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MAJOR ARTICLE

The Impact of Cold Ambient Temperature in the Pattern of Influenza Virus Infection

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Background. Prior literature suggests that cold temperature strongly influences the immune function of animals and human behaviors, which may allow for the transmission of respiratory viral infections. However, information on the impact of cold stimuli, especially the impact of temporal change in the ambient temperature on influenza virus transmission, is limited.

Methods. A susceptible-infected-recovered-susceptible model was applied to evaluate the effect of temperature change on influenza virus transmission.

Results. The mean temperature of the prior week was positively associated with the number of newly diagnosed cases (0.107 [95% Bayesian credible interval {BCI}, .106–.109]), whereas the mean difference in the temperature of the prior week was negatively associated (−0.835 [95% BCI, −.840 to −.830]). The product of the mean temperature and mean difference in the temperature of the previous week were also negatively associated with the number of newly diagnosed cases (−0.192 [95% BCI, −.197 to −.187]).

Conclusions. The mean temperature and the mean difference in temperature affected the number of newly diagnosed influenza cases differently. Our data suggest that high ambient temperature and a drop in the temperature and their interaction increase the risk of infection. Therefore, the highest risk of infection is attributable to a steep fall in temperature in a relatively warm environment.

Keywords. cold stimuli; influenza; SIRS model.

Respiratory viruses cause seasonal epidemics and impose a significant burden on society. For example, an influenza season in the United States has been reported to lead to approximately 334 000 admissions and could cause an annual financial loss of 87.1 billion dollars, including projected statistical life values [1]. Influenza virus infection is a significant cause of mortality in high-risk populations, such as the elderly, as evidenced by >67% of influenza virus–associated fatalities occurring in those aged >65 years [2]. Therefore, it is essential to understand the mechanism of viral spread that causes infection, in order to reduce the excessive mortality caused by the virus infection.

Previous reports have suggested that humidity and ambient temperature affect the spread of the influenza virus [3–20]. Inhalation of cold air, which is always dry, decreases the mucociliary clearance of inhaled viruses from the upper respiratory airways [21]. Other suggested mechanisms of increased susceptibility to influenza virus infection include decreased host immune function by cold exposure [22]. While the exact influence on humans has been controversial, evidence from rodents and other animal models demonstrated a decrease in immune cell function by cold exposure, leading to increased respiratory virus infections [23]. Moreover, epidemiological studies have consistently shown the seasonality of influenza virus spread in the winter in a temperate climate [6, 17]. However, most of the studies so far have only evaluated the effect of low ambient temperature on the transmission and spread of the virus [3–15], and the number of studies focusing on the degree of change in ambient temperature has been limited [16–20]. Therefore, we constructed a model that evaluates the effects of both temperature and its degree of change.

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METHODS

Data Collection

We collected data from a publicly available database of the National Institute of Infectious Diseases of Japan that reports on the prefectural sentinel surveillance of newly diagnosed patients infected with influenza virus between 10 September 2012 and 21 February 2021 [24]. This report started in 1999 based on the legal mandate that reports the incidence of influenza virus infection over 5000 designated sentinel surveillance points spread throughout Japan. All influenza cases diagnosed at designated medical facilities are incorporated in the data. The diagnostic criteria included a presentation of all 4 clinical symptoms (sudden onset of clinical symptoms, high fever, upper respiratory symptoms, and systemic symptoms including general malaise) suggestive of influenza or part of clinical symptoms together with positive test results for the rapid antigen kit, which used either nasal aspirates, nasal wipes, or pharyngeal wipes [25].

The reported numbers were adjusted to the number per 100 000 population per week using the Dynamic Surveys of Medical Institutions and Hospital Report and the National Census [26]. The dynamic surveys of medical institutions and hospital reports are updated every 3 years. Therefore, we used the latest information for the corresponding season. The population was standardized using data from the national census survey result of 2015 [27].

The number of newly diagnosed influenza patients per prefecture per week was calculated based on the following equation (Supplementary Table 1):

$$I_{ij} = \frac{h_i \times rp_{ij}}{P_i} \times 100\ 000 \qquad (1)$$

where the I is a standardized number of newly diagnosed patients with influenza virus infection of week j ($j = 1, \ldots, 408$) in prefecture i ($i = 1, \ldots, 47$), h is the number of medical institutions or hospitals, rp is the number reported positive for influenza virus infection, and P is the population.

