1}+0.25Y_{t-2}$ weighted by the distribution of infectivity. The final calculation formula is $Rt = (0.5Y_{t+6}+0.25Y_{t+7}+0.25Y_{t+5}) / (0.5Y_t+0.25Y_{t-1}+0.25Y_{t-2})$.

It seems very simple and can be very easily calculated using Excel; however, it can also be calculated without a computer. So, let us try to do it.

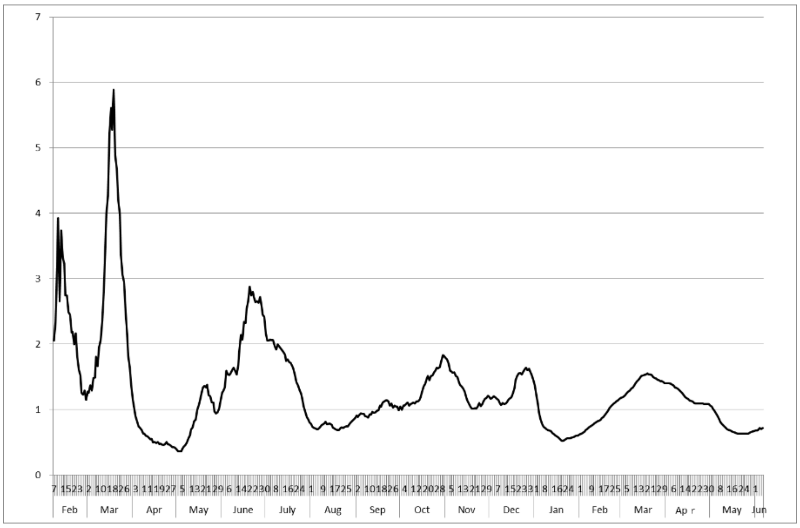
■Evaluation of the countermeasure policy

Next, let us consider how and whether the countermeasure policy affects Rt or does not affect Rt at all. For example, the so-called Omi proposition, issued on June 18, 2021, proposed that no audience was the least risky option in the Olympic and Paralympic Games. Half of you probably feel that this was an obvious conclusion; the other half may feel like it is a kind of Copernicus's revolution! However, no evidence was presented to support the proposition that no audience provided the least risk. When using a countermeasure with a limited audience smaller than half of the capacity or less than 5,000 was applied, did the infection risk remain? Were there people infected after attending a big event as an audience? Fortunately, we have not heard such a report from the media in Japan. If they proposed the risk to the audience without any evidence, it was not based on scientific evidence. It may have been emotional prejudice by nonprofessionals.

These kinds of emotional prejudices first appeared during the public argument on whether the Go to Travel campaign should cease or continue at the end of 2020. At that time, media and so-called "professionals" insisted that the Go to Travel campaign would promote movement and thus increase infection risk. As a result, it was argued that the campaign would cause a third wave, and therefore it should be stopped immediately to control the outbreak and prevent a health care system collapse.

This argument appears to be true — but is that really the case? If it was just a prejudice without any evidence, then the prejudice resulted in the end of the campaign causing massive damage to the travel industry and related persons. The validity should be argued based on scientific evidence; science has to prove whether common sense is true or not.

How does one present evidence? Here, we used the Rt in the attached excel file, shown in the figure. Note that our Rt was calculated on the basis of the actual distribution of reporting delay, incubation period, and virus shedding pattern. Thus, it is probably slightly different from your calculation above. However, it is possible to use the previously calculated series of Rt to check the following.



Supposing that a countermeasure policy such as the Go to Travel campaign was in place for period A, then it follows that this policy would not be in place for period B. If Rt for period A would then be much smaller than period B, we could conclude that the countermeasure policy indeed reduces Rt. Thus, the countermeasure policy is effective. Conversely, if Rt for period A would be almost comparable with or larger than Rt for period B, we would conclude that the countermeasure policy was ineffective in reducing Rt.

In fact, in many cases, there was no substantial difference between Rt during the two periods. For example, the average of Rt for period A was larger than the average of Rt for period B, but the difference was not small. In this case, we could propose the effectiveness of the countermeasure, but the evidence might be too weak. Statistical analysis could solve this ambiguity, but it is beyond the scope of this paper. You can learn all about it at university if you are interested.

