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Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis

You Li, Rachel M Reeves, Xin Wang, Quique Bassat, W Abdullah Brooks, Cheryl Cohen, David P Moore, Marta Nunes, Barbara Rath, Harry Campbell, Harish Nair, on behalf of the RSV Global Epidemiology Network and RESCEU investigators*



Summary

Background Influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus are the most common viruses associated with acute lower respiratory infections in young children (<5 years) and older people (≥65 years). A global report of the monthly activity of these viruses is needed to inform public health strategies and programmes for their control.

Methods In this systematic analysis, we compiled data from a systematic literature review of studies published between Jan 1, 2000, and Dec 31, 2017; online datasets; and unpublished research data. Studies were eligible for inclusion if they reported laboratory-confirmed incidence data of human infection of influenza virus, respiratory syncytial virus, parainfluenza virus, or metapneumovirus, or a combination of these, for at least 12 consecutive months (or 52 weeks equivalent); stable testing practice throughout all years reported; virus results among residents in well-defined geographical locations; and aggregated virus results at least on a monthly basis. Data were extracted through a three-stage process, from which we calculated monthly annual average percentage (AAP) as the relative strength of virus activity. We defined duration of epidemics as the minimum number of months to account for 75% of annual positive samples, with each component month defined as an epidemic month. Furthermore, we modelled monthly AAP of influenza virus and respiratory syncytial virus using site-specific temperature and relative humidity for the prediction of local average epidemic months. We also predicted global epidemic months of influenza virus and respiratory syncytial virus on a 5° by 5° grid. The systematic review in this study is registered with PROSPERO, number CRD42018091628.

Findings We initially identified 37 335 eligible studies. Of 21 065 studies remaining after exclusion of duplicates, 1081 full-text articles were assessed for eligibility, of which 185 were identified as eligible. We included 246 sites for influenza virus, 183 sites for respiratory syncytial virus, 83 sites for parainfluenza virus, and 65 sites for metapneumovirus. Influenza virus had clear seasonal epidemics in winter months in most temperate sites but timing of epidemics was more variable and less seasonal with decreasing distance from the equator. Unlike influenza virus, respiratory syncytial virus had clear seasonal epidemics in both temperate and tropical regions, starting in late summer months in the tropics of each hemisphere, reaching most temperate sites in winter months. In most temperate sites, influenza virus epidemics occurred later than respiratory syncytial virus (by 0·3 months [95% CI -0·3 to 0·9]) while no clear temporal order was observed in the tropics. Parainfluenza virus epidemics were found mostly in spring and early summer months in each hemisphere. Metapneumovirus epidemics occurred in late winter and spring in most temperate sites but the timing of epidemics was more diverse in the tropics. Influenza virus epidemics had shorter duration (3·8 months [3·6 to 4·0]) in temperate sites and longer duration (5·2 months [4·9 to 5·5]) in the tropics. Duration of epidemics was similar across all sites for respiratory syncytial virus (4·6 months [4·3 to 4·8]), as it was for metapneumovirus (4·8 months [4·4 to 5·1]). By comparison, parainfluenza virus had longer duration of epidemics (6·3 months [6·0 to 6·7]). Our model had good predictability in the average epidemic months of influenza virus in temperate regions and respiratory syncytial virus in both temperate and tropical regions. Through leave-one-out cross validation, the overall prediction error in the onset of epidemics was within 1 month (influenza virus -0·2 months [-0·6 to 0·1]; respiratory syncytial virus 0·1 months [-0·2 to 0·4]).

Interpretation This study is the first to provide global representations of month-by-month activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus. Our model is helpful in predicting the local onset month of influenza virus and respiratory syncytial virus epidemics. The seasonality information has important implications for health services planning, the timing of respiratory syncytial virus passive prophylaxis, and the strategy of influenza virus and future respiratory syncytial virus vaccination.

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Research in context

Evidence before this study

We searched PubMed for any studies published between Jan 1, 2000, and Nov 30, 2018, that reported global seasonality of influenza virus, respiratory syncytial virus, parainfluenza virus, or metapneumovirus, using the search terms "(influenza OR RSV OR respiratory syncytial virus OR parainfluenza OR PIV OR metapneumovirus OR MPV) AND (seasonal* OR activity) AND (global OR worldwide)". We identified 11 studies reporting global seasonality, including one reporting influenza virus and respiratory syncytial virus, eight reporting influenza virus, and two studies reporting respiratory syncytial virus; no studies were found reporting global metapneumovirus or parainfluenza virus seasonality. According to these studies, both influenza virus and respiratory syncytial virus peaks were well aligned with winter months in temperate regions, while greater diversity in timing was observed in the tropics; both viruses presented weak latitudinal gradients in the annual timing of epidemics by hemisphere, with peaks occurring later with increasing latitude. Eight of 11 studies were based on country-level data and thus were unable to account for subcountry-level variations, whereas the remaining three studies only reported the peak or onset month of the epidemics. In addition to seasonality results, three of 11 studies reported the correlation between meteorological factors, such as temperature and humidity, and influenza virus epidemics, suggesting the possibility in predicting viral epidemics globally. However,

issues related to data availability impeded these studies from looking further into the prediction of viral epidemics.

Added value of this study

To our knowledge, this is the first systematic analysis of global monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus at both country and subcountry levels. On a global scale, we modelled the association between temperature and relative humidity and the activity of influenza virus and respiratory syncytial virus. We also developed an online interactive tool for predicting local epidemic months and we predicted the global monthly epidemics of influenza virus and respiratory syncytial virus on a 5° by 5° grid.

Implications of all the available evidence

The seasonality information of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus is key for health services planning. The prediction tool developed in our study is helpful in predicting the onset months of local influenza virus and respiratory syncytial virus epidemics, and it serves as a supplement to existing surveillance. This tool, together with the summarised seasonality information, will help with the optimisation of respiratory syncytial virus immunisation strategies that rely on the information of local respiratory syncytial virus season, especially in most middle-income and lower-income countries where routine respiratory syncytial virus surveillance is not available.

Introduction

Influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus are the four major viral pathogens associated with acute lower respiratory infection and these represent a substantial burden of disease particularly in young children (<5 years)¹ and older people (≥65 years).^{2,3} Globally, influenza virus is estimated to cause 39.1 million acute lower respiratory infection episodes (95% uncertainty interval 30.5–48.4) and 58 200 deaths (44 000–74 200) annually; and respiratory syncytial virus is estimated to cause 24.8 million episodes (19.7–31.4) and 76 600 deaths (55 100–103 500) annually.⁴ To date, no global burden estimate has been reported for parainfluenza virus and metapneumovirus.

