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Article

Low temperature and low UV indexes correlated with peaks of influenza virus activity in Northern Europe during 2010-2018

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Abstract: With the increasing pace of global warming, it is important to understand the role of meteorological factors in influenza virus (IV) epidemics. In this study, we investigated the impact of temperature, UV index, humidity, wind speed, atmospheric pressure, and precipitation on IV activity in Norway, Sweden, Finland, Estonia, Latvia and Lithuania during 2010-2018. Both correlation and machine learning analyses revealed that low temperature and UV indexes were the most predictive meteorological factors for IV epidemics in the Northern European countries. Our in vitro experiments confirmed that low temperature and UV radiation preserved IV infectivity. Associations between these meteorological factors and IV activity could improve surveillance and promote development of accurate predictive models for future influenza outbreaks in Northern Europe.

Keywords: influenza, epidemics, weather, temperature, UV

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1. Introduction

Influenza A (H1N1 and H3N2 subtypes) and B (B/Yamagata and B/Victoria lineages) viruses (IV) cause yearly epidemics with a substantial number of infected individuals requiring primary healthcare services and hospitalization [1, 2]. Up to 650,000 people are estimated to die each year from IV infections [3].

It is now becoming evident that meteorological factors are associated with seasonality of IV epidemics [4, 5]. Low temperature and low humidity have been shown to enhance IV transmissibility in temperate climates at high latitudes, whereas high humidity favored outbreaks in low latitudes in tropical and subtropical zones. In mid-latitudes, semiannual outbreaks result from alternating cool and rainy conditions [6-11]. Solar or UV radiation has also been suggested to have an influence on the seasonal influenza epidemics in temperate climates [12, 13]. In fact, temperature, humidity, and UV radiation among other factors (genetic and social) may be valuable indicators to include in influenza surveillance for accurate prediction of future influenza outbreaks in different climate zones.

Here, we explored the association between six meteorological factors (temperature, UV index, humidity, wind speed, precipitation, and pressure) and IV activity in Norway, Sweden, Finland, Estonia, Latvia and Lithuania during 2010-2018. In particular, we utilized correlation analysis and machine learning modeling as well as *in vitro* experiments to show that low temperature and UV index were the most predictive meteorological factors for high IV activity. Thus, our results highlighted an important role of temperature and UV index in influenza epidemics in Northern Europe.

2. Materials and Methods

2.1. The "NorthernFlu" consortium

To better understand the etiology of influenza epidemics in in Norway, Sweden, Finland, Estonia, Latvia and Lithuania a "NorthernFlu" consortium was established in 2017. It consists of epidemiologists, clinicians and researchers from Norway, Sweden, Finland, Estonia, Latvia and Lithuania. The consortium aims to determine the impact of meteorological, societal, and genetic factors on IV stability and transmissibility and to improve prediction, prevention and treatment of severe IV infections.

2.2. Data Collection

Weekly statistics of the specimens' number positive for influenza across six analyzed countries were collected from World Health Organization (WHO) website through a FluNet global web-based tool [14]. The virological data entered into FluNet were collected from National Influenza Centers (NICs) of the Global Influenza Surveillance and Response System (GISRS) and other national influenza reference laboratories collaborating actively with GISRS, or were uploaded from WHO regional databases. Daily statistics of five meteorological factors (temperature (°C), humidity (%), wind speed (mph), pressure (Hg), precipitation (cm)) was manually exported from web-interface of Weather Underground service for six capitals. The Weather Underground accumulates information from National Weather Service (NWS), and over 250,000 personal weather stations (PWS). Time series (cloud-free erythemal) of UV index data were obtained from operational Tropospheric Emission Monitoring Internet Service (TEMIS) ozone data archive.

2.3. Statistical Analysis

FluNet database provided a weekly statistics of specimens positive for influenza viruses, whereas meteorological factor data were measured daily. Therefore, we adjusted each meteorological factor (median) per week.

In order to investigate the potential relationship between meteorological factors and influenza activity (number of IV positive specimens) in all analyzed countries, correlation analysis and machine learning based modeling were applied. The Pearson correlation coefficient (r) analysis between each meteorological factor and influenza activity was calculated using “stats” R package with a threshold of significance at $p = 0.05$.