We will make use of the Go to Travel campaign as a specific example. The Go to Travel campaign was initiated from July 22 to December 28, 2020; we will refer to this as period A. Defining period B may be more difficult and perhaps arbitrary because the first and second emergency statuses were declared right before and after the campaign, it may therefore be pertinent to exclude the periods during which the emergency status was in place from period B so as to avoid any confounding effects. Consequently, we will tentatively define period B as June 1, 2020, the day after the first emergency status ceased, to January 7, 2021, the day before the second emergency status was activated, excluding period A.

First, let us make a figure of the two Rt series for both periods on the same domain. Which average is larger? Did the two lines almost overlap? To measure the degree of overlap, one can draw a histogram of Rt for both periods. As mentioned before, the supposed definition of period B in this argument is just an example. Let us compare them using the previously calculated Rt in the excel file and another definition of period B.

■Effect of a no audience policy.

When you read this paper, the Olympic and Paralympic Games will already have closed. Alternatively, it may have been canceled a few days before the opening. Whatever it may be, let us consider the effect on the infectiousness of an audience during the big event as argued in the Omi proposition using the data.

Following the implementation of the first emergency status, audiences had not yet been banned for big events. However, during the 2020 season, the opening of professional baseball games in Japan was delayed until June 19. Even after the start, there was no audience until July 10, when it was limited to 50% of the capacity or a maximum of 5,000. Therefore, period A with respect to the no-audience policy can be defined as the period from June 19 to July 10, while period B can be defined as the period from July 11 onward. Seasonality, especially during the cold winter season, might affect infectiousness; we tentatively set the last day of the post-season match as the end of period B.

How about averages, figures, or histograms? Was infectiousness with a restricted audience larger than with no audience?

■ Exercise

We consider the effect of the audience using data from 2020. So, naturally, the next question is, how about the 2021 season? This is your homework.

The 2021 professional baseball season in Japan started at the end of March, with the audience limited to less than 50% of the capacity or 5,000. On April 8, 2021, a third emergency status was declared in Tokyo, Osaka, and Hyogo, during which no audience was allowed during the games. Because the emergency status was applied to some prefectures only, one game had an audience, while another had none. Therefore, unlike for 2020, we cannot divide periods the A and B for the whole of Japan. It is necessary to calculate the Rt and determine periods A and B for each prefecture to examine the effect. Alternatively, a scatter diagram showing infectiousness and the reported number of audience members in a game (instead of setting periods A and B) may be insightful.

■Supplemental Exercise (if the Olympic games were to be held): Would the Olympic and Paralympic Games exacerbate the outbreak?

Consider the proposition by Omi in June 2021 that the Olympic and Paralympic Games be closed for safety. Did the main concern at that time, that the Olympic and Paralympic Games would exacerbate the outbreak, come true? Unfortunately, the games have not yet opened, and thus, we do not know the answer at this moment. However, we can guess its impact on the outbreak from experience with professional baseball games in 2020 and 2021; though it is reminiscent of ex ante speculation, an ex post evaluation is necessary since propositions without ex-post evaluation are just simple prejudice. For this exercise period A should be the Olympic and Paralympic Games session. In contrast, period B should include before and after the games, similar to how it was defined in the example above. You should consider many different definitions of period B and evaluate your proposal.

■Personal countermeasures

Because much of your life is spent in groups at school, infectious diseases may easily circulate. Therefore, personal countermeasures may be necessary for schools to prevent large outbreaks that cause the cancelation of events or class/school closures. How should we implement countermeasures at school?

First, the most important point is early detection. If we can identify something indicating an outbreak, we could take countermeasures earlier. One example of this could be through routine health monitoring, such as checking your body temperature every day — do you do this? It is important to stay home from school when you fall ill. Schools summarize information about reasons for your absence from school in surveillance reports, which are used to monitor for action. In Shimane Prefecture, all schools and nursery schools participate in the (nursery) school surveillance system and exchange information about the outbreak situation in local areas such as Izumo city or prefecture wide, timely every day. For example, whenever aberrations are found, if the number of absentees in Izumo City has been increasing, this information is provided to students, teachers, and other related people, and countermeasures are immediately recommended.