Seasonality information of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus is important in health services planning and the development of appropriate disease prevention and control strategies, including immunisation strategies. The demand for a global overview of the seasonal patterns of these four main viruses has been growing steadily because it helps to understand the seasonality in those under-reported countries or regions where the burden of viral respiratory infections is substantial while health-care resources are insufficient. For example, the seasonality of one country could be possibly estimated

given the information of countries in geographical proximity or any other global patterns. As a result, several reports^{5–15} have described the global seasonality of influenza virus and respiratory syncytial virus (appendix pp 9–11). In these studies, both influenza virus and respiratory syncytial virus circulation peaks were well aligned with winter months in temperate regions, while greater diversity in timing was observed in the tropics; and both viruses showed weak latitudinal gradients in the annual timing of epidemics by hemisphere, with peaks occurring later with increasing latitude. However, seasonal patterns of these two viruses are still poorly understood in tropical and subtropical regions where seasonal patterns could not be well described simply by indicators, such as peak timing or beginning and end of epidemics, as done in temperate regions. Only three studies^{5,7,10} reported monthly country-level activity of influenza virus; nevertheless, these reports were unable to characterise any within-country variations that could help to understand the latitudinal gradient of viral activity. In addition to the seasonal patterns reported, some studies^{6,8,14} reported pronounced correlations between meteorological factors, such as temperature and humidity, and influenza virus epidemics, suggesting the possibility in prediction of viral epidemics on a global scale. However, issues related to data availability impeded

See Online for appendix

these studies from looking further into the prediction of viral epidemics.

To address the data gaps in global seasonality of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus, we compiled data from a systematic literature review, online datasets, and unpublished research data at both country level and subcountry level, and did a systematic analysis of global monthly activity of these four viruses. Furthermore, with the compiled dataset, we aimed to model viral epidemics on a monthly basis using site-specific meteorological predictors.

Methods

Search strategy and selection criteria

We collected viral activity data for influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus from a range of sources, including a systematic literature search, online public datasets, and the research datasets shared by the collaborators from Respiratory Syncytial Virus Global Epidemiology Network (RSV GEN).¹⁶

We searched three bibliographical databases (MEDLINE, Embase, and Global Health), for articles reporting activity of influenza virus, respiratory syncytial virus, parainfluenza virus, or metapneumovirus using a tailored search strategy. The literature search used the terms (with synonyms and closely related words) “influenza virus”, “respiratory syncytial virus”, “parainfluenza virus”, “human metapneumovirus”, and “acute lower respiratory infection” combined with “seasonality”, “surveillance”, “periodicity”, and “temporal variation” (appendix pp 1–2). In the present study, records related to all-cause acute lower respiratory tract infection that did not include any of the four viruses above were excluded. We limited the literature search to the period of Jan 1, 2001, to Dec 31, 2017. We did not include studies published before 2000 because seasonality could change in the long term and our objective was to report on current global seasonality. References cited in retrieved articles were also examined for eligibility. No language restrictions were applied. Inclusion and exclusion criteria can be found in the appendix (p 3).

We included open-access online data from WHO FluNet,¹⁷ Pan America Health Organization FluID,¹⁸ Japan National Institute of Infectious Diseases,¹⁹ Hong Kong Department of Health,²⁰ Canada FluWatch,²¹ and New Zealand Ministry of Health.²² Detailed information about these data are in the appendix (p 12). We also included viral activity data shared by RSV GEN, which is a collaboration of more than 70 investigator groups primarily in low-income and middle-income countries that was initially established to estimate the disease burden of acute lower respiratory tract infection associated with respiratory syncytial virus.¹⁶ Detailed information on RSV GEN data are in the appendix (pp 13–16).

Data extraction was done independently by YL and jointly by RMR and XW through a three-stage process, as

detailed in the appendix (pp 3–4). Any discrepancies were resolved through discussion among YL, RMR, and XW. The protocol for this systematic literature search is registered on PROSPERO (number CRD42018091628).

Quality assessment

For each article included in the systematic literature review, a quality assessment was independently done by YL and jointly by RMR and XW. The quality assessment comprised three brief questions regarding data representativeness, test practice, and timely reporting (questionnaire in the appendix [p 4]). Data representativeness indicated if the seasonality reported in the study could be representative of the seasonality in that given site. Test practice indicated if there were any changes in terms of viral testing during the study period that could affect the reported seasonality. Timely reporting indicated if issues related to the timing of reporting test positives affected the seasonality results. Any disagreement was addressed through discussion. For each of the three questions, all studies were given a rating between A (very good) and D (bad). Any study that was rated as D in any of the three questions in the quality assessment was excluded.

Data analysis

To ensure good comparisons of the seasonality results among all sites, we added the number of cases by month across all years reported for each data record. We converted any weekly data to monthly data by using the R package `wktmo` before we added these data by month.

We defined geographical regions as temperate (latitude less than -23.5° or more than 23.5°) and tropical (latitude between -23.5° and 23.5°). We defined meteorological seasons as spring (March–May in the northern hemisphere; September–November in the southern hemisphere), summer (June–August in the northern hemisphere; December–February in the southern hemisphere), autumn (September–November in the northern hemisphere; March–May in the southern hemisphere), and winter (December–February in the northern hemisphere; June–August in the southern hemisphere).

For each month, we calculated annual average percentage (AAP) as a measurement of the strength of virus activity by the formula:

$$AAP_i = \frac{n_i}{\sum_1^{12} n_i} \times 100\%$$

where i denotes the month and n denotes the number of cases. We plotted heat maps displaying the activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus in each site sorted by latitude.

In the main analysis, we estimated the duration of epidemics by the minimum number of months to account for a total AAP of 75%, a modified method based on Caini

and colleagues.⁷ The modified method could account for sites with more than one season per year. The estimation for the duration of epidemics was done by first sorting monthly AAP into descending order and then identifying the first n months to account for AAP of 75%, with each month being an epidemic month and n being the duration of epidemics. The onset month of epidemics at each site was defined by the first month of the longest consecutive epidemic months. We applied Pearson's correlation to assess the correlation between the onset month and the latitude and longitude of the sites. To present the relationship between latitude and duration of epidemics, we plotted duration of epidemics against the latitude of the sites using local regression (LOESS) smoothing by virus, with the parameter span in LOESS set as 0.60.

We did subgroup analyses, determined a priori, to compare the duration of epidemics of viruses of interest using the same method as stated above. We prespecified three comparison groups: influenza virus subtypes (influenza virus A vs influenza virus B), influenza virus versus respiratory syncytial virus, and respiratory syncytial virus versus metapneumovirus. For each comparison group, we did the analyses only among those sites with complete data of the viruses in the comparison group.

