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Viral transmissibility of SARS-CoV-2 accelerates in the winter, similarly to influenza epidemics

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The transmissibility of SARS-CoV-2 is anticipated to increase in the winter because of increased viral survival in cold damp air and thus would exacerbate viral spread in community. Analysis to capture the seasonal trend is needed to be prepared for future epidemics. We compared regression models for the 5-week case prior to each epidemic peak week for both the COVID-19 and influenza epidemics in winter and summer. The weekly case increase ratio was compared, using non-paired t tests between seasons. In order to test the robustness of seasonal transmission patterns, the normalized weekly case numbers of COVID-19 and influenza case rates of all seasons were assessed in a combined quadratic regression analysis. In winter, the weekly case increase ratio accelerated before epidemic peaks, similarly, for both COVID-19 and influenza. The quadratic regression models of weekly cases were observed to be convex curves in the winter and concave curves in the spring/summer for both COVID-19 and influenza. A significant increase of case increase ratio (3.19 [95%CI:0.01-6.37, \(P = .049\)]) of the COVID-19 and influenza epidemics was observed in winter as compared to spring/summer before the epidemic peak. The epidemic of COVID-19 was found to mirror that of influenza, suggesting a strong underlying seasonal transmissibility. Influenza epidemics can potentially be a useful reference for the COVID-19 epidemics.

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BACKGROUND

COVID-19 has spread worldwide within a few months and resulted in millions of deaths globally.\(^1\)\(^2\) As previously observed for the 2009 influenza pandemic (Flu 09 pdm), a novel invasive respiratory virus in a naïve population, initial epidemic waves occurred randomly throughout the year and dependent upon time of arrival. This non-seasonality was observed for COVID-19 in Japan, where the first epidemic wave occurring in March was followed by subsequent epidemics in July, December, April before the largest epidemic occurring around the Olympic Games, which started on July 22, 2021.\(^3\) A current burning question is whether patterns of COVID-19 cases will become seasonal as was the case for the 2009 influenza pandemic H1N1 virus and is the case for our endemic respiratory infections (seasonal coronaviruses and influenza).\(^4\)\(^5\) Numerous studies have addressed the drivers of seasonality common to respiratory viruses, with significant roles for human behavior and environmental factors affecting viral stability and transmission in the environment, and the human immune response.\(^6\) Temperature and humidity in particular contribute to seasonal increases in transmission and a case has been made for a role of the seasonal decrease in UV radiation.\(^7\)\(^-\)\(^15\) Several recent studies have found that low temperature and low humidity lead to an increase in the transmission rates and \(R_0\) of SARS-CoV-2 in Europe and the USA.\(^16\)\(^17\) In addition, a more global analysis also found higher transmission and mortality rates in the colder climates of the Northern and Southern hemispheres, with more pronounced seasonality in the Northern hemisphere where larger seasonal amplitudes of environmental parameters occur.\(^18\) However, in all cases warmer weather was not found to be sufficient to curtail transmission rates in the absence of intervention policies. Moreover, in our recent study, the coughing rate of COVID-19 patients significantly...
increased in the cold temperatures that were associated with a more rapid increase of infections during winter.19