Data for ambient temperature were downloaded from the database of the Japan Meteorological Agency [28]. An index point per prefecture was decided, and the temperature for the corresponding period was obtained for that index point (Supplementary Table 2). The average temperature was calculated according to the weekly period corresponding to the sentinel surveillance period.

Model Simulation

Using the data obtained as explained above, we created a simulation model to evaluate the effect of temperature and its changes on the spread of influenza virus. Factors included in the model to predict the number of newly infected cases of influenza virus infection were the transmissibility of the virus itself, the population at risk of infection, and the number of those with the infection in the population.

Our model was based on a deterministic susceptible-infected-recovered-susceptible (SIRS) model with Bayesian parameter fitting. We used the number of newly diagnosed patients with influenza virus infection per 100 000 population per week, modified from preceding reports [29, 30]. Details of the SIRS model are described in the Supplementary Material.

We hypothesized that the transmission rate β is determined by the temperature and an unknown regional factor that follows the equation:

$$log\beta_{ij} = b_1 LMT + b_2 DMT + b_3 LMTDMT + b_{4i} \qquad (2)$$

where b_1, b_2, and b_3 are regression coefficients and b_{4i} is the intercept that determines the regional factor for the individual periods. The lagged mean temperature (LMT) stands for the average temperature of the preceding week, and the differentiated mean temperature (DMT) stands for the difference between the average temperature of the preceding week compared to the week prior. Therefore, LMT represents the cold ambient temperature, and DMT represents a cold stimulus. Overall, the current model incorporates low temperature, change in temperature, and regional factors as possible determinants of influenza virus transmission rate β in a log-like function.

We then hypothesized that LMT and DMT are the main factors contributing to influenza virus transmission. To identify the best model that describes the effect of each of these factors, we constructed the following 3 models: (1) a model that includes LMT and DMT as well as the interaction of LMT and DMT (model 1); (2) a model that includes only LMT and DMT (model 2); and (3) a null model that includes only the regional factor and not LMT or DMT (model 3). We hypothesized that a proportion of the susceptible population at the start of the assessment (S_{i1}) was 65% of the regional population [31, 32].

Data Analysis

The comparison of the fit of the model was based on the deviance information criterion (DIC), where the smallest DIC suggests the recommended model.

The point estimate of each parameter was calculated using the posterior mean, and the uncertainty in the model was evaluated using the 95% Bayesian credible interval.

The analysis and model creation was performed using Python version 3.7 and Tensorflow Probability 0.13.

RESULTS

Number of Influenza-Infected Patients and Local Ambient Temperature

During our evaluation period between 10 September 2012 and 21 February 2021, the reported average weekly new cases of influenza virus infection per 100 000 population were 419.9 cases, with a maximum of 7639.9 cases. There was a tendency for a higher frequency of infection reported in the southwestern district of Japan. This southwestern district includes the top 3 prefectures where the number of weekly cases per 100 000 population was highest: Oita (558.78 cases), Nagasaki (545.28 cases), and Okinawa (543.25 cases).

The average temperature during this period was 15.65°C and varied between 9.337°C and 23.476°C depending on the district. The number of newly diagnosed influenza patients per 100 000 population and ambient temperature distributions are shown in Supplementary Tables 1 and 2, respectively.

We identified 8 peak incidences of influenza virus infection during our observation period. During winter (between

Table 1. Model Comparisons for Influenza Cases in Japan, 10 September 2012 to 21 February 2021, Using Deviance Information Criterion

Description of Models	pD	DIC
Regional variables and temperature variables with an interaction term	50.3	3 883 135
Regional variables and temperature variables without an interaction term	49.0	3 889 663
Regional variables only	48.0	4 076 986

Abbreviations: DIC, deviance information criterion; pD, effective number of parameters in the model.

Table 2. Posterior Mean of the Parameters Included in Model 1 and Their 95% Credible Intervals

Parameter	Definition	Posterior Mean (95% BCI)
b_1	Effect of LMT on transmission rate	0.107 (.106–.109)
b_2	Effect of DMT on transmission rate	−0.835 (−.841 to −.829)
b_3	Effect of interaction between LMT and DMT on transmission rates	−0.192 (−.197 to −.187)
u	Constant percentage of recovered transfer to susceptible	0.010 (.010–.010)

Abbreviations: BCI, Bayesian credible interval; DMT, differentiated mean temperature; LMT, lagged mean temperature.

January and March), the influenza virus infection rate was higher than in summer. The temperature was highest during the summer between July and September.