To study the relationship between seasonal timing of the viruses, we did cross-correlation analyses for each site between influenza virus A and B, between influenza virus and respiratory syncytial virus, and between respiratory syncytial virus and metapneumovirus using -5 to 5 months of lag (a total of 11 correlation analyses). In consideration of the multiple correlation analyses within each site, we adjusted the significance level to 0.004 using the Bonferroni method ($0.05/11 \approx 0.004$). If significant correlation results were observed at a site, we reported the lag that maximised the correlation coefficient as the difference in timing between the viruses. We also calculated the monthly overlapping AAP between each pair of viruses stated above and the overall annual overlapping AAP.

For each site included, we extracted meteorological data from the site's nearest weather station provided by the US National Centers for Environmental Information using R package GSODR. We modelled monthly AAP of virus activity using mean-centred monthly temperature and relative humidity as predictors in a LOESS model. This model is based on the assumption that for each month, the relative strength of viral activity (ie, AAP) is associated with the relative measurements of the selected meteorological factors (ie, mean-centred temperature and relative humidity). Details of model assumption, data preparation, model comparison, and model assessment are in the appendix (pp 5–6). The model-predicted AAP values for each site were then used to calculate the epidemic months (ie, a dichotomous result for each month, epidemic, or non-epidemic). We required a minimum of 120 sites with 100 or more positives per virus for more robust models. With the

available data, we were able to model influenza virus (including influenza virus subtypes) and respiratory syncytial virus only.

To assess the model performance, we predicted the monthly AAP at each site using the model trained by data from the remainder sites (ie, leave-one-out method) as the first step; on the basis of the predicted AAP, we then calculated the epidemic months and assessed the agreement between the predicted epidemic months and the observed epidemic months by calculating Cohen's κ , sensitivity, specificity, positive predictive value, and negative predictive value. We also calculated the mean difference in months between the predicted and the observed onset of epidemics (ie, prediction error) and its 95% CI.

On the basis of the model, we estimated the global epidemic months of influenza virus and respiratory syncytial virus on a 5° by 5° scale using gridded temperature and relative humidity data in 2013–17 from the HadISDH dataset (4.0.0.2017f).^{23,24} Moreover, using the R package Shiny, we developed an online interactive tool for the prediction of local epidemic months of influenza virus and respiratory syncytial virus. The user manual of this tool is in the appendix (pp 7–8).

All data analyses were done using R software (version 3.4.3). The seasonality data and key R functions developed for the analysis are available through the Edinburgh DataShare.²⁵

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We initially identified 37 335 studies via our literature search. After excluding duplicates, the systematic literature search identified 21 065 records, of which 1081 (5.1%) full-texts articles were assessed for eligibility. 542 (50.1%) studies were further checked for availability of monthly data and for any duplicate data. A total of 185 (17.1%) studies were included at the final stage of the literature review (appendix p 69); details of these studies and their quality assessment results can be found in the appendix (pp 17–39). We included 246 sites for influenza virus, 183 sites for respiratory syncytial virus, 83 sites for parainfluenza virus, and 65 sites for metapneumovirus. The number of positives, and length in years of data from the published literature and other sources are in the appendix (p 40). Compared with data from the published literature, data from other sources had a greater number of positive samples and were collected over a longer time-span. The geographical distribution of the sites included was mapped and categorised by virus (figure 1 shows influenza virus,

respiratory syncytial virus, parainfluenza virus, and metapneumovirus; appendix [p 70] shows influenza virus subtypes). Influenza virus A (H1N1) was not included in the analysis due to the small number of sites included ($n=39$).

Figure 2 shows the global monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus by latitude (results of influenza virus subtypes the appendix pp 71–72). Animated figures of global monthly activity of these four viruses can be found in the ShinyApp. Distinct seasonality of virus activity was observed in most sites for the four viruses. Latitudinal variations of the onset month of epidemics were also observed, although patterns varied by virus. Detailed results of epidemic months grouped by country are in the appendix (pp 41–66).

Influenza virus epidemics occurred consistently during January–March in most temperate sites in the northern hemisphere and during June–August in most temperate sites in the southern hemisphere. These patterns became less pronounced closer to the equator, with the emergence of summer epidemics in some sites. Variable timing of epidemics was observed in tropical sites. In both hemispheres, the onset of the major influenza virus epidemics was later with increasing latitudes (northern hemisphere: $r=0.36$, $p<0.001$; southern hemisphere: $r=0.47$, $p=0.003$).

Respiratory syncytial virus activity showed a latitudinal gradient in the timing of epidemics in each hemisphere. In the northern hemisphere, respiratory syncytial virus activity was initiated in July in tropical sites. The activity was initiated later with increasing latitude until it reached high-latitude sites around January. Subsequently, the respiratory syncytial virus activity started to wane before another round of activity was initiated around July in tropical sites. Similar patterns were observed in the southern hemisphere, where respiratory syncytial virus activity was initiated around January in tropical sites first and around June in high-latitude sites. Interestingly, in the tropics, the timing of respiratory syncytial virus epidemics was similar within each hemisphere but differed greatly between hemispheres, with only a few exceptions in equatorial sites; this pattern was not observed with any influenza virus. In both hemispheres, the onset of major respiratory syncytial virus epidemics was later with increasing latitudes (northern hemisphere: $r=0.50$, $p<0.001$; southern hemisphere: $r=0.54$, $p<0.001$).

In addition to latitudinal gradients in influenza virus and respiratory syncytial virus onset month, we observed longitudinal patterns in Europe where most sites had similar latitudes but different longitudes. The onset month of both influenza virus and respiratory syncytial virus epidemics was observed to be later in the east (ie, higher longitudes) than the west (influenza virus: $r=0.46$, $p=0.006$; respiratory syncytial virus: $r=0.45$, $p=0.025$), while no significant latitudinal patterns were observed in this region (influenza virus: $r=0.07$, $p=0.694$;