Infection-independent upper respiratory symptoms, including coughing rate, increase in winter because of cold damp air and thus would exacerbate viral spread by infected individuals. Laboratory studies have shown that SARS-CoV-2 invasion increases at lower temperatures, likely through higher viral attachment to a key host receptor, Angiotensin-converting enzyme 2.20 Additionally, unlike other pathogenic coronaviruses, SARS-CoV-2 replicates more efficiently at the cooler temperatures found in the upper respiratory tract.21 Like influenza, the major transmission routes of coronaviruses are droplet nuclei in the air, fomites and for COVID-19 in particular, increasing evidence for a role of aerosols.22,23 COVID-19 and influenza are respiratory diseases and share many clinical features.24-29 Incubation periods are 2-14 days for COVID-19 and 1-4 days for influenza. With the exception of the unusual symptoms associated with COVID-19 (eg, ageusia (loss of sense of taste) and anosmia (loss of sense of smell)), the predominant differences with influenza are severity in complications. Epidemiological data regarding a seasonal signature underlying SARS-CoV-2 transmissibility are, however, limited. One of the challenges is taking into account the varied intervention measures taken by governments and the population itself. The implementation of extreme and widespread imposed lockdowns, individual social distancing measures and behavioral changes, other non-pharmaceutical interventions along with the development of varying degrees of herd immunity will all influence the magnitude of epidemics.30-32 However, the extent to which these factors impact on the initial weeks of the epidemic trajectory and smother any seasonality in transmissibility is less certain.33 Herein, we compare the weekly trend of infection and the case increase ratio of infection during the epidemics occurring in winter, spring, and summer, by using the COVID-19 and influenza patient data in Tokyo. We assess the extent to which seasonality in disease incidence can be observed for both viral respiratory infections. The surveillance data of COVID-19 included all cases occurring between February 2020 and August 2021 and the surveillance of influenza included influenza (influenza like illness) cases diagnosed at sentinel clinics between 2005 and 2006 to 2010 and 2011 epidemic seasons.34

METHODS

We used the data of national surveillance of infectious diseases in Japan for COVID-19 and influenza. Weekly epidemiological features before epidemic peak were analyzed for COVID-19 and influenza.

COVID-19 data

We used the COVID-19 surveillance data from Tokyo between first week of February 2020 and second week of August 2021. The data included sex, age group (10-year age group bins) of all individuals who had PCR-confirmed the COVID-19 positive infections (irrespective of whether they were symptomatic). In addition, the number of symptomatic cases by clinical onset date were downloaded from the open data source on the web.35 In Tokyo, vaccination for the COVID-19 was started in April 2021 and the coverage was 34.2% as of second August 2021.36 An estimated infection date was taken to be 4 days prior to the date of onset of symptoms, being the average incubation period.37 In Japan, the PCR laboratory testing was conducted by either local health offices or the prefectural governments or hospitals, by nasal or throat swabs for patients who presented with fever, or continuous coughing, or feeling unwell. Active surveillance with PCR testing was carried out by local health office for the people who had been in contact with an infected person, or who participated at a same public event or had been present in the same place as the infected person. Thus, family members living with an infected person were tested and participants of the events where there had been a cluster of patients were encouraged to visit the COVID-19 designated call center of either central or local health offices. These centers arranged PCR testing through the designated hospital near the resident. Except for those who were tracked in the aforementioned circle of close contact with the infected person, the surveillance with PCR testing was based on symptoms shown by patients. When the result of PCR testing arrived, the local health office conducted interviews with the PCR-positive patients to obtain personal information (sex and age group) and symptom onset date. We describe the baseline information of the patients for the study period (based on the PCR-confirmed date) and depict the number of weekly infections calculated by the estimated infection date. The social interventions which were implemented during the study period were reviewed from the website of Tokyo Prefectural government.38 Whole virus genome sequence was conducted at the National Institute of Infectious Diseases and the result was reported on the web site (NIID).39,40

Influenza sentinel data

We used the national sentinel influenza surveillance data for Tokyo.41 The sentinel influenza surveillance in Tokyo is conducted over 300 sentinel clinics that monitor the average of the weekly number of influenza cases per sentinel site. The data included the 2005-2006 [Flu 06] to the 2010-2011 [Flu 11] influenza epidemics in the winter and the novel 2009 swine influenza A(H1N1) pandemic [Flu 09 pdm] in the summer. The influenza surveillance data were used from the open source on the website.42 RT-PCR testing of epidemic virus subtypes and strains was conducted for about 10 % of all cases and the results reported on the web site of NIID.41,42

Seasonal trends in infectivity

To assess the time-series trend of the increase in the number of infections, a quadratic regression model was fitted for the weekly number of infections for the 5-week period prior to each epidemic peak week for both the COVID-19 and influenza epidemics. This 5-week period was used as representative of the growth phase of the epidemic. We calculated the weekly case increase ratio (the ratio between the number of cases of the current week and the number of cases of the previous week) for the 5-week period. The quadratic regression models and case increase ratio were then compared between the winter, spring and summer epidemics. In order to