Fitness of the Model

Table 1 shows the results of DIC for the 3 models constructed. This result shows that model 1 has the most superior fit to the other 2 models. Therefore, our result suggests a temporal change in the transmission rate of the virus throughout Japan, and the transmission rate varied following the absolute temperature, the change in the ambient temperature, and their interaction.

Effect of Temperature on the Rate of Influenza Transmission

Table 2 shows the result obtained from constructing model 1. The result shows that the transmission rate of the influenza virus is negatively associated with DMT and the interaction between LMT and DMT. On the other hand, LMT is positively associated with influenza virus transmission. Therefore, the effects of LMT and DMT are dependent on each other.

Figure 1 is a graphical representation of the results of our model, showing the result of β when either the LMT (Figure 1*A*) or the DMT (Figure 1*B*) was fixed at its mean value (LMT: 15.65°C, DMT: 0°C). Figure 1*A* shows that a large drop in temperature causes the most significant increase in the transmission rate of the virus. Figure 1*B* shows the change in β according to the mean ambient temperature, showing that the transmission rate of the virus increases with higher temperatures. As represented by Oita in Figure 2*B*, cities in the southwestern part of Japan have a higher mean ambient temperature, leading to a higher transmission rate than cities in other parts of Japan, such as Tokyo (Figure 2*A*).

DISCUSSION

We evaluated the effect of ambient temperature and the change in the ambient temperature and their interaction on the rate of influenza virus transmission in Japan. Our result shows that all 3 factors included in the model—LMT, DMT, and the interaction of LMT and DMT—are essential factors associated with the transmission of the influenza virus.

Influenza virus infections are mainly caused by droplet and contact infections. A previous study showed that in a low-temperature environment, the phospholipids of the virus become more ordered, which may improve the stability of the virus in airborne transmission [33]. Another laboratory study showed that the viral spread is enhanced in low-temperature environments and that cold, dry weather conditions are more likely to favor influenza virus infection because they may increase the survival rate of influenza viruses [34]. These results suggest that influenza viruses are more prevalent in temperate, cold, and dry weather conditions due to the improved survival rate of the viruses.

Previous studies show growing evidence that temperature is closely linked to influenza virus infection [3–20]. Many studies have shown a relationship between low ambient temperature and the influenza virus epidemic, which contradicts our current results that showed a weak positive relationship between influenza virus spread with LMT. However, a major difference between our study and prior studies is that we have also included the effects of temperature change and its interaction with LMT in our model. Hence, our results suggest that a sudden drop in the ambient temperature directly affects the physiology of the human body that interacts with the susceptibility to influenza virus infection. An influenza virus epidemic is known to cause a significant amount of death, and therefore we may speculate that a sudden drop in temperature could affect the transmission rate of the influenza virus, leading to excessive mortality as evidenced by the fact that a sudden drop in temperature has been reported to increase the risk of death [35]. Another explanation for the difference in the results obtained could be explained by the robustness of the data used in our analysis compared to previous reports in terms of the use of data spanning multiple seasons, as well as the difference in temperature by using data obtained from the whole country.

Other studies have reported similar results to our findings. Observational studies from Sweden and Finland examined the association between cold stimuli and influenza, which showed a robust negative effect of DMT, consistent with the findings of our current study [19, 20]. Overall, our findings add to the results from previous reports that the addition of change in the temperature affects the influenza transmission rate, which may explain previously unexplained epidemic patterns proposed in prior literature [36].