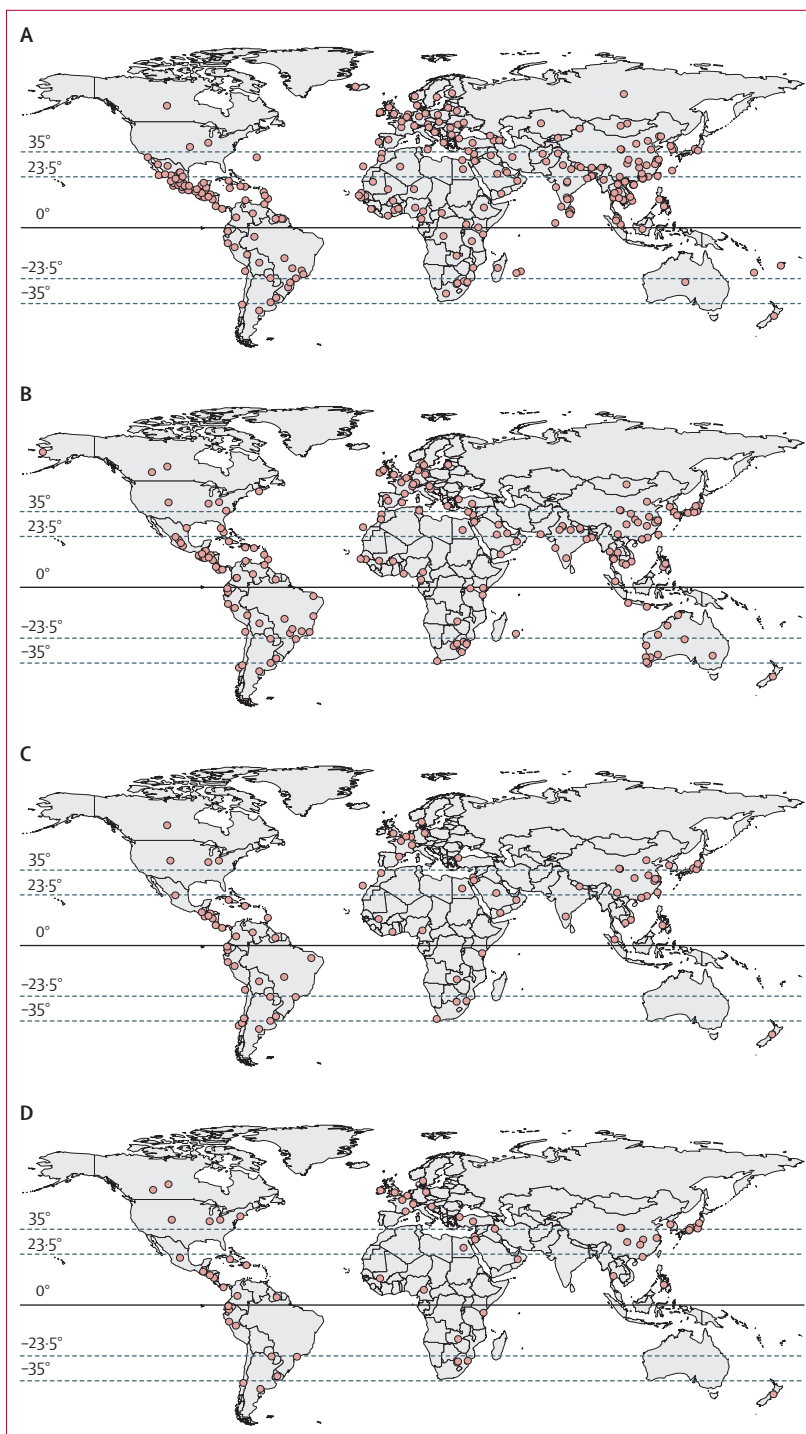
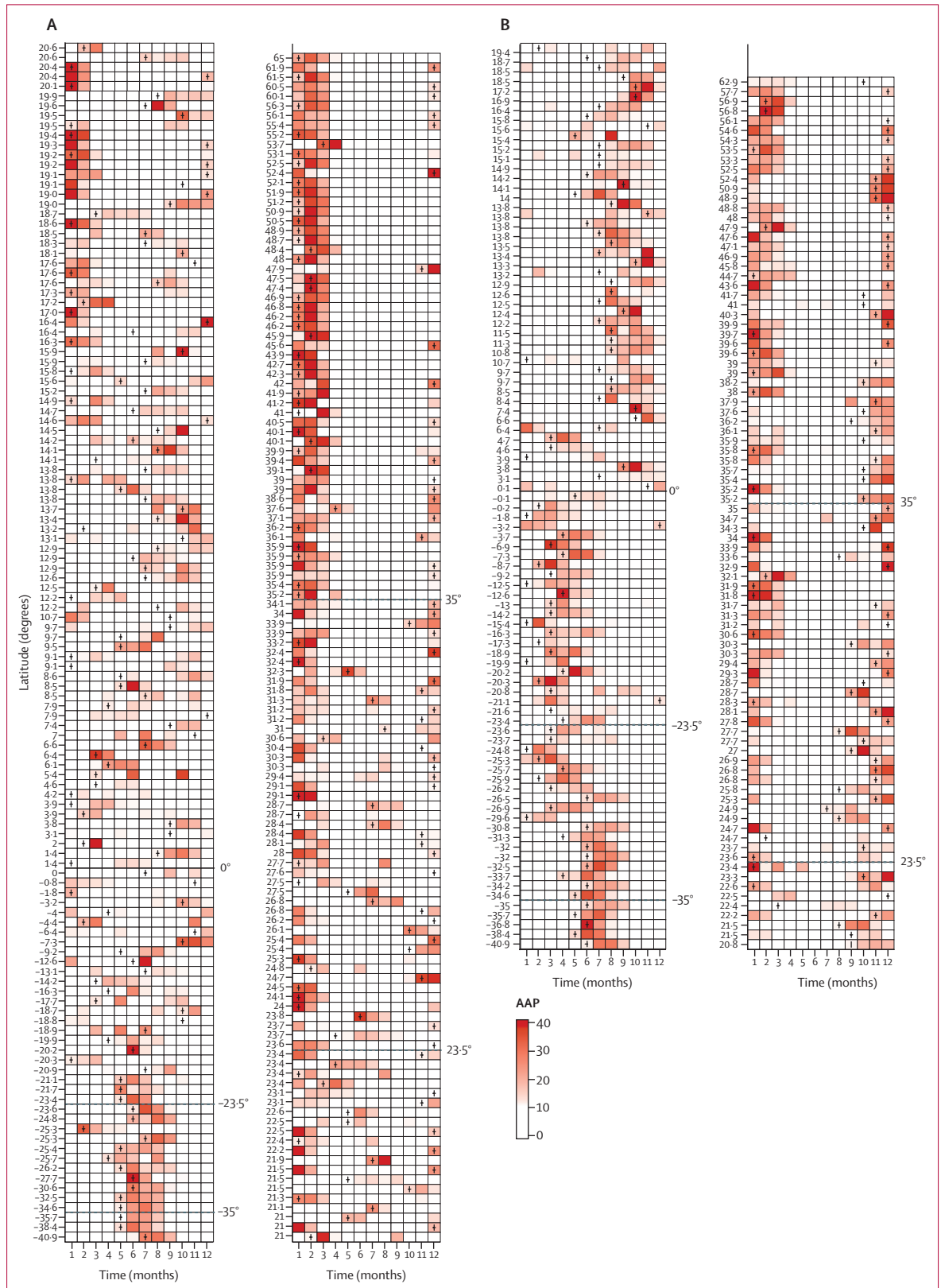


Figure 1: Study sites included in the analysis

(A) Influenza virus. (B) Respiratory syncytial virus. (C) Parainfluenza virus. (D) Metapneumovirus.

respiratory syncytial virus: $r=0.11$, $p=0.610$). The average difference in the timing of onset between the west and east of Europe (defined geographically by 20° E) was 0.6 months for influenza virus and 0.8 months for respiratory syncytial virus.