Table 1

| Age group | Proportion (%) within total case (Male/Female) |
|-----------|-----------------------------------------------|
| Total     | 286,868 (56.1/43.9)                             |
| 0-10      | 3.41(1.77/1.64)                                 |
| 10s       | 6.73(3.55/2.18)                                 |
| 20s       | 29.08(15.38/13.70)                              |
| 30s       | 19.83(11.88/7.95)                               |
| 40s       | 15.67(9.73/5.95)                                |
| 50s       | 12.18(7.16/5.02)                                |
| 60s       | 5.40(3.19/2.21)                                 |
| 70s       | 3.88(2.03/1.85)                                 |

*Based on results between February 1, 2020 and August 15, 2021 for Tokyo. The results also included antigen testing but the majority of testing conducted was PCR testing.

1Based on results between 2005-2006 and 2010-2011 epidemic seasons for Tokyo.
analyze epidemic impact just before peaking, we compared the seasonal weekly case increase ratio for the accumulated number of cases between the third week and the fifth weeks of the study period, using non-paired t-tests. We also observed the trend for the first 5 weeks at the start of the epidemic, starting with the first weekly increase in number of cases.

To assess the statistical significance and the robustness of the association of season and virus with cases over time, the weekly COVID-19 case numbers and influenza case rates were normalized for each time period of 5 weeks to yield values between 0 and 1 using the following formula: \( \frac{x_i - \text{min}(x)}{\text{max}(x) - \text{min}(x)} \) where \( x_i \) is the number of cases or case rates at month \( i \). These normalized values were then used together from all time periods in a combined quadratic regression analysis. Firstly, the regression used all data from the Winter and Spring/Summer periods with season and virus (The COVID-19 or Influenza) fitted as co-variables. Then the seasons were analysed separately. The epidemics, using the normalized values, were tested for autocorrelation and as there was no significant autocorrelation, model sensitivity was assessed through a permutation test. The permutation test used is the classical permutation test, which is an exact test, in which the distribution of the test statistic under the null hypothesis is obtained by calculating all possible values of the test statistic under all possible rearrangements of the observed data points. Permutation tests are, therefore, a form of resampling with replacement. The fit of the quadratic model was compared to that using generalized linear models. All statistical analyses were performed in Genstat version 20.43.

**RESULTS**

**COVID-19 case and predominant virus strain**

There was a total of 286,868 PCR-positive cases. Among the age groups, the cases in the 20s age group were the highest (29.08%) followed by 30s age group (19.83%), 40s age group (15.67%), and 50s age group (12.18%) (Table 1). Of these PCR positive infections, 219,545 (76.5%) were symptomatic (excluding positive samples of patients whose onset date was unspecified [22.4%]).

The 5 epidemic waves occurred in winter, spring, and summer (period A–E in Fig 1). The epidemics in summer, which were the second and the fifth epidemic waves, occurred at a similar time; started increasing in June and decreased from August.

During the first 4 epidemic waves (period A to D in Fig 1), the number of infections decreased during the social interventions. By contrast, the fifth epidemic wave (period E in Fig 1) that occurred around the Olympic Games continued to increase in the number of infections despite interventions being implemented. (Fig 1) This intervention included encouraging people to stay in, stop selling alcoholic drinks at restaurants and close shops earlier than 8 pm. The peak of the epidemic was the highest in the fifth epidemic wave and the second highest peak was in the third epidemic wave that occurred around December 2020. The predominant virus strains were, B.1.1 in the period A, B.1.1.284 in the period B, B.1.1.214 in the...
period C, B.1.1.7 (Alpha variant) in the period E, and B.1.617.2 (Delta variant) in the period E.