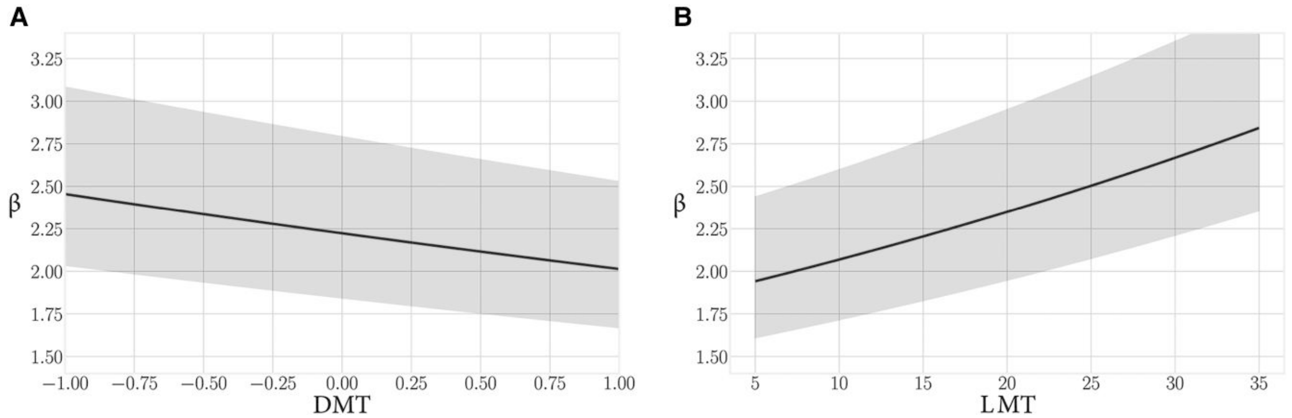

Figure 1. Relationship between changes in differentiated mean temperature (DMT) (*A*) or lagged mean temperature (LMT) (*B*) and the transfer rate. The black line is the average for each region, and the shaded area represents the range for each region, with the 2.5th percentile value as the lower limit and the 97.5th percentile value as the upper limit. *A*, LMT is fixed at 15.65°C, and *B*, DMT is fixed at 0°C, the average temperature in Japan.

In temperate climates, where temperatures change throughout the year, influenza epidemics that last for an average of 3.8 months occur in winter when ambient temperatures drop, regardless of the country [37]. However, other climate zones, including tropical and subtropical climates, have also shown a tendency for influenza to spread when temperatures drop [14, 15]. Our results showing the interaction of decreasing temperatures in high-temperature zones and prior evidence of epidemic patterns in both temperate and other climate zones suggest that the influenza epidemic pattern may be shaped by cold stimuli rather than simple low temperatures.

This study had several limitations. First, we could not control for social factors such as demographic changes, population inflow or outflow, and vaccination rates. Recent studies have shown that a decrease in vaccination coverage is associated with increased influenza incidence [38]. However, our study focused on influenza epidemics over a long period of 8 years in multiple locations, reducing the effect of such factors. Second, our analysis also did not include other climate factors, such as humidity. Humidity is a climate factor that has been shown to impact the viral transmission rate significantly [39]. Therefore, additional validation is needed to assess the impact of cold stimuli compared to other climate factors. Finally, this

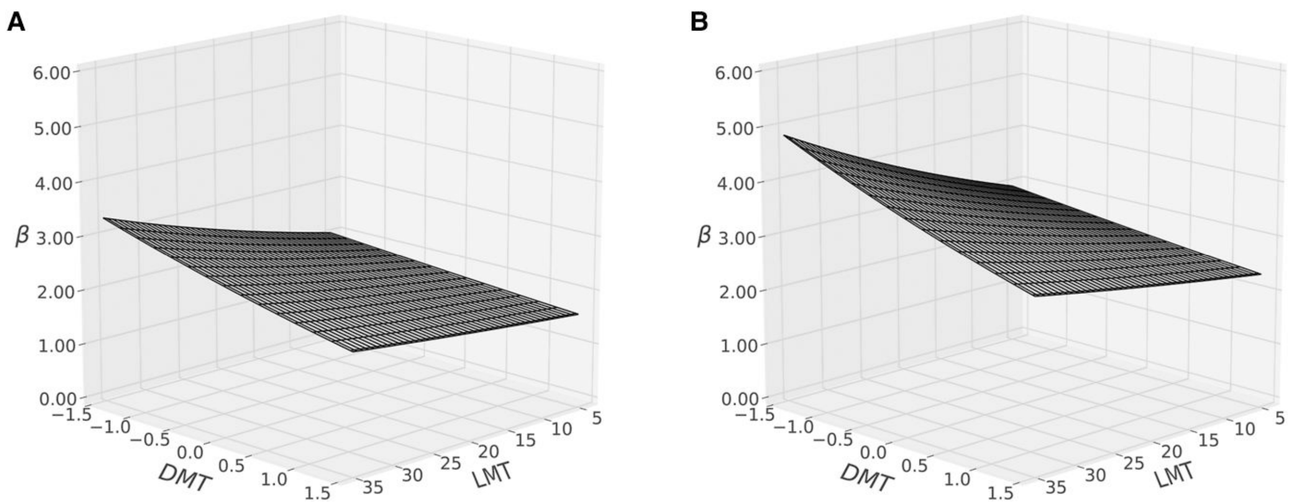

Figure 2. The following planes in 3 dimensions show the posterior means of influenza transmission rates in 2 regions of Japan according to lagged mean temperature (LMT) and differentiated mean temperature (DMT). *A*, Tokyo, the central city of Japan. *B*, Oita, located in the southwestern part of Japan, with the largest posterior mean of regional parameters. The fact that the axial range of LMT is 30.0°C whereas DMT is 3.0°C shows that even a slight change in DMT has a significant effect on the transfer rate β.

study is based only on Japanese epidemiological information. While this may be a limitation, the Japanese climate spans between subarctic and subtropical zones due to its geographic location, with the majority residing in the temperate climate zone. Japanese society is also characterized by relatively small economic and health disparities [40]. These characteristics, taken together, could explain why we were able to identify climate effects as being significant in our study.