For the machine learning modeling, Random Forest (RF) was optimized to find the most predictive meteorological factors of influenza activity. More specifically, for each country, the time-series measurements of all six meteorological factors were used as input features (explanatory variables) and the number of IV-positive specimens as an output variable for the model. The optimal Random Forest hyper-parameters, which are estimated from the data and used to train the most accurate model, were identified using Bayesian optimization (mlrMBO R-package, version: 1.1.1), with five times repeated 10-fold cross validation. The optimized RF model (with lowest cross-validation error, root-mean-square deviation (RMSE)) was used to estimate the contribution of each meteorological factor as a predictive performance of IV activity. This was done by random permutation of the measurements of one of the meteorological factors, while keeping measurements for all other factors constant, followed by estimation of the impact of this procedure on the model accuracy (i.e. percentage mean decrease in accuracy). RF R-package version 4.6-14 was applied for the model training, with the following hyper-parameters used for optimization: number of trees, number of randomly sampled features at each tree split (mtry), and minimum size of terminal nodes.

To find correlation between colder winters and increase in number of influenza-positive specimens for six country, we applied Cox-Stuart statistical test. In particular, the median winter temperatures (2010-2018) were calculated by taking a median of daily temperatures between 1st of December and the 28th of February. Then, the median winter temperatures were ordered by the number of total IV-positive specimens for each country each year. A Cox-Stuart statistical test was applied to the ordered median winter temperatures to find any significant increasing or decreasing trends (threshold of significance was set to $p=0.05$).

2.4. Experimental validation

Human telomerase reverse transcriptase-immortalized retinal pigment (RPE) cells, which represent excellent model system to study IV-host cell interaction, were grown in Dulbecco's Modified Eagle's medium (DMEM)-F12 supplemented with 50 U/ml PenStrep, 2 mM L-glutamine, 10% FBS, and 0.25% sodium bicarbonate (Sigma-Aldrich) [15]. The virus growth medium (VGM) contained 0.2% BSA, 2 mM L-glutamine, 0.35% $NaHCO_3$, and 1 µg/mL L-1-tosylamido-2-phenylethyl chloromethyl ketone-trypsin (TPCK)-trypsin (Sigma-Aldrich) in DMEM-F12 (Gibco).

GFP-expressing influenza A/PR8-NS116-GFP strain (PR8-GFP) was purified by centrifugation in sucrose gradient as previously described [16, 17]. The purified virus was incubated at different temperatures for 48h. Alternatively, the virus was exposed to UVC (λ = 254 nm) or to UVB (λ = 302 nm) using Hoefer UVC 500 Ultraviolet Crosslinker (20 J/cm^2) or VM25/30/GX trans-illuminator as UV sources, respectively. RPE cells were infected with the viruses at a multiplicity of infection (moi) of 1. After 24 h GFP expression was measured in infected cells using fluorescent microscope (Zeiss Observer Z1).

3. Results

3.1. Influenza virus activity during 2017-2018 season

A total of 62296 IV-positive specimens were collected from Norway, Sweden, Finland, Estonia, Latvia and Lithuania from September 1, 2017 to August 31, 2018 (Fig. 1). The highest number of IV-positive specimens was collected from Norway (34895), whereas the lowest number of samples was

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from Finland (231). Among positive specimens in six countries, only 11% were classified: 3744 were influenza A viruses (71% of A/H3 and 29% of A/H1) and 2866 were influenza B viruses (97% of B/Yamagata and 3% of B/Victoria). Most IVs were detected between 1st and 14th weeks of 2018 (Fig. 1), with the peak of influenza occurred between January 29, 2018 and March 11, 2018 (5th to 10th weeks). The only exception was Latvia, where the peak of influenza activity occurred between 9th and 12th weeks (Fig. S1).