Influenza case and predominant virus subtype and strains

There was an average total of 1196.82 cases per sentinel site. Among the age groups, the number of cases in the under 10 years of age group was the highest (52.44%) followed by 10s age group (24.21%), 30s age group (7.91%), and 20s age group (6.58%) (Table 1). The majority of the seasonal epidemics occurred in January, although the Flu 07 was delayed until February. The predominant virus subtype and strain varied among A(H1N1), A(H1N1)pdm09, A(H3N2), and B lineage, each season. (Supplementary Fig S1)

Seasonal trends in weekly case increase ratio

The weekly COVID-19 and influenza infections increased the case increase ratio toward the peak in the winter (Fig. 2A-i, ii, 2B-i, ii, and S1) as compared with the infections in the summer and spring (Fig. 2A-iii, iv and 2B-iii, iv, and S1). The increase ratios of the accumulated number of cases between the third and the fifth weeks compared with the number of cases in the third week in the winter were: 11.6 [95%CI:9.5-14.1] (COVID-19, period A), 4.1 [95%CI:3.9-4.3] (COVID-19, period C), 7.2 [95%CI:6.9-7.5] (Flu 06), 3.8 [95%CI:3.7-4.0] (Flu 07), 4.5 [95%CI:4.2-4.7] (Flu 08), 4.5 [95%CI:4.3-4.7] (Flu 09 seasonal), 9.0 [95%CI:8.6-9.4] (Flu 11). Conversely, in the summer and spring, the increase ratios of the accumulated number of cases between the third and the fifth weeks compared with the number of cases in the third week were: 3.6 [95%CI:3.4-3.9] (COVID-19, period B), 3.6 [95%CI:3.5-3.8] (COVID-19, period D), 3.7 [95%CI:3.6-3.8] (COVID-19, period E), 3.6 [95%CI:3.4-3.7] (Flu 09 pdm). The average of these case increase ratios between the third and the fifth weeks were, 6.8 [95%CI:6.6-10.0] in the winter, and 3.6 [95%CI:3.5-3.7] in the summer and spring (excluding the Flu 07 season when the epidemic was delayed for approximately one month). Using non-paired t test, a significant increase of case increase ratio (3.19 [95%CI:0.01-6.37, P < .049]) of the COVID-19 and influenza epidemics in the winter was observed as compared with the spring/summer epidemics. By contrast, during the initial 5 weeks of the epidemics, all COVID-19 and influenza epidemic waves were convex (Supplementary Fig S2).

A quadratic regression was then fitted to all the data combined. In the combined season analysis, the cases in the winter season were found to be significantly different from the summer season (t = 3.08, P = .003) but there was no difference between the 2 viruses (t = 1.00,
The linear component of the quadratic regression was not significant, \( t = -0.18, P = 0.858 \), whereas the quadratic component was significantly positive (i.e., convex) \( (t = 3.12, P = 0.003) \). The model explained 81.5% of the variance. In the Spring/Summer only analysis, there was again no significant association of virus type \( (t = -0.2, P = 0.848) \) and both the linear and quadratic components were significant \( (\text{Linear}: t = 6.85, P < 0.001; \text{quadratic}: t = -2.24, P = 0.039) \); the quadratic component was here concave (Fig 3A). The model explained 96.8% of the variance. In the Winter only analysis, virus type was again not significant \( (t = 1.26, P = 0.216) \) and both the linear and quadratic components were significant \( (\text{Linear}: t = -2.32, P = 0.027; \text{quadratic}: t = -4.30, P \leq 0.001) \); the shape here is distinctly convex (Fig 3B). The model explained 80.1% of the variance. The permutation test confirmed the model fits, with the probability for the model being 0.001 as determined from 999 random permutations. The quadratic models fitted the data better than generalized linear models that explained 96.5% and 69% of the variance in summer and winter respectively.

**DISCUSSION**

We found a more rapid increase of both COVID-19 and influenza cases in the weeks preceding the epidemic peaks in the winter as compared with the summer and spring. The result suggests that, as for seasonal influenza, the transmissibility of SARS-CoV-2 increases in the winter. The lower summer case increase ratios in the summer also suggest that less clement conditions diminish viral transmissibility. Thus, despite the novelty of SARS-CoV-2, the virus is exhibiting the same seasonal tendencies as influenza. All viruses causing upper respiratory tract infections show seasonality to some extent. At the least seasonal end of the spectrum are the non-enveloped viruses, including the rhinoviruses and adenoviruses, which are present throughout the year. These viruses do, however, survive better at higher humidity and lower temperatures. Enveloped viruses with significant winter predominance include Respiratory Syncytial Virus, Influenza and coronaviruses. One reason for the higher winter viability of influenza viruses is the negative impact of warmer temperatures on the viral envelope structural stability. The same has been...
suggested to be the case for SARS-CoV-2 and is consistent with our findings. There is now evidence that viral invasion increases at lower temperatures through increased binding to a key host receptor.