For the animated figures see <http://resceu.ecdf.ed.ac.uk/shiny/ShinyGIF/>



(Figure 2 continues on next page)

Seasonality of parainfluenza virus was not as distinct as influenza virus or respiratory syncytial virus. Parainfluenza virus epidemics were found mostly in spring and early summer months in both the northern and southern hemispheres. Metapneumovirus epidemics occurred in late winter and spring in most temperate sites, but the timing of epidemics was more diverse in the tropics.

Overall, virus-specific latitudinal patterns were observed in duration of epidemics (appendix p 73). Parainfluenza virus had longer duration of epidemics (6.3 months [95% CI 6.0–6.7]) than the other three viruses. The duration of influenza virus epidemics varied greatly by latitude, with shorter duration (3.8 months [3.6–4.0]) in temperate sites and longer duration (5.2 months [4.9–5.5]) in the tropics. Within influenza virus subtypes, influenza virus A(H1N1)pdm had the shortest duration of epidemics (3.3 months [3.1–3.5]), followed by influenza virus A(H3N2) (4.2 months [3.9–4.4]) and influenza virus B (4.5 months [4.3–4.8]), regardless of the latitudes; the durations of influenza virus A(H1N1)pdm, A(H3N2), and B showed similar latitudinal patterns. Compared with influenza virus, the duration of epidemics of respiratory syncytial virus and metapneumovirus was stable (respiratory syncytial virus: 4.6 months [4.3–4.8]; metapneumovirus: 4.8 months [4.4–5.1]). Subgroup analyses using site-matched data replicated the results of the comparisons above (appendix pp 74–75).

Results from subgroup analysis using sites with complete data of influenza virus A and B showed that influenza virus A and B activity were significantly correlated in 67 (78%) of 86 temperate sites and 55 (55%) of 100 tropical sites. In the temperate region, influenza virus A epidemics occurred 0.6 months (95% CI 0.3 to 0.9) earlier than influenza virus B. In the tropics, no clear temporal order was observed (lag=0 [95% CI -0.5 to 0.5]) and this lack of clear temporal order was largely due to the greater variability in the timing of epidemics in the northern tropics (appendix p 76)

Influenza virus and respiratory syncytial virus activity were significantly correlated in 28 (67%) of 42 temperate sites and 28 (59%) of 47 tropical sites. Influenza virus epidemics occurred later than respiratory syncytial virus in most temperate sites with the average lag of 0.3 months (95% CI -0.3 to 0.9), while no clear temporal order was observed in the tropics (lag=0.1 [-0.9 to 1.2]; appendix p 76).

Respiratory syncytial virus and metapneumovirus activity were significantly correlated in 83% of temperate sites (29 of 35) and in 62% of tropical sites (14 of 22). In the temperate region, metapneumovirus epidemics occurred 1.7 months (95% CI 1.1–2.3) later than respiratory syncytial virus, while no clear temporal order was observed in the tropics (lag=0.2 [95% CI -0.9 to 1.3]; appendix p 76)

We found that 61.2% (95% CI 58.6–63.9) of influenza virus A and B activity overlapped annually, that

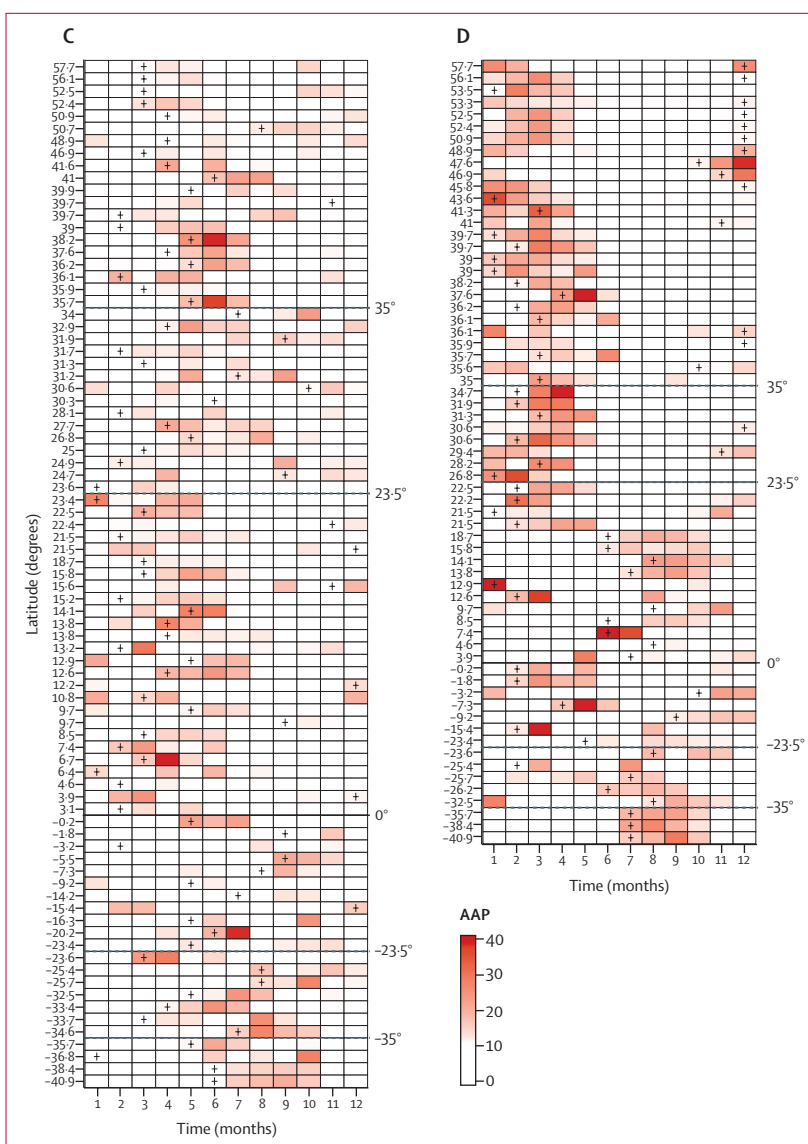


Figure 2: Heat maps of global monthly activity of influenza virus (A) and respiratory syncytial virus (B), parainfluenza virus (C), and metapneumovirus (D), sorted by latitude. AAP=annual average percentage. + denotes the onset month of virus epidemics.