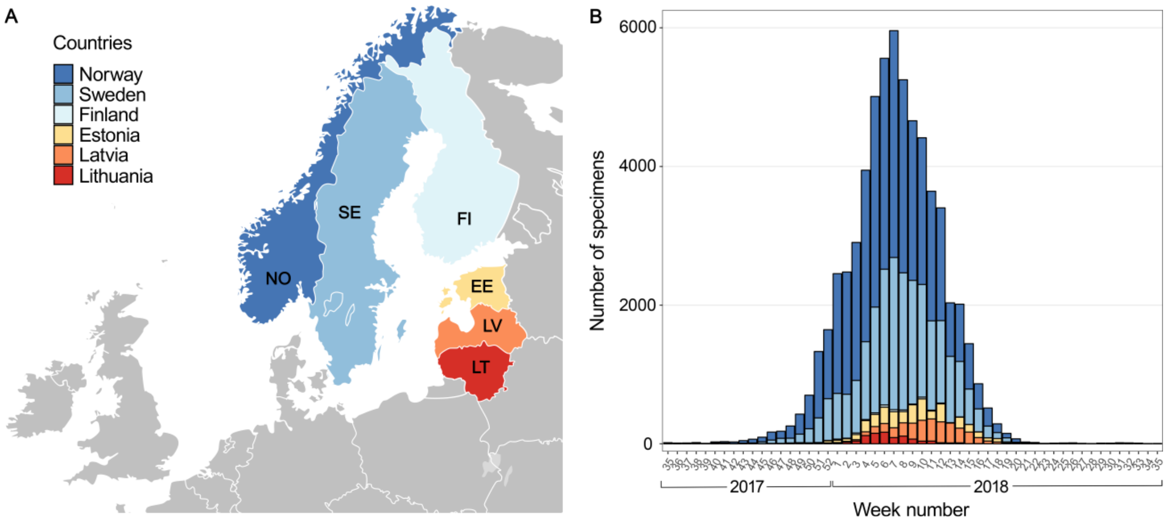

Figure 1. Weekly number of detections of influenza viruses in six Northern European countries, 2017–2018. (A). Map showing six Northern European countries included in analysis. "A blank Map of Europe in SVG format", which is available at Wikimedia Commons, was used as a template. (B) Stacked bar chart representing number of influenza-positive specimens distributed across six countries between week 35 of 2017 and week 34 of 2018. Each country is shown as a bar in the same color as A.

3.2. Temperature and UV index are the most predictive meteorological factors of IV epidemic in 2017-2018 in Northern Europe

We obtained daily statistics for six meteorological factors (temperature, UV index, humidity, wind speed, atmospheric pressure, and precipitation) from web-interface of Weather Underground and operational Tropospheric Emission Monitoring Internet services for Norway, Sweden, Finland, Estonia, Latvia and Lithuania from September 1, 2017 to August 31, 2018 (Fig. S1 and S2).

We analyzed correlation between each meteorological factor and IV activity to find significant associations and to measure the strength of linear association between variables using Pearson correlation coefficient. As the correlation analysis does not always provide an accurate picture of cause and effect, especially in nonlinear systems, where interdependence between variables is complex, we validated our results by optimizing a machine learning Random Forest model. The model was optimized for each of the analyzed countries with average explained variation of 71%.

Both correlation and machine learning analyses revealed that temperature was the most predictive meteorological factor of influenza activity in all six Northern European countries (Fig. 2). UV index was the second most predictive in all countries, except Latvia. The humidity was the third most important factor associated with IV activity. Other meteorological factors, including wind speed, precipitation, and pressure showed low correlation with the peaks of IV activity and were not among the most predictive features of machine learning Random Forest model.

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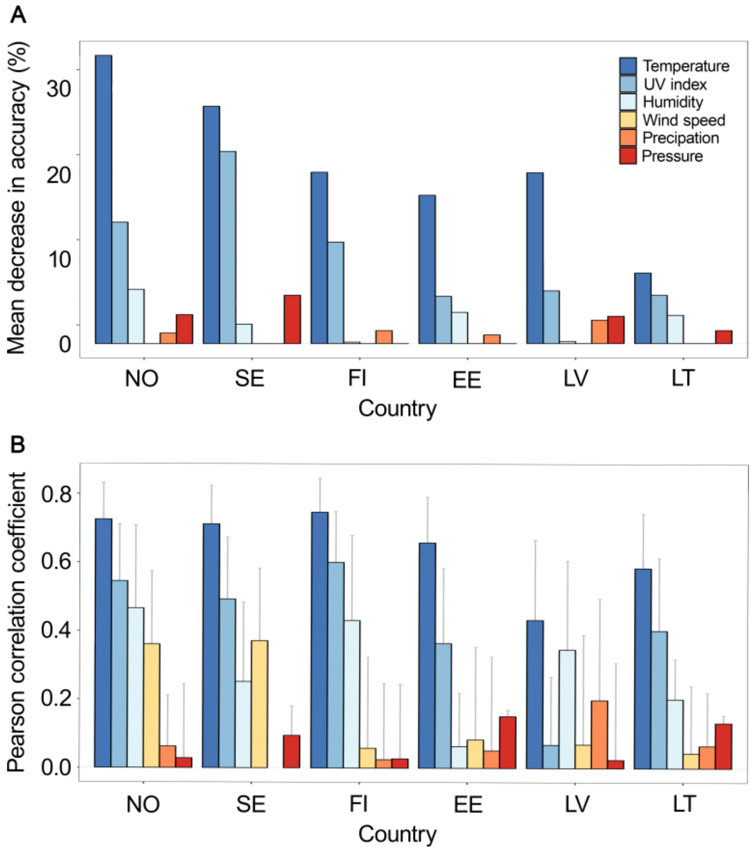