The similarity of the seasonal epidemic trajectories is all the more remarkable given the different basic reproductive numbers ($R_0$) of seasonal influenza (median 1.28), pandemic 2009 influenza (1.46), the SARS-CoV-2 ancestral variant (2.5) and the delta variant (5.08). The higher $R_0$ of the SARS-CoV-2 variants would be expected to alter the rate of the acceleration to the peak, but not necessarily the shape (convex or concave). Our estimated case increase ratio can be similarly interpreted for $R_0$ and this can clearly be seen for the Delta variant during the Olympics in Figures 1 and 2, where there is a rapid increase in total case numbers, but which still displays a concave trajectory. Despite its higher transmissibility, however, the infection rate tailed off as with the other non-winter epidemics. The same such epidemic situation occurring in winter would therefore be predicted to lead to a much higher case rate.

At the start of each epidemic, all the COVID-19 and influenza epidemic curves were convex. This suggests that at the very beginning of the epidemics the attack rate is relatively high regardless of seasonality. This could reflect household or workplace level transmission and/or case clusters. Then, in the following weeks, transmission would spread to the community level and thus be more affected by seasonality, hence leading to the convex curve in the winter and the concave curve in the summer.

One of the major constraints to interpreting our data and therefore a limitation to our study, is comparing influenza data that predominantly come from children with COVID-19 data that come from an older population. Behavioral differences in children vs the adult population can strongly impact age-specific case rates. Schools provide a fertile ground for the spread of classical pediatric diseases, including influenza, but until recently the role played by children in transmission of SARS-CoV-2 has been considered relatively minor. By contrast, the spread of SARS-CoV-2 in the adult population has been recognized to be aggravated by superspreading events at many types of social gatherings, such as church services, political rallies and music festivals. The tendency for pathogens to generate clusters varies significantly according to the pathogen in question, suggesting that both human behavior and the nature of the infection itself are important. For the severe acute respiratory syndrome coronavirus (SARS-CoV), the clustering parameter $k$ was estimated to be 0.16 and the Middle East respiratory syndrome coronavirus (MERS-CoV 2012) 0.25, indicating clustering. Estimates of SARS-CoV-2 are currently uncertain, but may be of the same order of magnitude, with an estimated 10% of the cases contributing to 80% of the spread. Influenza cases, by contrast, are less aggregated in space. However, despite these limitations in data comparisons among different age groups with associated behavioral differences, the nature of the 2 viruses does generate the same seasonal patterns.

A second potential confounder for all these trends might have been the influence from non-pharmaceutical interventions (NPIs) that have been implemented from time to time. However, in Tokyo, except for the first epidemic wave, the practice of NPIs was very limited and that was only for restaurants and shops. Thus, any effect of NPIs might have been limited as compared to other cities in the world where rigorous NPIs were applied. Indeed, the justice system does not permit mandatory lockdowns and thus the government could only announce non-compulsory remote working requests. Analysis of the first epidemic wave did identify a significant decrease in mobility, using mobile phone data. However, calculations of $R$ suggested that the value was already low ($\sim 0.3$) prior to the announcement, thus rendering even such low-level restriction requests superfluous.

Insofar as the epidemiological data of COVID-19 are limited and given the apparent similarity in seasonality with influenza, it would seem reasonable to suggest that SARS-CoV-2 will eventually join our current seasonal respiratory viruses. Such predictability would enable improved public health planning for testing, intervention and hospital space. Although the Delta variant behaved as predicted despite its high transmissibility, the very recent emergence of the Omicron variant raises another challenge, especially in the light of its apparent capacity to evade the current vaccine-induced immune response. While Omicron variant can evade the vaccine-induced immune responses, this lineage is less pathogenic, possibly indicating adaptation of the virus to its human host and thus one step away of becoming an endemic seasonal virus. Continued study of the epidemics is needed to extend upon the results presented here.