This study evaluated the effect of ambient temperature and its change on the influenza virus transmission rate using data from the sentinel surveillance performed in various parts of Japan over 8 years. The result showed that, contrary to a previous hypothesis that cold temperature alone affects the spread of the influenza virus, both high ambient temperature and a drop in the temperature and their interaction increase the risk of infection. The drop in the ambient temperature was a more potent effector on the influenza virus transmission rate. Our result provides a novel explanation and potential for predicting influenza virus outbreaks during the influenza season.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. N. Y. conceived and designed the entire study. S. K. developed the statistical model and performed simulations. All authors interpreted the results, and E. M. wrote the article. All authors contributed to and approved the final version of the article. All authors had access to and verified all data and were responsible for the decision to submit the manuscript for publication.

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References

1. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine **2007**; 25:5086–96.
2. Paget J, Spreeuwenberg P, Charu V, et al. Global mortality associated with seasonal influenza epidemics: new burden estimates and predictors from the GLaMOR Project. J Glob Health **2019**; 9:020421.
3. Tsuchihashi Y, Yorifuji T, Takao S, et al. Environmental factors and seasonal influenza onset in Okayama city, Japan: case-crossover study. Acta Med Okayama **2011**; 65:97–103.
4. Chong KC, Goggins W, Zee BC, Wang MH. Identifying meteorological drivers for the seasonal variations of influenza infections in a subtropical city—Hong Kong. Int J Environ Res Public Health **2015**; 12:1560–76.
5. Chong KC, Lee TC, Bialasiewicz S, et al. Association between meteorological variations and activities of influenza A and B across different climate zones: a multi-region modelling analysis across the globe. J Infection **2020**; 80:84–98.
6. van Noort SP, Aguas R, Ballesteros S, Gomes MGM. The role of weather on the relation between influenza and influenza-like illness. J Theor Biol **2012**; 298: 131–7.
7. Peci A, Winter AL, Li Y, et al. Effects of absolute humidity, relative humidity, temperature, and wind speed on influenza activity in Toronto, Ontario, Canada. Appl Environ Microbiol **2019**; 85:e02426-18.
8. Qi L, Liu T, Gao Y, et al. Effect of meteorological factors on the activity of influenza in Chongqing, China, 2012–2019. PLoS One **2021**; 16:e0246023.
9. Gomez-Barroso D, Leon-Gomez I, Delgado-Sanz C, Larrauri A. Climatic factors and influenza transmission, Spain, 2010–2015. Int J Environ Res Public Health **2017**; 14:1469.
10. Ianevski A, Zusinaite E, Shtaida N, et al. Low temperature and low UV indexes correlated with peaks of influenza virus activity in Northern Europe during 2010–2018. Viruses **2019**; 11:207.
11. Singh DE, Marinescu MC, Carretero J, Delgado-Sanz C, Gomez-Barroso D, Larrauri A. Evaluating the impact of the weather conditions on the influenza propagation. BMC Infect Dis **2020**; 20:265.
12. Hu W, Williams G, Phung H, et al. Did socio-ecological factors drive the spatiotemporal patterns of pandemic influenza A (H1N1)? Environ Int **2012**; 45:39–43.
13. Tamerius JD, Shaman J, Alonso WJ, et al. Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. PLoS Pathog **2013**; 9:e1003194.
14. Baumgartner E A, Dao CN, Nasreen S, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. J Infect Dis **2012**; 206:838–46.
15. Wang XL, Yang L, He DH, et al. Different responses of influenza epidemic to weather factors among Shanghai, Hong Kong, and British Columbia. Int J Biometeorol **2017**; 61:1043–53.
16. Zhang Y, Feng C, Ma C, et al. The impact of temperature and humidity measures on influenza A (H7N9) outbreaks—evidence from China. Int J Infect Dis **2015**; 30:122–4.
17. Roussel M, Pontier D, Cohen JM, Lina B, Fouchet D. Quantifying the role of weather on seasonal influenza. BMC Public Health **2016**; 16:441.