Figure 2. Association between six meteorological factors (temperature, UV index, humidity, wind speed, precipitation, and pressure) and influenza activity in six Northern Europe countries (Norway, Sweden, Finland, Estonia, Latvia and Lithuania) between week 35 of 2017 and week 34 of 2018. (A) Contribution of each meteorological factor to predictive performance of machine learning Random Forest model trained to predict the influenza activity. The contribution is measured as percentage mean decrease in accuracy (the higher the bar, the more important the factor). (B) Correlation between meteorological factors and influenza activity.

3.3. Temperature and UV index are the most predictive meteorological factors of IV epidemic in 2010-2017 in Northern Europe

To confirm our finding, we analyzed associations between six meteorological factors and IV activity in six European countries during 2010-2017. Both low temperature and low UV index remained the most predictive meteorological factors of IV activity peaks (Fig. 3). Interestingly, the peaks of IV activity occurred on average at -1.9 °C (range -19.9°C to 26.0°C) and UV index of 0.7 (range 0.13 to 7.1). Moreover, colder winters contributed to increase of IV activity only in Finland and Lithuania (Fig. S3).

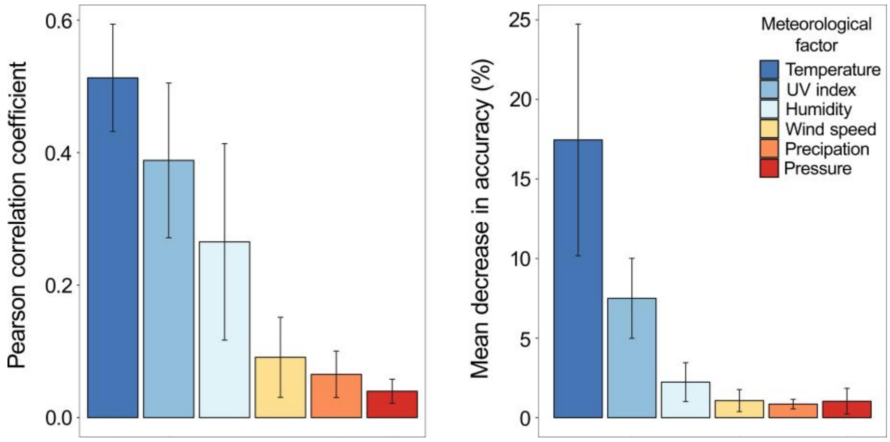

Figure 3. Association between meteorological factors (temperature, UV index, humidity, wind speed, precipitation, and pressure) and influenza activity in six Northern Europe countries averaged for the period from week 35 of 2010 and week 34 of 2017. Left panel: Correlation analysis between meteorological factors and influenza activity. Right panel: Contribution of each meteorological factor to predictive performance of machine-learning Random Forest models trained to predict the IV activity in six Northern European countries. Contribution is measured as percentage mean decrease in accuracy (the higher is a bar, the more important feature is). Both metrics are averaged for the period from 2010 to 2017 epidemic seasons.