59.5% (55.4–63.6) of influenza virus and respiratory syncytial virus overlapped, and that 60.3% (55.6–65.0) of metapneumovirus and respiratory syncytial virus overlapped. The percentages did not differ significantly between temperate and tropical regions (appendix p 77).

The model with mean-centred temperature and mean-centred relative humidity was selected for our main analysis (detailed results of model comparison and selection are in the appendix [pp 67, 78]).

The observed (appendix p 79) and model (figure 3) predicted monthly virus activity against mean-centred temperature and relative humidity was calculated. Lower temperature was associated with higher influenza virus and respiratory syncytial virus activity. When temperature

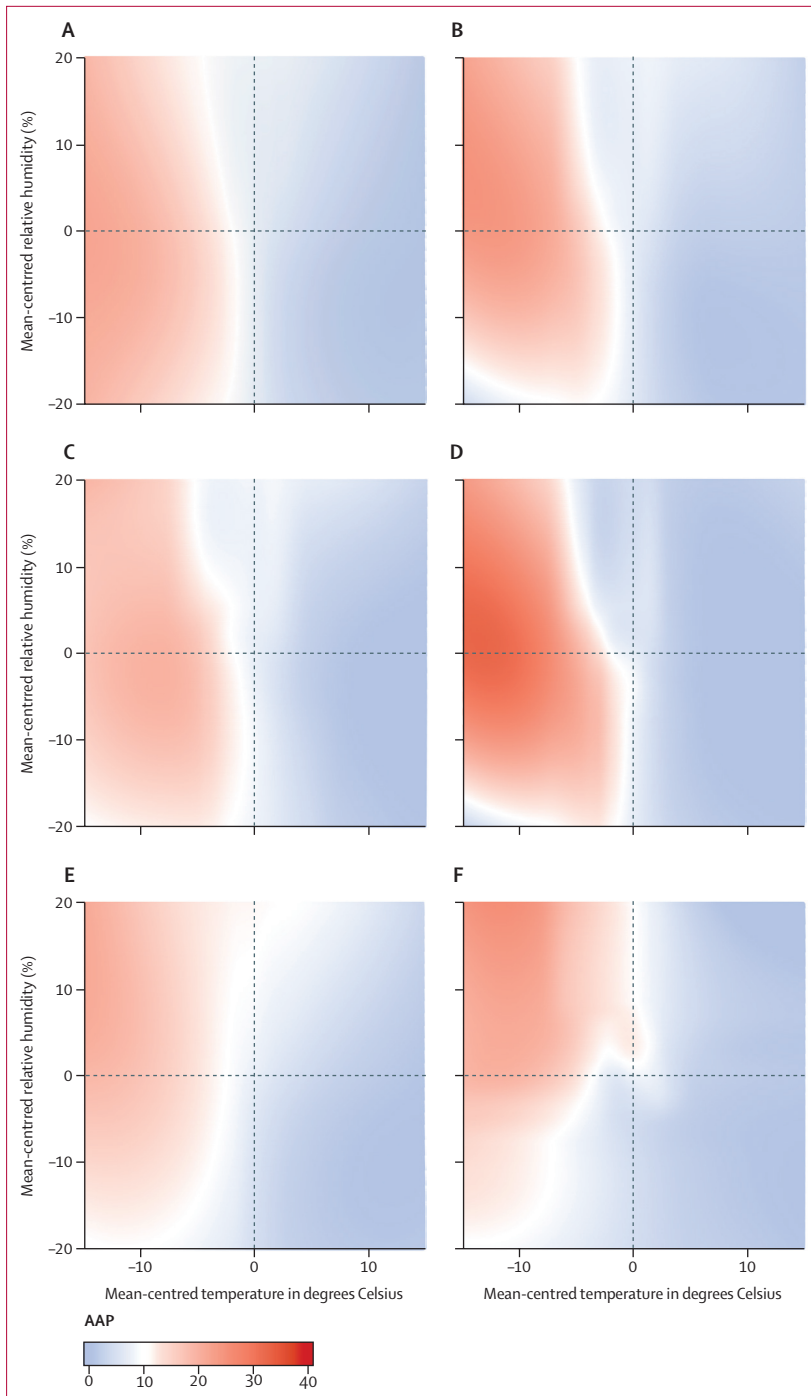


Figure 3: Model-predicted output of monthly activity of influenza virus and respiratory syncytial virus against mean-centred temperature and relative humidity

(A) Influenza virus (B) Influenza virus A. (C) Influenza virus B. (D) Influenza virus A(H1N1)pdm. (E) Influenza virus A(H3N2). (F) Respiratory syncytial virus. AAP=annual average percentage.

See Online for video

was lower than the annual average, higher relative humidity was also associated with higher respiratory syncytial virus activity but not with higher influenza virus activity. When temperature was higher than the

annual average, higher relative humidity was associated with higher influenza virus activity, especially for influenza virus A(H3N2), whereas this pattern was not observed for respiratory syncytial virus.

Regarding the predictability of the model, the results of the leave-one-out cross validation are shown in the appendix (p 68). Overall, the model had good accuracy across all viruses in predicting local epidemic months. Better predictability was observed in the temperate regions than in the tropics, especially for influenza virus. Regarding the prediction of the onset month of epidemics, the model prediction error was -0.2 months (95% CI -0.6 to 0.1) for influenza virus and 0.1 months (-0.2 to 0.4) for respiratory syncytial virus.