18. Park JE, Son WS, Ryu Y, Choi SB, Kwon O, Ahn I. Effects of temperature, humidity, and diurnal temperature range on influenza incidence in a temperate region. Influenza Other Respir Viruses **2020**; 14:11–8.
19. Sundell N, Andersson LM, Brittain-Long R, Lindh M, Westin J. A four year seasonal survey of the relationship between outdoor climate and epidemiology of viral respiratory tract infections in a temperate climate. J Clin Virol **2016**; 84:59–63.
20. Jaakkola K, Saukkoriipi A, Jokelainen J, et al. Decline in temperature and humidity increases the occurrence of influenza in cold climate. Environ Health **2014**; 13:22.
21. Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. Acta Otolaryngol **2002**; 122:183–91.
22. Reynes B, van Schothorst EM, Keijer J, Palou A, Oliver P. Effects of cold exposure revealed by global transcriptomic analysis in ferret peripheral blood mononuclear cells. Sci Rep **2019**; 9:19985.
23. Jhaveri KA, Trammell RA, Toth LA. Effect of environmental temperature on sleep, locomotor activity, core body temperature and immune responses of C57BL/6J mice. Brain Behav Immun **2007**; 21:975–87.
24. National Institute of Infectious Diseases of Japan. Infectious diseases weekly report (IDWR). https://www.niid.go.jp/niid/en/idwr-e.html. Accessed 8 January 2023.
25. Ministry of Health, Labour and Welfare of Japan. Notification of physicians and veterinarians under the Infectious Disease Control Law. https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-28.html. Accessed 12 January 2023.
26. Ministry of Health, Labour and Welfare of Japan. Survey of medical institutions. https://www.mhlw.go.jp/english/database/db-hss/mi.html. Accessed 8 January 2023.
27. Statistics Bureau, Ministry of Internal Affairs and Communications of Japan. Population census 2015 statistical maps of Japan. https://www.stat.go.jp/english/data/chiri/map/c_koku/2015.html. Accessed 8 January 2023.
28. Japan Meteorological Agency. Historical weather data. https://www.data.jma.go.jp/gmd/risk/obsdl/. Accessed 8 January 2023.
29. Huang X, Clements AC, Williams G, Mengersen K, Tong S, Hu W. Bayesian estimation of the dynamics of pandemic (H1N1) 2009 influenza transmission in Queensland: a space-time SIR-based model. Environ Res **2016**; 146:308–14.
30. Lawson AB, Song HR. Bayesian hierarchical modeling of the dynamics of spatio-temporal influenza season outbreaks. Spat Spatiotemporal Epidemiol **2010**; 1:187–95.
31. He D, Dushoff J, Eftimie R, Earn DJ. Patterns of spread of influenza A in Canada. Proc Biol Sci **2013**; 280:20131174.
32. Dorigatti I, Cauchemez S, Ferguson NM. Increased transmissibility explains the third wave of infection by the 2009 H1N1 pandemic virus in England. Proc Natl Acad Sci U S A **2013**; 110:13422–7.
33. Polozov IV, Bezrukov L, Gawrisch K, Zimmerberg J. Progressive ordering with decreasing temperature of the phospholipids of influenza virus. Nat Chem Biol **2008**; 4:248–55.
34. Lowen AC, Mubareka S, Steel J, Palese P. Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog **2007**; 3:1470–6.

35. Guo Y, Barnett AG, Yu W, et al. A large change in temperature between neighbouring days increases the risk of mortality. PLoS One **2011**; 6: e16511.
36. Shaw Stewart PD. Seasonality and selective trends in viral acute respiratory tract infections. Med Hypotheses **2016**; 86:104–19.
37. Li Y, Reeves RM, Wang X, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Global Health **2019**; 7: e1031–45.
38. Manzoli L, Gabutti G, Siliquini R, Flacco ME, Villari P, Ricciardi W. Association between vaccination coverage decline and influenza incidence rise among Italian elderly. Eur J Public Health **2018**; 28:740–2.
39. Barreca AI, Shimshack JP. Absolute humidity, temperature, and influenza mortality: 30 years of county-level evidence from the United States. Am J Epidemiol **2012**; 176:S114–22.
40. Ikeda N, Saito E, Kondo N, et al. What has made the population of Japan healthy? Lancet **2011**; 378:1094–105.