3.4. Low temperature and low UV radiation preserve IV infectivity in vitro

To validate the association between IV activity and low temperature and UV indexes, we performed an *in vitro* experiments using GFP-encoding influenza A/H1N1 virus and human RPE cells. Purified virus was incubated at different temperatures for 48h or exposed to UVC or UVB radiation for different times. We monitored virus-mediated GFP expression in RPE cells. We observed that increasing temperature and prolonged exposure to UVC, but not UVB, reduced A/H1N1-mediated GFP expression in infected cells (Fig. 4A). Moreover, viruses exposed to high temperature or prolonged UVC radiation were unable to kill RPE cells, consistent with the above results (Fig. 4B and 4C). These results suggest that low temperature and UV intensity preserved IV infectivity.

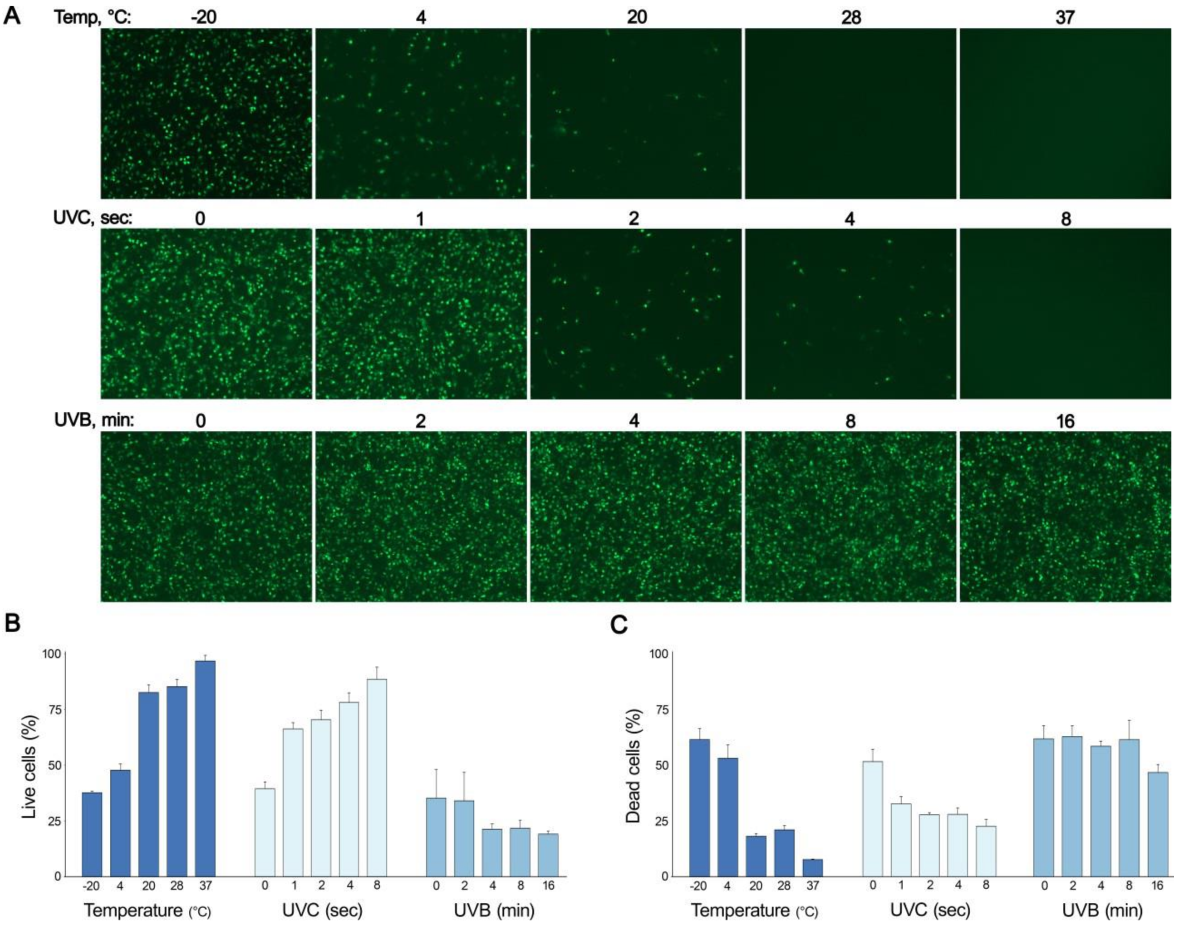

Figure 4. Effect of temperature and UV radiation on stability of GFP-encoding influenza virus (IV). (A) Effect of temperature and UVB and UVC radiation on IV-mediated GFP expression. IV was incubated at indicated temperatures for 48 h or exposed to UVB or UVC radiation for the indicated times. RPE cells were subsequently infected with the virus. GFP expression was visualized using fluorescent microscopy. (B) Effect of temperature-, UVB- and UVC-exposed IV on viability of infected RPE cells. Viruses were obtained and RPE cells were infected as for panel A. Viability of cells were measured using Cell Titer Glow assay. Mean ± SD, n=3. (C) Effect of temperature- and UVB- and UVC-exposed IV on death of infected RPE cells. Viruses were obtained and RPE cells were infected as for panel A. Death of cells were measured using Cell Tox Green assay. Mean ± SD, n=3.

4. Discussion

In this study, we used correlation and machine learning analyses to quantify the impact of six meteorological factors (temperature, UV index, humidity, wind speed, atmospheric pressure, and precipitation) on the IV activity in six Northern European countries (Norway, Sweden, Finland, Estonia, Latvia and Lithuania) during 2010-2018. We demonstrated that the low temperature and low humidity were associated with annual peaks of IV activity in analyzed countries. This is in agreement with previous observations that low temperature and low humidity favored IV outbreaks in temperate climates at high latitudes [18, 19]. Moreover, we showed that low UV indexes were among the most predictive meteorological factors for IV epidemics.

Our experiments with UVB-, UVC- or temperature-exposed viruses supported the associations. In particular, we showed that low temperature and UVB, but not UVC preserved infectivity of IV in vitro. It should be noted, that exposure to UVC radiation inactivated the virus. However, UVC is absorbed by atmosphere and, therefore, could not reach the earth surface and affect IV-host interaction. Moreover, high levels of UVB could activate host immune response to viral infections during summer time.