Second, it is important to counter by cutting off the circulation of viruses. Last year, we learned that SARS-CoV-2 could infect us through droplets or contagion; therefore, we should wear masks as a countermeasure for droplet infection coupled with hand washing and disinfection, as needed to counter contagion. How often and when do you wash your hands?

Handwashing prevents the virus from proliferating, as it can only replicate by invading cells, such as those of the mucous. However, it cannot invade the skin; it simply attaches to the surface. If it is attached to the surface of an object, it gradually loses its activity; therefore, washing hands is the most powerful countermeasure to protect against infection.

The third countermeasure is decreasing susceptibility and increasing immunity, which can be achieved through natural infections and vaccination. At the end of June 2021, immunization of medical staff and older adults is underway, and immunization of adults younger than 65 years, with underlying diseases has started. After that, you will receive the vaccination. While vaccination provides immunity against infection, it may not be perfect, and some vaccinated individuals are still infected — though rarely. In this context, personal countermeasures such as wearing masks, maintaining social distance, and washing hands are still necessary to prevent infection. Moreover, the current vaccine is based on the original strain, and thus it might confer weaker protection against the mutated strain. Additionally, a further mutated strain might emerge in this winter or the near future, from which the current vaccine cannot protect. In this case, we will have to receive a vaccine every year, similar to influenza.

■Variant strains

You have learned about how SARS-CoV-2, a type of coronavirus, causes COVID-19, and currently, its variant strain is of great concern. All viruses, including influenza viruses, are thought to vary their genomes a little continuously over time. Did you ever see a model of DNA with a double helix structure at school? (It was discovered by Dr. Watson and Dr. Crick on February 21, 1953.) Many viral genomes consist of RNA, which is similar to DNA but has only one chain; therefore, mistakes when copying are more common. This difference also means that their evolutionary speed is much higher than that of the animate with DNA. SARS-CoV-2 is an RNA virus that is usually thought to mutate at a rate of approximately one nucleotide every two weeks.

The name of the variants was initially a geographical name based on the country where it was first discovered, such as England or India. However, due to concerns about discrimination, the WHO changed the nomenclature of the variant strains on May 31, 2021, to use Greek letters (such as alpha and beta). As of June 11, 2021, the alpha strain has almost replaced the original strain; however, the delta strain is projected to replace the alpha strain due to its infectiousness, which is higher than that of the alpha strain. (https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2484-idsc/10434-covid19-43.html)

However, in cases where the new variant strain is more infectious than the older dominating strain, personal countermeasure recommendations will probably not be changed. This is because keeping up with social distancing, wearing masks, and washing hands effectively prevent infection. The current vaccines are thought to be effective in avoiding mutated strains; however, they may not be effective for mutations in the near future. Therefore, we may need to take a shot every year, such as influenza.

■To be a society without prejudice or discrimination.

Last year, you learned about prejudice and discrimination in the history of infectious diseases. We asked you to read the Preamble of Infection Control Law aloud. “Meanwhile, in the past in Japan, there was groundless discrimination or prejudice against patients suffering from leprosy, acquired immunodeficiency syndrome (AIDS), and other infectious diseases, and those suffering from a similar illness. The Japanese public must take these facts seriously and apply them as moral lessons for the future.” This passage may be our homework. Nevertheless, why are prejudice and discrimination still repeated throughout history?

In the COVID-19 outbreak, because it was an emerging disease and there were many unknowns, people were anxious. By learning more about the characteristics of the disease and gaining protection from vaccination and/or taking appropriate personal countermeasures, this anxiety might be resolved. However, when information is insufficient or biased, many people are misled, leading some of us to occasionally speak badly to or hurt others to relieve anxiety slightly. This uneasiness frequently leads to prejudice or discrimination in society.

COVID-19 will likely mutate in the future, therefore, we need to remain vigilant in our countermeasures to keep the outbreak in check. Moreover, we should collect information about epidemiological characteristics, including vaccine efficacy, so that we can be cautious without being overly afraid. We believe that scientific knowledge and judgment can lead us to a society without prejudice or discrimination.