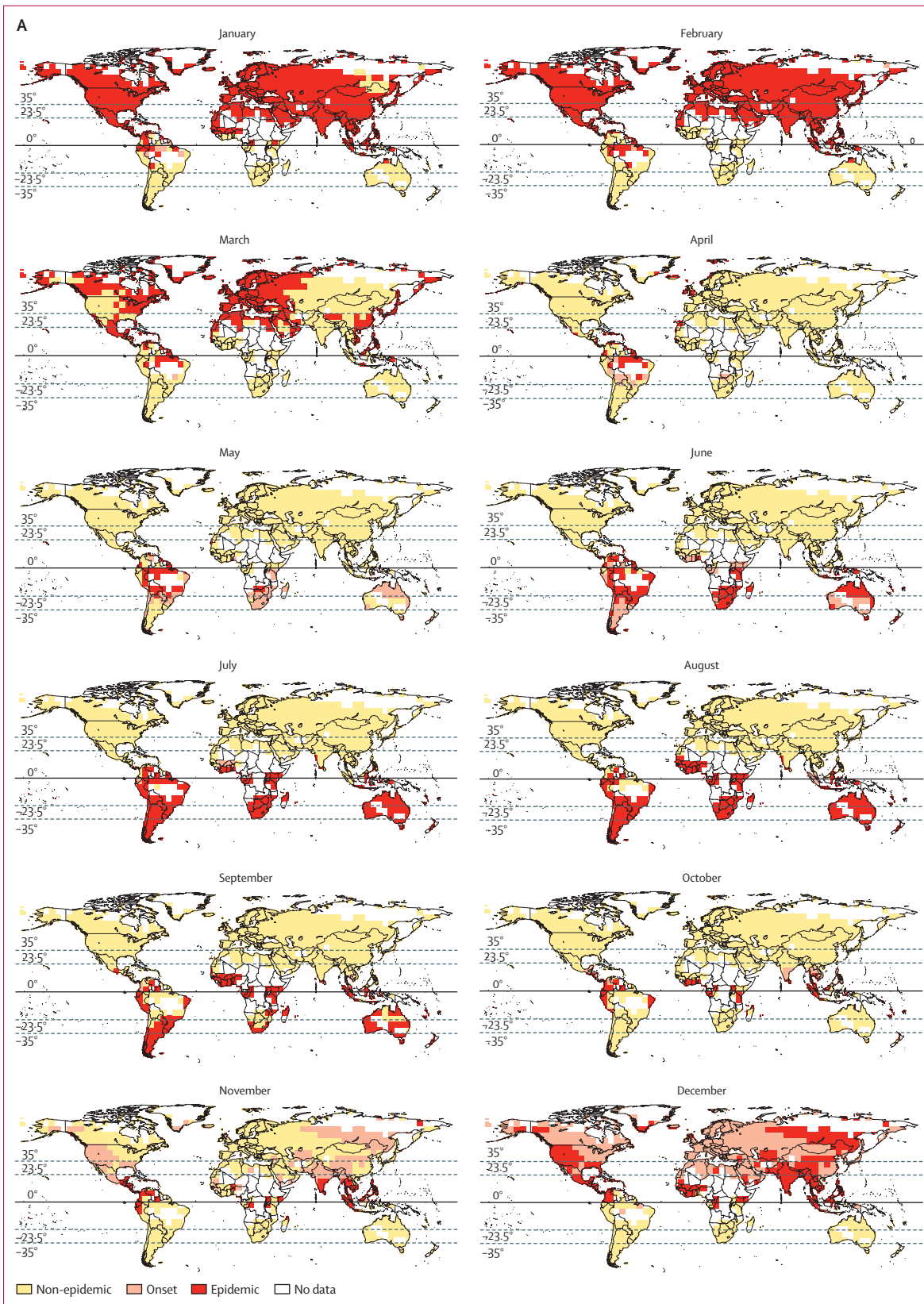
Moreover, on the basis of the model, we present the estimated global epidemic months of influenza virus and respiratory syncytial virus on a 5° by 5° scale, including the onset of the epidemic months (figure 4; supplementary video).

Discussion

To our knowledge, this is the first systematic analysis of global monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus at national and subnational levels. With strict criteria, we compiled laboratory-confirmed viral activity from a literature review, online surveillance datasets, and shared datasets by collaborators. We present global maps of monthly virus activity for influenza virus (including types and subtypes), respiratory syncytial virus, parainfluenza virus, and metapneumovirus, showing the distinct seasonal patterns for each virus. We found that latitudinal patterns in duration of epidemics were diverse among the four viruses.

Our results suggest that the global seasonal patterns of influenza virus and respiratory syncytial virus are different in terms of both timing and duration of epidemics. However, in a previous global review by Bloom-Feshbach and colleagues,¹¹ the authors concluded that seasonal patterns of influenza virus and respiratory syncytial virus were broadly similar in timing. The difference between the results of our study and those of Bloom-Feshbach and colleagues¹¹ is likely to be due to the smaller number of sites included in their review compared with the present study (influenza virus: 246 sites vs 77 sites; respiratory syncytial virus: 183 sites vs 96 sites).

Our study also found that seasonality was slightly different among influenza virus types and subtypes, similar to the findings from previous country-level regional reports.^{26,27} In our study, influenza virus A epidemics occurred 0.6 months (95% CI 0.3 to 0.9) before influenza virus B in the temperate sites but no clear temporal order was seen in the tropical sites (lag=0 [-0.5 to 0.5]). Moreover, we identified some interesting patterns that had not been reported in previous reports; the latitudinal patterns of epidemic



(Figure 4 continues on next page)

duration were similar among influenza virus subtypes, with influenza virus A(H1N1)pdm being the most seasonal virus (duration of epidemics 3·3 months [3·1 to 3·5]), followed by influenza virus A(H3N2) (4·2 months [3·9 to 4·4]) and influenza virus B (4·5 months [4·3 to 4·8]), regardless of the latitudes.

Compared with influenza virus and respiratory syncytial virus, year-round laboratory-confirmed data of metapneumovirus and parainfluenza virus are scarce and no global report on the seasonality of these two viruses is available. In the present study, we found that parainfluenza virus epidemics occurred most often in the spring and early summer months in each hemisphere; metapneumovirus epidemics occurred in late winter and spring in most temperate sites, but the peaks were more diverse in the tropics. Parainfluenza virus had longer duration of epidemics, which could be explained by the different circulation timings in each parainfluenza virus subtype.^{28,29} Metapneumovirus had similar patterns to respiratory syncytial virus in duration of epidemics, which might reflect known genetic similarities between the two viruses.³⁰ However, these two viruses did not co-circulate at most sites. In the temperate regions, metapneumovirus occurred 1·7 months (95% CI 1·1–2·3) after respiratory syncytial virus; in the tropics, no clear temporal order was observed. The non-co-circulation of respiratory syncytial virus and metapneumovirus indicates possible interference between these two viruses warranting further study.