It was shown that low winter temperatures correlated with both influenza incidence and global mortality, which mainly affected 65s and older [20-22]. Low UV indexes could also be associated with global mortality. Indeed, data from six Northern European countries reported to the EuroMOMO project showed an excess mortality from all causes between the beginning of Januaries and the end of Februaries in 2010-2018, and coincided with IV epidemic peaks, low temperature and low UV indexes.

Previous association studies showed that warmer winters could contribute to the decrease in IV activity in Europe and US [20, 23]. In particular, the mild epidemics were associated with warm winters, which were followed by cold winters with severe IV outbreaks with early onset. The authors proposed that fewer people were infected with influenza during warm winters, thereby leaving an unnaturally large fraction of susceptible individuals in the population going into the next season leading to early and severe epidemics. Our study does not support association between warmer winters and decrease in IV activity, because such trend was observed only for 2 of 6 analyzed countries for the period from 2010 to 2018.

5. Conclusions

Inclusion of temperature, UV indexes and other meteorological parameters in the IV surveillance systems could further our understanding of virus stability and transmissibility in the world, and help to develop accurate predictive models of influenza epidemics. Moreover, combination of epidemiological, meteorological and genetic studies could unravel the evolution of influenza viruses and, consequently, improve early intervention and long-term control strategies of future influenza outbreaks.

Supplementary Materials: The following are available online at http://www.mdpi.com/XXXX. Figure S1: Weekly influenza virus activity and daily temperatures across six Northern European countries between September 1, 2017 and August 31, 2018. Figure S2: Weekly influenza virus activity and daily UV indices across six Northern European countries between September 1, 2017 and August 31, 2018. Figure S3: Graph showing relation between the number of influenza-positive specimens and the median winter temperatures (2010-2018) in six Northern European countries.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

IV: influenza virus; UV: ultraviolet; GFP: green fluorescent protein; RPE: human telomerase reverse transcriptase-immortalized retinal pigment cells; moi: multiplicity of infection; hpi: hours post infection; WHO: World Health Organization; NIC: National Influenza Center; GISRS: Global Influenza Surveillance and Response System; NWS: National Weather Service; PWS: personal weather stations; TEMIS: Tropospheric Emission Monitoring Internet Service; RF: Random Forest; RMSE: root-mean-square deviation; DMEM: Dulbecco's Modified Eagle's medium; TPCK-trypsin: L-1-tosylamido-2-phenylethyl chloromethyl ketone-trypsin.

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