The mechanisms that shape the global seasonal patterns of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus remain unclear. Possible mechanisms include contact rates between susceptible and infected hosts, virus survival, and host immunity. Possible seasonal stimuli include temperature, humidity, precipitation, solar radiation, travel of work flows, and other factors.³¹ In our study, all four viruses had different global patterns of timing and duration of epidemics; these patterns are unlikely to be well explained by non-virus-specific factors alone, and potential spurious correlations between any non-virus-specific factors and virus activity should be considered. For example, travelling pattern is a potential factor that affects transmission but is not likely to explain the observed seasonal patterns well due to its non-virus-specific nature. Therefore, we did not select non-virus-specific factors in our candidate models. The two predictors that we included, temperature and relative humidity, were associated with the seasonality of influenza virus and respiratory syncytial virus in different ways. Although lower temperature was associated with higher activity of both influenza virus and respiratory syncytial virus, higher relative humidity was associated with higher influenza virus activity when temperature was above annual average and was associated with higher respiratory syncytial virus activity when temperature was lower than the annual average. Experimental studies on

the transmission and survival of these viruses are needed to confirm our findings. Our findings regarding the predictors of influenza virus were similar to the two types of influenza virus peaks, “cold-dry” and “humid-rainy”, proposed by Tamerius and colleagues.¹⁴ However, their model was based on the activity of influenza virus of a dichotomous nature—ie, peak and non-peak.¹⁴ In our study, we modelled the activity of influenza virus and respiratory syncytial virus in a continuous nature, thus allowing for increased flexibility in our prediction.

On the basis of the gridded dataset of monthly temperature and relative humidity on a 5° by 5° scale,^{23,24} we mapped the global average epidemic months in 2013–17. The results indicated that for those countries with a wide range of climate patterns, the viral epidemics varied within the country. For example, influenza virus and respiratory syncytial virus epidemics occurred earlier in northern Australia than in southern Australia.

Our study provides global maps of monthly virus activity, which have important implications for public health strategy. For influenza virus, vaccination is the most effective way to prevent disease.³² Seasonality data from existing country-level surveillance help to inform the timing and composition of influenza virus vaccines, but such surveillance is unable to account for any within country variations and undersampled areas. By incorporating data from published and unpublished studies, our study potentially fills the data gap at subnational level and for countries with no surveillance programme. This additional knowledge is particularly important for geographically large countries and tropical regions where great variations of virus activity might exist, as found in our study. For respiratory syncytial virus, the seasonality information is important for immunisation strategy. In high-income countries, the administration of palivizumab prophylaxis, a respiratory syncytial virus-neutralising monoclonal antibody mainly used among high-risk infants, needs to be timed according to the local respiratory syncytial virus season given the short duration of its protection. For middle-income and lower-income countries, respiratory syncytial virus seasonality information is important for the development of affordable biological equivalents of palivizumab and any vaccines with short duration of protection.³³ Moreover, the length of a respiratory syncytial virus season defined by the duration of epidemics in our study is stable at 4–5 months across all sites, by contrast with influenza virus, which has irregular seasonality or year-round activity in the tropics. This information could help optimise immunisation programmes by focusing on the predefined respiratory syncytial virus seasons in both temperate and tropical regions. Unlike influenza virus, for which surveillance data are widely available, respiratory syncytial virus surveillance data are still scarce and WHO is in the process of implementing a global respiratory syncytial virus surveillance programme.³⁴ For all the viruses, the seasonality information is helpful in

health services planning, especially when viruses co-circulate and impose pressure on hospital beds. It is also important for the patients' clinical management and for the appropriate use of antibiotics in the context of increased antimicrobial resistance and insufficient health resources in some settings.³⁵

This study, however, is not without its limitations. First, similar to most studies of this type, the accuracy of the global activity data reported could be limited by the variety of methods applied in the studies and surveillance systems included. We were also unable to account for the variability regarding the age groups and severity of viral infections included at each site. Although we aspired to have good geographical representation, we applied strict inclusion criteria and did additional quality assessment to exclude studies in which the reported seasonality was likely to be biased by study participants, testing practice, or reporting practice. Second, for better comparison across different sites, we calculated monthly AAP by aggregating multiyear data to establish virus activity. Although multiyear surveillance data suggest that the year-to-year change of influenza virus and respiratory syncytial virus onset is within 1 month for most sites,^{5,12} aggregating multiyear data could obscure the seasonal patterns of those sites with more notable year-to-year changes in seasonality. In particular, we were unable to identify multiyear periodicity of respiratory syncytial virus activity, which has been reported in some countries in northern Europe.³⁶ Third, we were unable to report global seasonal patterns of any subtype of respiratory syncytial virus, parainfluenza virus, or metapneumovirus due to a paucity of relevant data reported; this exclusion of subtypes could obscure the seasonality results of respiratory syncytial virus, parainfluenza virus, and metapneumovirus, particularly parainfluenza virus since the seasonal patterns were reported to differ greatly by type.^{28,29} Fourth, compared with influenza virus and respiratory syncytial virus, fewer sites reported data on metapneumovirus and parainfluenza virus, thus limiting the representativeness of the results. Fifth, we were only able to summarise the global seasonality on a monthly basis instead of on a weekly basis due to the scarcity of weekly data (eg, only 20% of respiratory syncytial virus data in our study were originally aggregated weekly) and methodological challenges to accommodate the different definitions for week (eg, a week can start with Saturday, Sunday, or Monday by different definitions). Sixth, due to the lack of granularity of our training data, our prediction model might not be able to reflect the possible changes of viral epidemics induced by subtle short-term climate changes. However, such prediction is possible with data that are more granular in the future (eg, multiyear weekly data). Finally, our model is restricted in its ability to predict the influenza virus epidemic months in the tropical region, partly due to the seasonality being unclear and its inability to establish association between viral activity

and meteorological factors. In the tropics, multiyear viral activity data from more countries are warranted and factors related to host immunity (eg, seasonal fluctuation of nutritional status)³⁷ can be considered in future modelling studies.

Given the substantial health-care burden caused by influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus, their seasonal patterns described in our study are important for related health services planning. The model is helpful in predicting the onset months of local influenza virus and respiratory syncytial virus epidemics. This model, together with the seasonality results presented, helps with the optimisation of any respiratory syncytial virus immunisation strategies that rely on the information of local respiratory syncytial virus season, especially in most middle-income and lower-income countries where respiratory syncytial virus surveillance might not be routine. Future studies should consider describing and modelling the activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus on a multiyear scale and should take into consideration the effects of climate change on respiratory viral epidemic seasonality.

Contributors

HN and HC conceptualised the study. YL led the literature review with contributions from RMR and XW. YL cleaned, analysed, and visualised the data. YL, HN, and HC interpreted the data. YL wrote the first draft with inputs from RMR, XW, HN, and HC. All other named authors contributed to collection of unpublished research data and interpretation and critically reviewed the initial manuscript. All other members of Respiratory Syncytial Virus Global Epidemiology Network (RSV GEN) contributed to data collection and reviewed the manuscript for intellectual content. All authors read and approved the final draft for submission.

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